MEASUREMENT OF LEFT VENTRICULAR FUNCTION IN ANAESTHETISED HORSES USING TRANSOESOPHAGEAL DOPPLER ECHOCARDIOGRAPHY

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DECLARATION

Mr. D. H. Bartram performed the thermodilution studies in this work and Dr. K.J. Blissitt and Mr. R.E. Clutton provided technical assistance in all studies involving general anaesthesia. Mr. H. Ross assisted in the development and writing of the computer software used for data acquisition. Dr. Paddy Dixon and Mr Henry Tremaine performed the surgery to exteriorise, and then relocate, the carotid arteries of the reasearch animals. The rest of this thesis is my own work and has not been presented to any University other than the University of Edinburgh. A paper from this thesis has been published in Supplement 19 of the Equine Veterinary Journal and is bound as a final appendix to this document. Five abstracts have been published in the Proceedings of the 5th International Congress of Veterinary Anaesthesia.

Lesley Elissa Young
August 1995

This work is dedicated to Shirley, Vivienne, Hailey, Jodie, Eddie, Chester, Legs, and Khaloof: 8 very special horses

"For some must watch while some must sleep"

Hamlet, Act 3, Scene 2.

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CHAPTER 5 : SENSITIVITY OF DOPPLER DERIVED INDICES OF LEFT VENTRICULAR FUNCTION TO ADMINISTRATION OF INOTROPIC AND VASODILATOR AGENTS IN ANAESTHETISED HORSES

ABSTRACT

Studies were undertaken using transoesophageal Doppler echocardiography to monitor left ventricular systolic function in anaesthetised horses. A 3.5 MHz transoesophageal probe was specifically developed in collaboration with Vingmed Sound for equine use. The indices of systolic function investigated were maximum acceleration of aortic blood flow (dv/dt_{max}), maximum blood flow velocity, (V_{max}), cardiac output (CO), left ventricular pre-ejection period (PEP) and left ventricular ejection time (ET).

The feasibility of the technique was demonstrated in a group of 8 healthy Thoroughbred horses anaesthetised using a standard protocol. It was established that two dimensional transoesophageal echocardiography provided a reference view of the left ventricular outflow tract and aorta that consistently allowed high quality Doppler echocardiographic measurement of aortic blood flow velocity. The flow envelopes obtained were suitable for measurement of indices of left ventricular systolic function. The repeatability of the measured indices was similar to that of the maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$), obtained simultaneously by cardiac catheterisation.

Cardiac output estimations made using transoesophageal Doppler echocardiography were compared with those obtained by thermodilution in the same group of horses under general anaesthesia. Cardiac output was altered by infusions of the sympathomimetic amine, dobutamine. Aortic velocity spectra obtained both by high pulse repetition frequency and continuous wave insonation modes were used to obtain the velocity time integral for calculation of cardiac output. The measurements derived from transoesophageal echocardiography agreed well with those obtained by thermodilution. Both correlation coefficients and limits of agreement between the two

techniques were better than those obtained from similar studies in standing horses using transthoracic echocardiography.

The sensitivity of the Doppler derived indices of left ventricular function to inotropic intervention was assessed in the final sequence of studies. As these indices are derived during the ejection period they are load dependent, so their response to changes in ventricular loading was also assessed and compared with the most commonly used index of myocardial contractility in horses, $LVdp/dt_{max}$. Three drugs were administered to the anaesthetised horses in a randomised sequence during three separate anaesthetic episodes. The drugs, dobutamine, dopamine and dopexamine were selected because of their relatively different effects on afterload, preload and contractility. Maximum acceleration of aortic blood flow was as sensitive to the changes in ventricular performance as $LVdp/dt_{max}$. Maximum aortic blood velocity showed the same qualitative response to infusion of the drugs but the changes were quantitatively less than in dv/dt_{max} and $LVdp/dt_{max}$. The systolic time intervals, PEP and ET, were also responsive to drug infusion; pre-ejection period shortened with each drug, whilst ET increased after dopamine and dopexamine, but was reduced by dobutamine.

These studies have shown that dv/dt_{max} is as sensitive as the invasive index $LVdp/dt_{max}$ for detecting changes in left ventricular performance. In addition dv/dt_{max} and V_{max} appear to be no more affected by changes in ventricular loading conditions than the isovolumic index $LVdp/dt_{max}$. It is concluded that transoesophageal Doppler echocardiography provides a minimally invasive technique for assessment of left ventricular systolic function in anaesthetised horses.

Chapter 1

REVIEW OF THE LITERATURE

GENERAL ANAESTHESIA AND CARDIOVASCULAR FUNCTION IN HORSES

General anaesthesia in horses produces cardiac depression and systemic hypotension (Gillespie, Tyler and Hall, 1969; Eberly, Gillespie, Tyler and Fowler, 1968). These adverse cardiovascular sequalae have been implicated in the higher incidence of intraoperative mortality in horses compared to other species (Johnston, Taylor, Holmes and Wood, 1995), and in the postoperative lameness which not infrequently accompanies general anaesthesia in horses (Richey, Hollans, McGrath, Dodman, Marshall, Court, Norman and Seeler, 1990; Lindsay, Robinson, Brunson and Majors, 1989; Grandy, Steffey, Hodgson and Woliner, 1987). Steffey and Howland (1978) showed that the equine cardiovascular system is more susceptible to the depressant effects of halothane than that in other species. Cardiovascular monitoring during equine anaesthesia is generally restricted to recording cardiac rate, rhythm and arterial blood pressure (Hubbel, 1991; Lumb and Wynn-Jones, 1985), and information concerning the mechanisms of cardiovascular dysfunction which occurs under general anaesthesia in this species has been limited by the invasive nature of the monitoring techniques that were previously available. However the availability of non-invasive echocardiography has removed many of these limitations. Two-dimensional echocardiography permits recording of dynamic images of the heart non-invasively (Feigenbaum, 1993), whilst techniques employing the Doppler principle can be used to record blood flow velocity from targeted areas of the heart and great vessels (Goldberg, Allen, Marx and Donnerstein, 1988). In human medicine ultrasound technology is being increasingly used for evaluation of left ventricular function under general anaesthesia (Skarvan, 1993; Shively, 1992).

The studies which form the basis of this thesis evaluate Doppler echocardiography for monitoring left ventricular function in anaesthetised horses. The studies were performed using an ultrasonic transducer sited in the oesophagus, a position, which from anatomic considerations, should provide optimal alignment with aortic blood flow for Doppler echocardiographic studies in this species (Ghoshal, 1975).

CARDIAC ULTRASOUND

Since its introduction in 1954 cardiac ultrasound has become an invaluable diagnostic tool in veterinary and human medicine. The history and development of 2-dimensional (2-D) transthoracic echocardiography in human medicine has been reviewed by Weyman (1994b) and Edler (1990). Long (1993) has reviewed the history and applications of 2-D transthoracic echocardiography in veterinary and equine medicine.

DOPPLER ECHOCARDIOGRAPHY

HISTORY AND DEVELOPMENT

The principle that the frequency of a wave could be altered after reflection off a moving target was first enunciated by the Austrian mathematician and physicist Christian Doppler (1803 - 1853). A biography of Christian Andreas Doppler and a description of the early history and development of the effect that subsequently bore his name is provided by Long (1993) and Eden (1985).

The first reported use of Doppler ultrasound to detect blood flow was by Satomoto (1956). The early devices recorded the intensity of the Doppler signal, not its frequency shift, and were therefore unable to quantify velocity. The goal throughout early development of Doppler devices was the determination of volumetric flow (Weyman, 1994e). The first true measurement of the Doppler shift frequency was

made by Franklin, Schlegal and Rushmer (1961). Their device employed continuous wave ultrasound and, whilst capable of measuring flow velocity, could not detect flow direction. As transducer technology advanced methods used in radio communication, were adapted to separate the forward and reverse components of the flow signal (Weyman, 1994e). The first Doppler transducers were developed commercially, not for cardiac use, but for detection of peripheral blood flow after pulse occlusion (Baker, Stegal and Schlegal, 1964). Doppler detection of aortic blood flow was a little slower to develop since the available continuous wave devices were sensitive to movement all the way along the beam path. This resulted in unwanted interference from neighbouring moving structures around the aorta. Light (1969) succeeded in recording blood flow velocity in the human aorta using continuous wave ultrasound. He suggested that the instrument might prove useful for assessment of the acceleration of aortic blood which had recently been proposed as an index of myocardial strength (Noble, Gabe, Trenchard and Guz, 1965; Rushmer, 1964). He also recommended the technique for diagnosis of aortic stenosis, a condition which resulted in an increase in maximum velocity of blood flow.

The velocity of the aortic blood flow was calculated from the Doppler frequency shift using the formula

$$V = \frac{c\,\Delta F}{2F_o \cos\vartheta}$$

c	speed of ultrasound in tissue
ΔF	Doppler frequency shift
F_o	frequency of emitted ultrasound
$\cos\vartheta$	cosine of the angle between the ultrasound beam and direction of flow

The problem of interference from neighbouring structures and failure to target specific vessel locations continued to hamper the long-term objective of flow

quantification. To achieve this aim, it is necessary not only to measure flow direction and mean flow velocity, but also to identify the point in the vessel to which that velocity applies and to measure the vessel's cross sectional area at that point. Only maximum velocity can be measured from a continuous wave signal and the area of the heart or vessel to which the maximum velocity applies cannot be established.

Development of pulsed Doppler echocardiography

In 1970 Baker described an ultrasound technique that allowed velocity to be measured at a specific depth (range-gating) and from a specific sampling site (the sample volume) . To achieve this the transducer transmitted a short burst of sound and then switched to receiving mode to await the return of the reflected back-scattered ultrasound. Because the velocity of ultrasound in tissue is fixed, the delay between transmission of the pulse of ultrasound and its return to the transducer is related directly to the distance between the transducer and the target. Range-gated systems adjust the time between transmission and reception of ultrasound pulses to accommodate the target depth selected by the operator. This ensures that only echoes reflected from structures at the target depth are recorded. The sound pulse transmitted from a pulsed Doppler device has both length and width. At any instant in time echoes can arise only from structures that lie in the volume of tissue occupied by the pulse (the sample volume) (Weyman, 1994c). Its length is determined by the wavelength of the sound and the number of cycles constituting a pulse. At least 5 cycles are generally transmitted in each pulse, which at a frequency of 3.0 MHz represents a pulse length of 2.5 mm (λ = 0.5 mm) (Feigenbaum, 1993). The width of the pulse, and therefore the sample volume, depends upon transducer size and frequency, and the extent that it is focused (Weyman, 1994c).

Devices utilising pulsed Doppler ultrasound allowed blood velocity information to be acquired from selected depths or areas in a vessel, satisfying one criterion for flow quantification. The angle of incidence between ultrasound beam and blood flow could

not be quantified, an important factor in estimating the accuracy of Doppler derived velocity estimations (Goldberg, Allen, Marx and Donnerstein, 1988), and the technique could not provide a means for measurement of the cross-sectional area of the vessel at the site of velocity recording. Early prototypes combining real time 2-D imaging with pulsed Doppler were unsuitable for cardiac work as they incorporated two separate transducers aligned to intersect at a selected depth within the scan plane (Weyman, 1994c). The two modalities were soon incorporated using the same transducer and 2-D guided, targeted Doppler echocardiography became possible, permitting flow recording from the heart and great arteries (Moritz, Shreve and Mace, 1976). Alignment of the ultrasound beam with flow could be visually appraised in two perpendicular planes thus improving the accuracy of velocity measurement (Griffith and Henry, 1978). In human cardiology the technical advances in data processing and the realisation that Doppler derived velocities could be used to estimate trans-valvular pressure gradients has elevated Doppler echocardiographic techniques to a position of major diagnostic importance. The Doppler techniques provide additional data which are complementary to that derived from standard imaging echocardiography and have established the echocardiogram as the definitive non-invasive diagnostic tool for cardiology (Weyman, 1994e).

Colour Flow Doppler echocardiography

In recent years a system has been developed for displaying Doppler information superimposed upon a 2-D or M-mode image. Doppler Colour flow mapping is a pulsed technique in which multiple sample volumes are used to record Doppler information from different areas of the heart (Sutherland and Fraser, 1989). Flow velocity is colour coded and displayed on the 2-D or M-mode image. Most instruments code flow towards the ultrasound transducer in red and away from the transducer in blue (Simpson and Sahn, 1984). These colours were selected because they give the greatest contrast with the surrounding endocardial borders and cardiac chambers, giving optimal

definition to the human eye in real time (Weyman, 1994d). The convention is somewhat contrary to Doppler's original concept that light from stars moving away from earth was shifted to the red end of the spectrum, and probably arose from early studies imaging human carotid arteries (Kisslo, Adams and Belkin, 1988). In these studies the workers arbitarily chose red to code the carotid arterial blood flow moving towards an ultrasound transducer in the suprasternal notch.

In addition to coding flow direction, the magnitude is also represented by varying the hues of the two primary direction colours; higher velocities being coded in lighter shades of red or blue (Goldberg, Allen, Marx and Donnerstein, 1988). Many machines also use the third primary colour, green, to code for variance in the flow signal (Nishimura, Miller, Callahan, Benassi, Seward and Tajik, 1985). The use of multiple velocity pulses along a single sight line allows the machine to calculate the variance of each sample relative to the mean velocity. Laminar flow should show little variance, whilst turbulent flow should have variance that is directly related to the degree of flow disturbance. Variance about the mean also occurs when flow within the sample volume is accelerating or decelerating, even when the flow is essentially laminar (Weyman, 1994d). The limits of variability at which a green colouration is assigned varies between manufacturers, as does the method used to determine variance (Goldberg, Allen, Marx and Donnerstein, 1988). As a result the use of variance in colour flow mapping in human cardiology remains controversial.

Colour flow mapping has revolutionised clinical diagnostic echocardiography (Simpson and Sahn, 1984). The technique allows rapid screening of cardiac chambers for evidence of abnormal blood flow and is non-invasive (Cooper, Nanda, Philpot and Fan, 1989). It is especially useful in neonates and children with congenital heart disease, and in adults for the semi-quantitative assessment of valve regurgitation, or the description of flow patterns in complex acquired disease (Sutherland and Fraser, 1989). The technique provides spatial orientation of regurgitant signals which can be used to

guide placement of a pulsed Doppler sample volume, or continuous wave ultrasound, for optimal velocity determination and accurate calculation of trans-valvular pressure gradients (Monoghan and Mills, 1989). Small eccentric regurgitant signals that are easily missed by pulsed or continuous wave techniques are readily identified by colour flow mapping.

Limitations of pulsed Doppler echocardiography

Range specificity by pulsed Doppler techniques, including colour flow mapping, imposes limitations on the maximum velocity that can be measured. Because the transducer must wait for the reflected echoes to return before the next pulse can be transmitted, the period between pulses is much longer than the pulse duration. As a result during the period when the pulse interacts with the target, the target moves only a fraction of a wavelength, so that the frequency shift cannot be calculated. Meanwhile in the period between pulses the target has moved much further and measurable changes in phase can have occurred (Weyman, 1994d). In pulsed techniques the Doppler waveform is reconstructed from a series of samples taken at regular intervals (the pulse repetition frequency). The upper limit of velocity detection is constrained by the pulse repetition frequency which imposes a maximum value to the highest velocity that can be detected unambiguously (the Nyquist limit) (Feigenbaum, 1993).

If higher velocities occur the frequency waveform cannot be reconstructed accurately, and the phenomenon of "aliasing" occurs (Goldberg, Allen, Marx and Donnerstein, 1988). Because of an insufficient pulse repetition frequency the Doppler shift frequency is under-sampled, i.e. the target moves faster than the systems ability to record its velocity (Weyman, 1994d). When this ocurs the velocity is coded as if it were occurring in the opposite direction (Feigenbaum, 1993). Quantitatively sampling frequency must be double the shift frequency to avoid velocity aliasing, as a result to measure high velocities unambiguously a high pulse repetition frequency is needed (Angelsen and Brubakk, 1976). The further a vessel is from the skin surface, the

longer will be the wait period required for the pulse of ultrasound to return to the receiver, thus the pulse repetition frequency is limited by the speed of sound in tissues. As a result the deeper the artery the lower is the velocity that can be measured by a pulsed system, adding a further range limitation.

High pulse repetition frequency Doppler systems (HPRF) sacrifice range specificity to increase the frequency of interrogation of distant targets. In this system multiple pulses are travelling through the tissue at any one time. This multiplies the sampling frequency by a factor of 2 or more, depending on the number of simultaneous pulses. The maximum velocity that can be measured is therefore increased, but at the expense of target ambiguity (Weyman, 1994d).

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography is the term used to describe the ultrasonographic study of the heart from the oesophagus using two-dimensional, M-mode, or Doppler echocardiography (Weyman, 1994a). The human oesophageal lumen is separated from the posterior pericardium by a thin muscular wall which causes minimal attenuation of an ultrasound beam allowing almost unrestricted access to the cardiac chambers.

HISTORY AND DEVELOPMENT

In contrast to transthoracic ultrasound early development of transoesophageal echocardiography began with studies which evaluated blood flow. Development of Doppler ultrasonics was primarily directed at quantification of volumetric flow (Baker, Stegal and Schlegal, 1964). Use of the oesophageal route was prompted by difficulties encountered in determining aortic blood flow velocity with transcutaneous continuous wave Doppler (See page 9). In an attempt to eliminate interference from moving structures around the aorta Side and Gosling (1971) measured thoracic aortic blood

flow by continuous wave Doppler from a transducer sited in the oesophagus. Daigle, Miller, Histand and Hokanson (1975) used pulsed Doppler from a oesophageal probe to measure blood velocity, volume flow and arterial wall motion. These workers validated the flow determinations obtained by the oesophageal probe against measurements obtained with implanted electromagnetic and ultrasonic flow cuffs and concluded that the simplicity, accuracy and non-traumatic nature of the probe gave it great potential for research and clinical applications. In 1979 pulsed Doppler from oesophageal ultrasound transducers was used to measure aortic blood velocity and to assess aortic haemodynamics in humans (Histand, Wells, Reeves, Sodal, Adamson and Willson, 1979; Wells, Histand, Reeves, Sodal and Adamson, 1979).

During the mid 1970s although 2-D and M-mode transthoracic echocardiography had gained widespread acceptance in human cardiology, severe limitations in the technique were discovered in patients with chronic obstructive pulmonary disease, barrel chests or obesity (Segal, Konecke, Kawai, Kotler and Linhart, 1976). The need for an alternative window from which to image the heart in these patients redirected interest to the oesophageal route. At about this time the previous emphasis on development of transoesophageal ultrasonography shifted from Doppler echocardiography to M-mode and 2-D imaging techniques. Frazin, Talano, Stephanides, Loeb, Kopel and Gunnar (1976) reported the use of a single element transducer for transoesophageal M-mode studies in humans. The end of the probe was fixed so there was only limited control of the ultrasound beam by the operator. The first 2-D images of the heart were recorded from the transoesophageal route by Hisanga and colleagues (1977), their transducer consisted of a single rotating element encased in an oil bag and mounted on a fixed gastroscope.

A major breakthrough in transoesophageal echocardiography came with the arrival of phased array technology. Schluter, Langenstein, Polster, Kremer, Souquet, Engel and Hanrath (1982) incorporated a miniature phased array transducer into the tip

of a commercially available gastroscope. Unlike the earlier mechanical transoesophageal transducers the phased array device no longer vibrated, increasing patient comfort. The oil bag which had ensured contact with the oesophageal wall in the early prototypes was no longer needed, as the end of the probe was flexible and the direction of the ultrasound beam could be steered by the endoscopic controls.

During the 1980s pulsed, continuous wave and colour flow Doppler were added to the basic 2-D imaging format of human transoesophageal echocardiography probes. Currently biplane transducers have become standard in human cardiology. These probes contain a second more proximal transducer array which is mounted parallel to the long axis of the probe and thus orthogonal to the distal transducer. The images from both transducers can be displayed simultaneously on the ultrasound screen greatly improving the three dimensional visualisation of cardiac anatomy and regional wall motion abnormalities (Pearson and Pasierski, 1991). Most recently transoesophageal transducers have been developed that allow the scan plane to be rotated around a central axis. The transducer is mechanically rotated through an arc of 180° and displays the angle of rotation on the screen. The first generation multiplane probes are large in diameter which currently limits their usefulness, but advances in technology may soon resolve this problem (Weyman, 1994a).

Applications of transoesophageal echocardiography in human medicine

In a recent position statement by the American College of Cardiologists transoesophageal echocardiography was officially recognised as an acceptable clinical procedure in the diagnosis of heart disease (Seward, Labovitz, Lewis, Martin, Pollick, Quinones, Ritchies, Snider and Stewart, 1992). The close anatomical proximity of the oesophagus to the heart, coupled with the use of near-focused, high frequency transducers permits superior images of many intracardiac structures to be obtained (Fisher, Stahl, Budd and Goldman, 1991). The quality of the 2-D images obtained is

better than with conventional transthoracic echocardiography because there is better spatial resolution of structures from the higher frequency transducer. Acoustic interference from the lungs and chest wall is avoided because the transducer is physically closer to posterior structures such as the left atrium, interatrial septum, mitral valve and descending aorta (Roelandt and Sutherland, 1988). Fifteen 2-D standard imaging planes of the heart obtainable by transoesophageal echocardiography have been described by the Echocardiography Committee of the American College of echocardiography (Seward, Khandheria, Oh, Abel, Hughes, Edwards, Nichols, Freeman and Tajik, 1988). Transoesophageal echocardiography also provides the opportunity to examine virtually the whole length of the thoracic aorta in long and short axis (Weyman, 1994a) and has gained widespread acceptance for emergency diagnosis of aortic aneurism where it offers significant advantages over other methods (Ballal, Nanda, Gatewood, Darcy, Samdarshi, Holman, Kirklin and Pacifico, 1991; Erbel, Engberging, Daniel, Roelandt, Visser and Rennollet, 1989). The technique is being increasingly used for detection of mitral chord rupture where superiority over conventional techniques has also been demonstrated (Alam and Sun, 1991; Sochowski, Chan, Ascah and Bedard, 1991). Transoesophageal echocardiography allows examination of native and prosthetic valves (Dittrich, McCann, Walsh, Blanchard, Oppenheim, Waack, Donahey and Wheeler, 1990). The latter create a particular problem for external scanning techniques because the prosthetic material produces intense echoes which severely limit their visualisation. Mitral regurgitation is readily visualised by transoesophageal echocardiography (Castello, Lenzen, Aguirre and Labovitz, 1992; Kisslo, 1989) although the ability of the technique to quantify the severity of regurgitation is the source of some debate (Khandheria and Oh, 1992; Kleinman, Czer, DeRobertis, Chaux and Maurer, 1989). The technique has also been used for examination of aortic and tricuspid valves and for diagnosis of infective endocarditis (Milchak and Plehn, 1991) and for diagnosis of embolic disease (Nagelhout, Pearson and Labovitz, 1991) and intracardiac masses (Fisher, Stahl, Budd

and Goldman, 1991). It is estimated that between 2 and 5 % of all echocardiograms being performed in major institutions in the USA are oesophageal (Khandheria and Oh, 1992; Weyman, 1994a).

The technique has been introduced into others areas in human medicine; transoesophageal echocardiography has been employed in stress echocardiography to detect coronary artery disease (Geiser, 1992; Zabalgoitia, Gandhi, Abi-Mansour, Yarnold, Moushmoush and Rosenblum, 1991) and to examine left ventricular function during exercise (Matsumoto, Hanrath, Kremer, Tams, Langenstein, Schluter, Weiter and Bleifeld, 1982).

Safety of transoesophageal echocardiography

At present there are no known risks to the human patient following an oesophageal ultrasound examination. The risk of bacteraemia has been shown to be slight (Steckelberg, Khandheria, Anhalt, Ballard, Seward, Click and Wilson, 1991; Melendez, Chan, Cheung, Sochowski, Wong and Austin, 1991; Daniel, Erbel, Kasper, Visser, Engberding, Sutherland, Grube, Hanrath, Maisch, Dennig and Schartl, Kremer, Angerman, Iliceto, Curtius and Mugge, 1991), the risk of oesophageal damage minimal (O'Shea, Southern, D'Ambra, Magro, Guerrero, Marshall, Vlahakes, Levine and Weyman, 1991) and the incidence of post-operative dysphagia was not increased after transoesophageal echocardiographic examination in anaesthetised human patients (Messina, Paranicas, Fiamengo, Yao, Krieger, Isom and Devereux, 1991).

Intraoperative use of transoesophageal echocardiography

In transoesophageal echocardiography the transducer is fixed in the oesophagus and controlled from a site distant to the patient, which makes it ideal for the intensive care unit or operating theatre (Bjerke, 1992). Matsumoto, Oka, Strom, Frishman, Kadish, Becker, Frater and Sonnenblick (1980) demonstrated that an ultrasound transducer sited in the oesophagus offered a stable location for continuous cardiac

examination in patients undergoing cardiac surgery. These authors concluded that the technique offered a new approach to continuous monitoring of ventricular performance during anaesthesia and surgery. The technique is particularly suited to cardiothoracic procedures since the heart lies directly on the oesophagus and echocardiography is still possible when the chest is open and the anterior pericardium is exposed to air. The stability of the transducer in the oesophagus also permits continuous recording of the same area for monitoring. The oesophageal position ensures that the transducer does not interfere with surgery and precludes the need for aseptic precautions. The development of intra-operative echocardiography continued during the 1980s. Kremer, Cahalan, Beaupre, Schroder, Hanrath, heinrich, Ahnefield, Bleifield and Hamilton (1985) used the technique to monitor left ventricular filling and contractility in 400 patients undergoing general surgery. They concluded that transoesophageal echocardiography had three fundamental advantages over existing monitoring systems in that it was inherently safer than cardiac catheterisation and allowed both direct assessment of left ventricular filling and provided direct information on global and regional left ventricular wall motion.

Two-dimensional transoesophageal echocardiography is now used most frequently for assessment of segmental wall motion abnormalities for detection of regional ischaemia (Skarvan, 1993; Shively, 1992; Milchak and Plehn, 1991). As a result the technique is now recognised as an important adjunct to anaesthesia for cardiothoracic procedures (Skarvan, 1993; Shively, 1992; Thys, Hillel, Konstadt and Goldman, 1987). Colour flow mapping from oesophageal transducers has also been exploited for intraoperative evaluation of valve repair (Shah and Shapiro, 1991) and in the surgical management of congenital heart disease (Hsu, Santulli, Wong, Drinkwater, Laks and Williams, 1991). The technique also provides a very sensitive technique for detection of air embolus (Cucchiara, Nugent, Seward and Messick, 1984).

The slow uptake of cardiological technology into anaesthesic monitoring largely results from lack of cross-disciplinary training in echocardiographic techniques (Skarvan, 1993) and the large capital outlay required (Bjerke, 1992). In the few centres where the technology has been adopted the echocardiographic converts have been vocal in their appreciation (Bjerke, 1992).

Transoesophageal echocardiography for measuring haemodynamic effects of anaesthetic agents

Transoesophageal echocardiography can be used to assess the effects of anaesthetic agents on cardiac function (Cahalan, Lurz and Schiller, 1988). For example the technique has been used to evaluate the effect of thiopentone during induction of anaesthesia in humans (Coriat, Bruere, Benammar, Houissa, Letouzey and Viars, 1987) and to compare the haemodynamic effects of propofol with other induction agents (Heinrich and Wilder-Smith, 1991; Mulier, Wouters, Van Aken, Vermaut and Vendermeersch, 1991). Echocardiographic techniques have also been used to evaluate the cardiovascular effects of the volatile agents, isoflurane, enflurane and halothane in humans (Heinrich, Fontaine, Fosel, Spilker, Winter and Ahnefeld, 1986). However, despite being ideally suited for monitoring haemodynamic effects of anaesthetic drugs transoesophageal echocardiography is still relatively under-used in this field.

Transoesophageal echocardiography in veterinary species

The first reports of transoesophageal echocardiography in dogs appeared in 1978, when the technique was compared with the transthoracic route for evaluation of valve function in beagles (Dennis, Nealeigh, Pyle, Gilbert, Leee and Miller, 1978). The technique received little further attention, and it was widely held that the canine heart imaged poorly via the transoesophageal route (Vandenberg and Kerber, 1990). Bashein and Martin (1991) countered this view in a letter to the editor of Anesthesiology stating that excellent long axis views of the left ventricle could be obtained from dogs. These authors concluded their correspondence by encouraging the

more widespread use of transoesophageal echocardiography for haemodynamic monitoring in experimental animals. Recently biplane transoesophageal echocardiography has been used in dogs (Loyer and Thomas, 1995) and cats (Kienle, Thomas and Rishniw, 1995). In dogs the technique provides superior visualisation of heart base structures and offers advantages over transthoracic techniques in the diagnosis of subaortic stenosis, pulmonic stenosis and patent ductus arteriosus (Thomas, 1994). Thomas and coworkers also noted that Doppler examination of left ventricular outflow yielded high quality signals which resulted from better alignment of the ultrasound beam with aortic blood flow. There have been no reports on the use of transoesophageal echocardiography in horses.

ASSESSMENT OF CARDIAC FUNCTION

The heart's main function is to deliver oxygenated blood to meet the metabolic requirements of the tissues. As a result, measurement of cardiac output has become a time-honoured method of assessing cardiac performance (Braunwald, 1992). Whilst determination of cardiac output provides a useful insight into the pumping ability of the heart, it is critically dependent on preload and afterload (Braunwald, 1971). The output of the heart is an ejection-phase index of cardiac performance since it is measured after the aortic or pulmonary valves have opened. In the normal animal cardiac output is regulated more by the loading conditions of the heart than by the fundamental contractile activity of the myocardium (inotropy / contractility). Only when myocardial function becomes compromised, in heart failure, or by the influence of negative inotropes, does inotropy become the major determining factor of cardiac output (Braunwald, 1971). Thus measurement of cardiac output alone may not be the best indicator of myocardial function.

Cardiac contractility is dependent on the fundamental properties of cardiac muscle cells including the rate of cross-bridge formation and the rapidity with which

they are recycled (Braunwald, 1992). Enhancement of myocardial cell excitation-contraction coupling results in an increase in force development for a given initial fibre length (Sonnenblick, 1962a). Contractility has been defined as "the performance of the heart if it were freed from the constraints of afterload and preload i.e what the heart is capable of doing rather than what it actually does" (Milnor, 1990c). For any given level of contractility myocardial fibre shortening varies directly with preload (initial fibre length) and indirectly with afterload (Ross, 1983). The increased force generation caused by increasing initial fibre length is well known as the Frank-Starling mechanism. It arises because of a sarcomere length-dependent availability of calcium ions and more optimal contractile filament overlap which enhances the developed force during contraction (Milnor, 1990c). In the intact animal afterload is closely related to aortic impedance (Milnor, 1990a), which is defined as the sum of the external factors that oppose ventricular ejection (Milnor, 1990a). Aortic impedance is the ratio of pressure to flow in the aorta. It is determined by the physical properties of blood and the vasculature, including blood viscosity and density, aortic diameter and elasticity, and the reflected pressure and flow waves generated in the distal systemic arteries (Nichols and O'Rourke, 1990a). When aortic impedance is raised an increasing proportion of the heart muscle's contractile activity is used to generate tension and a corresponding smaller fraction to shorten myocardial fibres. In the extreme case if afterload exceeds the maximum force generating capacity of the ventricle, ejection ceases (Braunwald, 1992).

To measure contractility requires a distinction between changes in mechanical performance caused by the Frank-Starling mechanism and those which are independent of muscle length. To achieve this in practice involves obtaining a variable generated by cardiac contraction that is independent of initial fibre length (heart size) and that is not affected by changes in ventricular afterload (aortic impedance) (Van den Bos, Elzinga, Westerhof and Noble, 1973). There has been an unrelenting search for such indices

able to reflect contractility in the intact heart (Lambert, Nichols and Pepine, 1983). It has been suggested that the large number that have been described indicates that no single measure is completely satisfactory (Milnor, 1990a).

ISOVOLUMIC INDICES OF MYOCARDIAL CONTRACTILITY

Maximum rate of rise of intraventricular pressure ($LVdp/dt_{max}$)

The early search for indices of contractility focused upon the rate of rise of intraventricular pressure and peak developed pressure by the left ventricle (Milnor, 1990a). The theoretical basis for use of intraventricular pressure is derived from its relationship with ventricular wall force through ventricular dimensions (Hefner, Sheffield, Cobbs and Klip, 1962). Before the aortic valve opens the rate of change of ventricular pressure is closely related to the simultaneous rate of change of wall tension (Wallace, Skinner and Mitchell, 1963). Provided that the increased force caused by increased heart size is balanced by an increased chamber diameter it is theoretically possible that $LVdp/dt_{max}$ may be independent of changes in preload (Van den Bos, Elzinga, Westerhof and Noble, 1973). However it was soon demonstrated that the increased force caused by increased fibre length and the Frank-Starling mechanism dominated the reduction in wall tension by the Laplace effect (Wallace, Skinner and Mitchell, 1963). Since $LVdp/dt_{max}$ occurs before the aortic valve opens it has been generally accepted that the index, being isovolumic, should be independent of afterload (Braunwald, 1992; Milnor, 1990a). In fact increases in aortic diastolic pressure have been shown to influence $LVdp/dt_{max}$ independent of alterations in contractility or left ventricular end diastolic pressure in dogs (Wallace, Skinner and Mitchell, 1963) and humans (Borow, Neumann, Marcus, Sareli and Lang, 1992; Mason, 1969). Wildenthal, Mierzwiak and Mitchell (1969) concluded that $LVdp/dt_{max}$ cannot be used confidently to evaluate ventricular performance unless changes in aortic pressure and the time of aortic valve opening are considered. Maximum rate of rise of left ventricular

pressure is also sensitive to changes in heart rate, increasing with increasing frequency of stimulation (Wallace, Skinner and Mitchell, 1963; Gleason and Braunwald, 1962).

Despite these limitations the index is widely used in human medicine, since it shows sensitivity to agents known to produce acute changes in contractility (Braunwald, 1992; Milnor, 1990a). The index is relatively simple to obtain, requiring only a high fidelity intracardiac micromanometer and an analogue differentiator. The index has also been used in horses (Brown and Holmes, 1979a) and has been employed to assess the effects of therapeutic agents and anaesthetic agents (Muir, 1992b; Hillidge and Lees, 1976). Brown and Holmes (1979a) showed that the peak dp/dt reliably occurred before aortic valve opening in the left ventricle of horses. It is therefore justifiable to use $LVdp/dt_{max}$ for evaluation of left ventricular function in this species provided its dependence on preload, afterload and heart rate are considered. In the right ventricle $LVdp/dt_{max}$ occurred after the pulmonary valve had opened in 5/8 horses in the study by Brown and Holmes (1979a), therefore use of $LVdp/dt_{max}$ as an index of right ventricular contractility is ill-advised, as it is not invariably an isovolumic event in this species (Van den Bos, Elzinga, Westerhof and Noble, 1973). Hillidge and Lees (1976) demonstrated that general anaesthesia with either ether or halothane reduced $LVdp/dt_{max}$ from resting values in ponies.

Other pressure related indices

Time to attain $LVdp/dt_{max}$ was advocated as a measure of left ventricular contractility in humans after studies in open-chest dogs revealed that dp/dt_{max} was increased by stretch and contractility. However time to peak dp/dt was unaffected by stretching the ventricle and was decreased with infusions of epinephrine (Reeves and Hefner, 1963). This index has been used in humans (Mason, Sonnenblick, Ross, Covell and Braunwald, 1967) and horses (Brown and Holmes, 1979b), but it appears to have few advantages over $LVdp/dt_{max}$ since only when alterations in the two variables are inversely related do they reflect absolute changes in contractility (Mason, 1969).

Studies by Nejad, Klein, Mirsky and Lown (1971) demonstrated that the peak value of the second differential of intraventricular pressure was essentially devoid of afterload and preload dependence, but sensitive to infusions of isoprenaline. The index was evaluated in horses by Brown and Holmes (1979a) who found great variability between horses and between cardiac cycles in individual horses. They concluded that because of the wide beat to beat variation the index would have limited sensitivity. The index never gained widespread popularity in human medicine, although Lambert, Nichols and Pepine (1983) showed that the peak second differential of left ventricular pressure ranked above $LVdp/dt_{max}$ in their sensitivity and specificity evaluation of 24 individual indices of myocardial contractility in anaesthetised dogs.

Relationships between dp/dt and developed pressure

The problem of preload dependence was thought to be alleviated by relating dp/dt to the developed pressure, where developed pressure is the left ventricular pressure - the end-diastolic pressure (Milnor, 1990a). Use of the value of dp/dt at a developed pressure of 40 mmHg was used since this value invariably occurred during isovolumic systole in most clinical circumstances (Braunwald, 1992). The index is less sensitive than simple $LVdp/dt_{max}$, but is useful for monitoring changes in individuals (Mason, Braunwald, Covell, Sonnenblick and Ross, 1971). The index is said to be relatively insensitive to changes in afterload and to be only mildly affected by moderate changes in preload (Mahler, Ross, O'Rourke and Covell, 1975). A similar index using dp/dt at an intraventricular pressure of 30 mmHg in horses has been described by Brown and Holmes (1979a), but there have been no further reports of its use in this species.

Indices based on calculated contractile element force-velocity relationships

The extent and maximum velocity of shortening for each myocardial contraction depends upon the load imposed on the muscle; the inverse relationship between the

tension developed and the velocity of shortening is known as the force-velocity relation (Braunwald, Sonnenblick and Ross, 1992). When the load is maximum the muscle fails to shorten and develops maximal tension during isometric contraction, conversely when there is no load the muscle shortens at its maximum velocity. It is not possible to measure the velocity of shortening at zero load, however multiple assessments made at different loads allows the resultant force velocity curve to be extrapolated back to zero (Sonnenblick, 1962b). Theoretically the maximum velocity of shortening of the unloaded contractile elements (CEV_{max}) provides an index of contractility that is independent of preload and afterload. However there is controversy surrounding the determination of CEV_{max} in isolated muscle and this is compounded for the intact heart (Braunwald, 1992). In an intact heart it is difficult to impose changes in afterload or study purely isometric beats. However a technique for measuring a mathematical relative of CEV_{max}, V_{CE} has been described which is derived using only the isometric period of systole (Van den Bos, Elzinga, Westerhof and Noble, 1973). This involves plotting dp/dt divided by developed pressure against the developed pressure and then extrapolating the curve to zero pressure. This extrapolation is beyond the range of the data and the sigmoid shape of the curve makes the extrapolation difficult. Van den Bos, Elzinger, Westerhof and Noble (1973) suggested that use of developed pressure was only feasible in open-chest preparations when intrapleural pressure could be assumed to be zero. Otherwise great fluctuations in transmural pressure rendered division by intraventricular pressure meaningless. Effectively this rules out use of this index in closed chest subjects, although the index was evaluated by Brown and Holmes (1979a) in horses when transmural pressure was not measured. These authors experienced similar difficulties to Van den Bos, Elzinger, Westerhof and Noble (1973) in extrapolating a sigmoid curve back to zero. They also suggested that the index was dependent on left ventricular end-diastolic pressure. A study in humans which evaluated a number of isovolumic indexes in humans under different loading conditions and inotropy concluded that V_{CE} lacked sufficient stability during acute changes in loading

conditions to warrent its use in the quantitative assessment of acute changes in inotropic state (Quinones, Gaasch and Alexander, 1976).

Overview of indices derived from intraventricular pressure

Although the value of$LVdp/dt_{max}$ is limited by heart rate and preload and afterload dependence, the index has been shown to be useful in the assessment of acute changes in inotropic state in humans (Mason, 1969; Gleason and Braunwald, 1962). Van den Bos, Elzinger, Westerhof and Noble (1973) concluded that $LVdp/dt_{max}$ was the only pressure-derived index that was feasible in closed chest subjects because of difficulty in measuring pressure across the left ventricular wall. The more complex derived indices appear to confer no real advantage over the first differential of left ventricular pressure in humans (Mahler, Ross, O'Rourke and Covell, 1975) or horses (Brown and Holmes, 1979a). It is generally accepted that indices are not suitable for comparison of myocardial contractility between individuals, but are useful for detection of directional changes within an individual (Braunwald, 1992; Van den Bos, Elzinga, Westerhof and Noble, 1973; Mason, 1969). Changes in $LVdp/dt_{max}$ can only be attributed to increased inotropy when end-diastolic pressure, aortic diastolic pressure and heart rate remain unchanged (Mason, 1969; Wallace, Skinner and Mitchell, 1963).

EJECTION PHASE INDICES OF LEFT VENTRICULAR FUNCTION

Maximum acceleration of aortic blood flow (dv/dt_{max})

In 1964 Rushmer used the term "initial ventricular impulse" to describe the dynamic properties of left ventricular ejection. Impulse was defined as the product of force and time, and was manifested by the peak velocity imparted to the aortic blood (Rushmer, 1964). Rushmer showed that ventricular impulse was increased by exercise, sympathetic stimulation and after long diastolic intervals, but was decreased by premature ventricular contractions, exsanguination hypotension, acute coronary occlusion and general anaesthesia. Maximum force exerted by the ventricle on the

blood is proportional to its maximum acceleration according to Newton's second law of motion (Noble, Trenchard and Guz, 1966). Use of maximum acceleration is only valid provided that the whole column of blood moves from the ventricle in a single mass i.e. there is true bulk flow of blood in the aorta (Noble, 1965). Theoretically this is likely when pulsatile flow occurs in a tube, since when the diameter of the tube increases the liquid begins to move more like a solid mass. The lateral variations in velocity in the liquid occur closer and closer to the boundary of the tube so that the velocity profile across the tube is essentially flat (Nichols and O'Rourke, 1990b). A flat aortic blood velocity profile has been demonstrated using hot film anemometers in dogs (Falsetti, Caroll, Swope and Chen, 1977; Seed and Wood, 1971). It is therefore considered justifiable to apply the laws of mass acceleration to the movement of blood from the myocardium (Noble, 1965).

Of equal importance in the assumption that dv/dt_{max} is proportional to the total force exerted by the contracting myocardium is the stipulation that at the time dv/dt_{max} occurs, force is being expended by the heart to accelerate the column of blood and not to overcome resistance (Noble, 1965). Throughout ventricular ejection, force is expended not only to accelerate blood, but also to distend the arteries and force blood through the peripheral vessels (Spencer, Johnston and Denison, 1958). However in the early stages of ventricular ejection, at the time of dv/dt_{max}, the left ventriclular contraction achieves high peak blood velocity and momentum before much blood has left the ventricle, thus producing the rapid initial ventricular impulse described by Rushmer (1964). In fact when dv/dt_{max} occurs only 5% of the stroke volume has been ejected, implying that opposition to left ventricular contraction is inductive and contraction is directed to overcoming inertia at this time (Noble, Gabe, Trenchard and Guz, 1965). Rushmer had suggested that both peak acceleration (dv/dt_{max}) and rate of rise of intraventricular pressure reflected the magnitude of the impulse generated by the contracting left ventricle, but it was the experimental work of Noble (1965) that

established dv/dt_{max} for evaluation of left ventricular contractility. He developed an implantable electromagnetic flowmeter for conscious dogs and demonstrated in a series of studies that dv/dt_{max} was more sensitive than stroke volume and $LVdp/dt_{max}$ for detecting changes in left ventricular function after coronary artery occlusion and after intracoronary injection of isoprenaline or calcium (Noble, Trenchard and Guz, 1966).

The theoretical basis of the use of dv/dt_{max} has been reviewed by Van den Bos, Elzinger, Westerhof and Noble (1973), who suggested that the index would not be independent of preload unless the increase in force produced by the Frank Starling mechanism was counteracted by an increase in mass of blood to be ejected. The index cannot be independent of afterload, since in the most extreme instance dv/dt_{max} is zero during an isovolumic beat. In a more physiological range of aortic pressures it is possible that maximum aortic acceleration might not be influenced by small changes in afterload since they may be insufficient to alter the mass of blood to be ejected (Van den Bos, Elzinga, Westerhof and Noble, 1973). In the studies by Lambert, Nichols and Pepine (1983) dv/dt_{max} showed increased inotropic sensitivity and less afterload and preload dependence than $LVdp/dt_{max}$.

Maximum acceleration has been used for assessing ventricular performance in humans with coronary artery disease (Bennet, Else, Miller, Sutton, Miller and Noble, 1974), although it failed to differentiate patients with heart failure grouped according to conventional $LVdp/dt_{max}$ in a study by Kolettis, Jenkins and Webb-Peploe (1976). Until the development of Doppler echocardiography measurement of dv/dt_{max} required implantation of electromagnetic flowmeters, so the technique had limited applications outside the laboratory. With increasing availability of Doppler technology, reports of the use of dv/dt_{max} appeared in the medical literature. Sabbah, Khaja, Brymer, McFarland, Albert, Snyder, Goldstein and Stein (1986) found that the index could be used to classify the severity of left ventricular failure in human patients.

In humans dv/dt_{max} was inversely related to afterload (Harrison, Clifton, Berk and DeMaria, 1989) and directly related to preload (Bedotto, Eichhorn and Grayburn, 1989). This led some workers to conclude that, along with other ejection phase indices, dv/dt_{max} was unable to differentiate changes in contractility from changes in loading conditions (Borow, Neumann, Marcus, Sareli and Lang, 1992). However other studies indicated that moderate increases in preload which increased stroke volume caused minimal changes to $dv/dt_{max,}$ compared to the very large increases in the variable that occurred after inotropes were administered (Bennett, Barclay, Davis, Mannering and Mehte, 1984). Similarly in anaesthetised dogs the index was more sensitive to changes in inotropy than preload (Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986) and afterload (Wallmeyer, Wann, Sagar, Czakanski, Kalbfleish and Klopfenstein, 1988). Maximum acceleration measured from transthoracic Doppler echocardiography in standing horses was sensitive to changes in inotropy caused by administration of inotropic and sedative agents (Young, Long, Darke and Jones, 1993).

Maximum aortic acceleration clearly provides a useful index of myocardial performance, but it is subject to the same limitations as $LVdp/dt_{max}$ imposed upon it by dependence upon loading conditions (Bedotto, Eichhorn and Grayburn, 1989; Gardin, 1989). This led Wallmeyer, Wann, Segar, Kalbfleish, Kloppfenstien (1986) to conclude that aortic acceleration was as sensitive as conventional indices to alterations in myocardial contractility, but that it was no better at defining inotropic state in absolute terms. In agreement with the conclusions of Van den Bos, Elzinger, Westerhof and Noble (1973) they also suggested that dv/dt_{max} was of value in detecting changes in cardiac function within an individual but not for comparing cardiac performance between individuals

Although Doppler echocardiography provides a method for measurement of aortic blood flow velocity, the maximum acceleration, as assessed from the velocity

spectra (See General methods: page 49) is not representative of the true maximum acceleration obtained by differentiation of the signal from a high fidelity flowmeter (Bedotto, Eichhorn and Grayburn, 1989). To obtain true maximum aortic acceleration requires special instrumentation capable of differentiating the early up-stroke portion of the flow envelope; most commercially available ultrasound systems are not equipped with this facility. The mean acceleration can be obtained by measuring from zero to peak velocity on the velocity spectra (Bedotto, Eichhorn and Grayburn, 1989). Although errors in determination of the time taken to attain peak velocity are believed to contribute to the high intra and inter-observer variability detected for this index (Gardin, Burn, Childs and Henry, 1984). It has also been suggested that mean acceleration is less sensitive to changes in inotropy than peak acceleration (Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986). Alternatively an estimate of maximum acceleration can be obtained by measuring the steepest gradient on the early up-stroke of the velocity spectra (See General methods: Figure 5). This was the technique adopted for these studies, however, it is accepted that the value obtained does not represent the true maximum acceleration as described by Nobel (1965).

Peak aortic velocity (V_{max})

The maximum velocity attained by the aortic blood flow was believed to reflect the magnitude of the initial ventricular impulse (Rushmer, 1964). Lambert, Nichols and Pepine (1983) showed that in anaesthetised dogs the index was similar in inotropic sensitivity and load dependence to $LVdp/dt_{max}$ and dv/dt_{max}. The relative sensitivities of V_{max} and dv/dt_{max} in reflecting changes in ventricular performance are unclear. Some workers considered that dv/dt_{max} was the most sensitive indicator (Sabbah, Khaja, Brymer, McFarland, Albert, Snyder, Goldstein and Stein, 1986; Noble, 1965), whilst others favoured use of V_{max} (Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986; Gardin, Iseri, Elkayam, Tobis, Childs, Burn and Henry, 1983). In common with dv/dt_{max}, V_{max} is inversely dependent on afterload (Bedotto, Eichhorn and

Grayburn, 1989; Wallmeyer, Wann, Sagar, Czakanski, Kalbfleish and Klopfenstein, 1988; Elkayam, Gardin, Berkley, Hughes and Henry, 1983) and directly related to preload (Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986). As a result the ability of either index to reflect absolute changes in contractility is similarly limited (Bedotto, Eichhorn and Grayburn, 1989), it seems likely therefore that both indices are of equal merit.

Velocity Time Interval (VTI)

The velocity time integral is derived by calculating the area under the median velocity of the aortic velocity flow envelope. The index is closely related to stroke volume (Mehte and Bennet, 1986; Haites, McLennan, Mowat and Rawles, 1984), and can be multiplied by vessel area and heart rate to provide an estimate of cardiac output (Hatle and Angelsen, 1985a). The limitations of stroke volume and cardiac output in assessing global ventricular performance have been discussed previously (See page 22). Velocity time integral, like stroke volume, is directly dependent on preload and is inversely influenced by afterload (Bedotto, Eichhorn and Grayburn, 1989).

The systolic time intervals

The systolic time intervals of the left ventricle (pre-ejection period and ejection time) have been used in the evaluation of ventricular performance (Lewis, Rittgers, Forester and Boudoulas, 1977; Filner and Karliner, 1976; Weissler and Schoenfeld, 1970; Weissler, Harris and Schoenfeld, 1969). The left ventricular ejection time (ET) is the interval during which the contracting ventricle exerts sufficient pressure to maintain the aortic valve open (Weissler and Schoenfeld, 1970). Ejection time is therefore dependent not only on both the duration of active contraction and the amount of myocardial tension developed, but also on the rate that pressure is elevated to aortic diastolic pressure during the pre-ejection period (PEP) (Lewis, Rittgers, Forester and Boudoulas, 1977). In general inotropic stimulation shortens PEP, whilst it is increased by myocardial failure (Weissler, Harris and Schoenfeld, 1968). In contrast both

negative and positive inotropy tend to decrease ET. An increase in inotropy increases the rate of development of pressure and the extent of fibre shortening, which have opposing effects on ET. Generally the increased velocity of shortening is predominant and overrides the effect of increased stroke volume thus shortening ejection time (Lewis, Rittgers, Forester and Boudoulas, 1977). Because of the opposite changes in PEP compared to ET, use of the ratio PEP/ET has become increasingly used in human cardiology, since it may identify left ventricular dysfunction when both ET and PEP are within normal limits. Ejection time is highly influenced by heart rate (Weissler, Peeler and Roahll, 1961) and various correction factors have been applied to normalise ET for heart rate in humans (Weissler, Harris and White, 1963). Pre-ejection period appears to be less influenced by heart rate than ET (Spodick, Doi, Bishop and Hashimoto, 1984), but both indices are affected by ventricular loading conditions in humans (Spodick, Doi, Bishop and Hashimoto, 1984) and dogs (Talley, Meyer and McNay, 1971). Pre-ejection period and ET, measured by transthoracic Doppler echocardiography, changed in response to inotropic and sedative agents in conscious horses (Young, Long, Darke and Jones, 1993).

OVERVIEW OF THE INDICES OF MYOCARDIAL CONTRACTILITY

From the preceding discussion it is clear that neither indices derived from cardiac catheterisation, nor those from Doppler echocardiography are capable of providing an absolute measure of ventricular contractility. Whichever index is selected it is necessary to consider both the loading conditions of the heart and the heart rate before any conclusions can be drawn regarding the effects of any intervention in an individual. However the problem of measuring muscle mechanics in the intact heart has been recognised for many years (Braunwald, 1992; Milnor, 1990a; Van den Bos, Elzinga, Westerhof and Noble, 1973). A rational approach to the problem involves using as complete a collection of data on flow, pressure and cardiac performance as

possible, not a single number (Milnor, 1990a). As was pointed out by Binks and Jewell (1972) "if an index is really simple, it's informational content is unlikely to be adequate".

Multiple indices of myocardial performance are provided by Doppler echocardiography. This confers great advantages for elucidation of ventricular performance, therefore if the variables are considered as an integrated group they should provide a more complete means of assessment of heart function.

AIMS OF THESE STUDIES

1. To investigate the feasibility of using transoesophageal Doppler echocardiography for noninvasive haemodynamic monitoring in anaesthetised horses.

2. To establish the repeatability of the indices of left ventricular performance derived from transoesophageal Doppler echocardiography in anaesthetised horses, and to compare their repeatability with that of maximum rate of rise of left ventricular pressure, systemic arterial blood pressure and heart rate obtained simultaneously from the same animals.

3. To compare cardiac output estimations obtained by transoesophageal Doppler echocardiography with those obtained by thermodilution in anaesthetised horses.

4. To assess the sensitivity of transoesophageal Doppler derived indices of left ventricular function in horses anaesthetised with halothane by changing afterload and inotropy with "sympathomimetic" (cardioactive) drugs.

Chapter 2:

GENERAL METHODS

HORSES

Studies were performed on eight Thoroughbred horses (four mares and four geldings), aged between three and six years (Appendix 1). The horses were bred for flat or National Hunt racing and were registered with the British Thoroughbred stud book authority[1] . Their mean weights over the duration of the studies ranged from 490 kg to 615 kg. At the time of purchase the horses were subject to a standard clinical examination and were judged healthy and fit for normal work. Cardiac auscultation was performed on each horse before its acceptance, and valvular dysfunction was not detected in seven horses. A grade 2, late systolic murmur characteristic of tricuspid regurgitation was detected in horse 8. Since mild tricuspid regurgitation is a common finding in horses bred for National Hunt racing (Patteson and Cripps, 1993) and the studies to be performed would involve the left ventricle only, the horse was included in the group. The studies took place between October 1992 and June, 1994 for mares and between December, 1993 and September, 1994, for geldings. Incoming horses were immunised against tetanus using a commercially available tetanus toxoid (duvaxyn T[2]). Two doses, separated by one month, were administered by intramuscular injection.

Animal Husbandry

The horses were housed indoors, in loose boxes, throughout the studies. Daily grazing was permitted in summer. Horses 1, 3 and 8 were broken to saddle and had been racing before they were purchased. The remaining animals (horses 2, 4, 5, 6, 7) were unbroken at the time of purchase and were broken to saddle before the studies began.

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[1] Wetherbys, Sanders Road, Wellinborough, Northamptonshire, UK.
[2] duvaxyn T, Solvay-Duphar Veterinary, Solvay House, Flanders Road, Hedge End Southampton, UK

All horses were kept in moderate work, and each performed ridden or lungeing exercise at a level appropriate to it's age and stage of training. This amounted to approximately 45 minutes of ridden or lungeing work at least 5 times per week. On days when the horses were not worked they were loose schooled in pairs for 20 minutes in a covered indoor arena.

Horses were exercised normally the day before each procedure and resumed normal work within 48 hours.

Surgical Preparation

The right carotid artery of each horse was raised to a subcutaneous position under general anaesthesia. Prophylactic antibiosis was provided by intramuscular administration of 6.0 $mg.kg^{-1}$ procaine penicillin and 10 $mg.kg^{-1}$ dihydrostreptomycin (Depomycin[3]). Drug administration was continued on a daily basis for a further 5 days after the day of surgery. Horses were premedicated with 100 $\mu g.kg^{-1}$ romifidine (Sedivet[4]) administered by intravenous injection. Five minutes later general anaesthesia was induced with an intravenous bolus of 2.2 $mg.kg^{-1}$ ketamine (Vetalar[5]). Anaesthesia was maintained by halothane (Halothane-M&B[6]) delivered in oxygen. The horses breathed spontaneously from a large animal circle system[7].

The skin was incised just dorsal to the jugular vein, at the level of the 4th cervical vertebra. Elevation of the skin prevented damage to the jugular vein when the incision was made. The cutaneous muscle and omohyoid muscles were split to gain access to the carotid artery and 7 cm length of the artery was then dissected free. It was then anchored in a subcutaneous position by raising it above the omohyoid muscle and suturing the muscle below it. The subcutaneous layer was closed with sutures and the

[3] Depomycin, Mycofarm UK Ltd, Science Park, Milton Road, Cambridge, UK.
[4] Sedivet, Boehringer Ingelheim(Vetmedica), Ellesfield Avenue, Bracknell, Herts, England, UK.
[5] Vetalar, Parke Davis Company (Veterinary), Usk Road, Pontypool, Gwent, Wales, UK.
[6] Halothane-M&B, Rhone Merieux Limited, Spire Green Centre, Harlow, Essex, England, UK.
[7] Large Animal Anesthesia Control Centre, North American Drager, 148, Quarry Road, Telford, PA. USA.

overlying skin opposed with surgical staples, these staples were removed 7-10 days later, then at least eight weeks were allowed to elapse for resolution of the surgical wound, before catheterisation was attempted.

Small subcutaneous suture abscesses developed in Horse 1, two weeks after surgery. Bacterial culture revealed a heavy growth of *Staphylococcus aureus* which was completely resistant to penicillin, but sensitive to trimethoprim and tetracycline. The problem resolved rapidly when affected sutures were removed and 30 $mg.kg^{-1}$ trimethoprim and sulphadiazine (Uniprim for Horses[8]) was administered daily in feed for 5 days.

Complete occlusion of the raised right carotid artery occurred at the site of relocation in Horse 7. The surgical wound had healed without problems in this animal and the relocation surgery was uncomplicated. However at the first cardiac catheterisation attempt, 3 months after the original surgery, palpation of the raised vessel revealed total absence of an arterial pulse. Feeling down the length of the artery after it had been surgically exposed confirmed that the vessel was occluded as far as the thoracic inlet. There was no evidence of infection nor abnormalities of the exterior of the vessel which could explain why a thrombus had formed. Since there was no blood flowing within the lumen, the subcutaneous tissues and skin incision were closed, without returning the occluded vessel to it's original site. Surgical relocation of the contra-lateral carotid artery was considered to constitute too great a risk to the horse, and was not performed. Horse 7 was not used in any studies involving left heart catheterisation.

[8] Uniprim for Horses, Cheminex Laboratories Ltd, 7, Godwin Road, Earlstrees Industrial Estate, Corby, Northants, UK.

ANAESTHETIC PROTOCOL FOR EXPERIMENTAL STUDIES

Preoperative Preparation

Food, but not water, was withheld from the horses from 20.00 hr of the day preceding the study. The skin overlying the left jugular vein was anaesthetised by surface application of Emla cream[9], followed by subcutaneous deposition of 2% lignocaine[10]. A 13 gauge over-the-needle catheter[11] was placed in the jugular vein through the desensitised skin.

Induction of General Anaesthesia

In a padded induction area 100 $\mu g.kg^{-1}$ romifidine (Sedivet[12]) were administered by intravenous injection through the pre-placed jugular catheter. Anaesthesia was induced by intravenous administration of 2.2 $mg.kg^{-1}$ ketamine (Vetalar[13]). The trachea was intubated with a 25 or 30 mm cuffed endotracheal tube which was adapted to allow collection of gas from its distal end.

Maintenance of General Anaesthesia

Anaesthesia was maintained by halothane (Halothane-M&B[14]), delivered from an out of circuit precision vaporiser (Vapor 19[15]), initially breathing was spontaneous from a large animal circle system. Once an adequate depth of anaesthesia was obtained the horse was transferred to a padded operating table and ventilation was controlled using intermittent positive pressure[16]. Initially ventilation rate and tidal volume were set at 10 breaths per minute and 7 litres respectively. A commercial blood gas analyser[17]

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[9] Emla Cream, Astra Pharmaceuticals Ltd, Kings Langley, UK.
[10] Xylocaine 2%, Astra Pharmaceuticals Ltd, Kings Langley, UK.
[11] Intaflon, Vygon Ltd, Cirencester, UK.
[12] Sedivet, Boehringer Ingelheim(Vetmedica), Ellesfield Avenue, Bracknell, Herts, England, UK.
[13] Vetalar, Parke Davis Company (Veterinary), Usk Road, Pontypool, Gwent, Wales, UK.
[14] Halothane-M&B, Rhone Merieux Limited, Spire Green Centre, Harlow, Essex, England, UK.
[15] Drage-Vapor 19.1, Dragerwerk, Aktiengesellschaft, Postfach 13 39, Moisinger Allee 53 55, D-2400, Lubeck, Der Bundesrepublik, Deutschland.
[16] Large Animal Anesthesia Control Centre, North American Drager, 148, Quarry Road, Telford, PA. USA.
[17] 283 pH - blood gas analyzer, Ciba-Corning Limited, Colchester Road, Halstead, Essex, UK.

was used to monitor arterial partial pressure of CO_2 ($PaCO_2$). Samples of arterial blood were withdrawn into heparinised syringes through a 20 gauge (1 mm external diameter) teflon catheter[18] placed in the right great metatarsal artery. The maximum interval between samples was 20 minutes and the blood was always analysed immediately after withdrawal, the value of $PaCO_2$ obtained was then corrected for the horse's body temperature. Minor adjustments of the ventilator controls were used to maintain arterial partial pressure of CO_2 ($PaCO_2$) between 35 and 45 mmHg. Halothane concentration was measured from end-expired gas sampled from the end of the endotracheal tube, using a calibrated anaesthetic gas monitor[19]. The vaporiser was adjusted throughout the procedure to maintain an end-tidal halothane concentration of 0.9%. If the anaesthetist noticed a 0.01% change in end tidal halothane concentration the vaporiser was adjusted accordingly. A base-apex electrocardiogram was continuously displayed on an oscilloscope[20] (See page 47 for lead configuration).

A minimum of three people was required for all studies. An anaesthetist (R.E. Clutton) supervised the well being of the horse and maintained end-tidal halothane and $PaCO_2$ at target levels. Cardiac catheterisation (see page 53) was performed by a second operator (K.J. Blissitt) assisted by a theatre nurse. The second operator was also responsible for catheter positioning and pressure data acquisition. The third operator (L.E.Young) positioned the transoesophageal echocardiography probe (see page 47), performed all echocardiographic studies and provided 2-D echocardiographic guidance for positioning micromanometers (see page 53).

[18] Venflon 2, Viggo Spectramed, Faraday Road, Swindon, Wiltshire, UK.
[19] Servo Gas Monitor 120, Siemens plc, 26- 28 Napier Court,Wardpark North, Cumberauld, UK.
[20] Datascope 500, Datascope Medical Company Ltd, Cambridge Science Park, Milton road, Cambridge,UK.

ECHOCARDIOGRAPHY

Transoesophageal Probe Design

A transoesophageal probe, suitable for use in horses, was developed by Vingmed Sound[21] in association with the Royal (Dick) School of Veterinary Studies. The probe was a high frequency annular phased array transducer designed according to the methods of Angelsen, Hoem, Dorum, Chapman, Grube, Gerckens, Visser and Vanndenbogaerde (1989). The ultrasound images were obtained from a 3.0 MHz transducer mounted at the end of a 160 cm human colonoscope (Figure 1). To avoid risk of thermal injury to the oesophagus when the probe was used for extended periods (Savino and Weiss, 1990), it was fitted with an integral thermistor and its internal temperature was displayed in the top left quadrant of the ultrasound monitor (Figure 2).

The first equine transoesophageal transducer was similar to a standard human transoesophageal probe, the distal end being manoeuvrable for 15 cm, by endoscopic controls. In human cardiology this manoeuvrability of the end of the probe is important as it allows acquisition of the multiple standard transoesophageal images (Fisher, Stahl, Budd and Goldman, 1991). However in horses during early studies, advancing the flexible probe against the resistance of the pharynx resulted in it bending, and in one case complete retroflexion of the distal end occurred. The 'U' bend produced was then unwittingly advanced through the pharynx into the oesophagus (Figure 3), once in the oesophagus the bend could not be straightened using the endoscopic controls. When the probe was withdrawn through the nose and the U bend approached the pharynx, it stimulated violent coughing and became wedged in this position. This rare complication of transoesophageal echocardiography has been reported only once in the medical literature (Kronzon, 1992). In human medicine if a gastroscope becomes retroflexed, it can be advanced into the stomach, where it can be easily straightened

[21] Vingmed Sound, Horten, Norway.

(Weyman, 1994a). Because of the relative lengths of the equine oesophagus and the transoesophageal echocardiography probe this option was not available. Instead it was necessary to insert a stomach tube into the horse's oesophagus through the contra-lateral nostril to the probe. The end of the stomach tube was then used to wedge the echocardiography probe tip. With the stomach tube fixed, the body of the probe was pulled backwards at the nostril. This technique successfully straightened the probe and the horse recovered uneventfully, but the probe was irreversibly damaged.

Subsequent studies with a new probe showed that suitable transoesophageal images could be obtained in horses with the endoscopic controls in the locked position. To minimise the risk of damage to the probe, it's distal end was stiffened using heat shrink sleeving (Figure 1). To facilitate insertion by lubrication of the oesophagus and to ensure good echocardiographic contact, lubricating fluid was delivered to the end of the probe through a length of vinyl tubing[22] affixed to the body of the colonoscope by adhesive tape[23]. Before insertion the tubing was pre-filled with lubricating fluid[24] and further fluid was instilled as the probe was advanced down the oesophagus (see page 47).

Vingmed CFM 700

All Doppler echocardiographic studies were performed using a Vingmed CFM 700[25] ultrasound system, with the 3.0 MHz transoesophageal probe. A 2.25 MHz transthoracic probe was used to derive aortic diameters (Chapter 4) and to assist in positioning intracardiac catheters (see page 53). The ultrasound system could perform 2-dimensional and M-mode, colour flow mapping, and spectral Doppler echocardiography. The spectral Doppler studies could be made using either high pulse repetition frequency (HPRF) or continuous wave (CW) insonation modes.

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[22] 800/101/250/800, Portex, Arterial Medical, Arterial House, 313 Chase Road, South Gate, London, UK.
[23] Sleek, Smith and Nephew Medical Limited, Hull, UK.
[24] Vet-Lubigel, Millpledge, Whinley's Estate, Church Lane, Clarborough, Retford, Herts, UK.
[25] Vingmed CFM 700, Diasonics, Sonotron, Bedford, UK.

Two Dimensional Imaging

The maximum depth for 2-D and M-mode imaging was 24 cm. The frame update rate varied between 19 and 55 frames per second, dependent upon the sector angle selected and the imaging depth. For most transoesophageal 2-D echocardiography the sector angle was 70° and the depth 20 cm, this resulted in a frame update rate of 22 s^{-1}. For transthoracic echocardiography an angle of 90° and depth of 24 cm resulted in an update rate of 19 s^{-1}. The frame update rate was continuously recorded by a digital indicator shown at the bottom right of the image sector, it was also displayed as the lower trace at the bottom of the ultrasound screen below the electrocardiogram (Figure 2).

The values for signal amplification (gain), and the threshold level for rejection of low amplitude signals (reject) were adjusted to give good definition of intracardiac structures. The temporal averaging facility of the echocardiogram was not used. Amplification was adjustable at five depth levels. For transoesophageal studies the amplification (gain) was minimal up to an imaging depth of 7 cm, then it was gradually increased to a maximum beyond 15 cm. The relationship between signal amplitude and intensity of the grey scale displayed could also be adjusted (compression). In these studies compression was set to give high contrast between cardiac structures and resulted in a black and white image with limited grey scale. Controls were pre-set for initial use of the transoesophageal probe, but were individually varied to obtain the best images in individual horses: Minimal adjustment of the gain was generally all that was required to optimise images in individual horses.

Transthoracic 2-D echocardiography was performed using the methods described by Long, Bonagura and Darke (1992).

Colour Flow mapping

The Vingmed CFM 700 initially produces a 2-D image and then superimposes the colour flow information. The colour image is constructed by designating different flow velocities towards the transducer at each of the multiple sampling sites in shades of red and flow velocities away from the transducer in shades of blue. Increasing mean velocities in either direction are encoded by lighter shades of red or blue. Variance / turbulence are depicted by adding increasing intensities of green to the velocity map.

At 20 cm, the maximum depth for colour flow mapping, the Nyquist limit was 0.6 $m.s^{-1}$. Thus when mean blood flow velocity exceeded 0.6 $m.s^{-1}$ aliasing of the colour flow signal occurred (see page 14).

The angle of the colour flow sector was kept between 35 and 45° in transoesophageal studies. Sector angle inversely influences the frame update rate of the colour flow and 2-D image. The annular phased array transducer in the transoesophageal echocardiography probe is mechanically steered through the sector angle to construct the ultrasound image (Weyman, 1994b). This imposes a finite rotational velocity on the transducer which also limits frame update rate. The rotational velocity can be modified by the 'quality' setting on the echocardiogram, which influences the number of ultrasound pulses per image beam. Whilst more detailed velocity information is generated by increasing the number of insonating pulses, the rotational velocity of the transducer is reduced, thus reducing the frame rate. A high frame rate is required when colour flow mapping is being used to detect abnormal short-lived regurgitant flow signals at fast heart rates. In the present transoesophageal studies the technique was used to aid placement of the spectral Doppler sample volume and not for detection of abnormal blood flow, thus frame update rate was of lesser importance. High quality images were therefore used at the expense of a lower frame update rate which varied between 9 and 12 frames s^{-1}. Since the system was being used to evaluate aortic blood flow velocity, not high velocity regurgitant flow, the velocity

reject value was fixed at a low value (0.31 $m.s^{-1}$). The amplification (gain) of the colour signal was set at one level below the setting which produced colour artefacts within the sector (Long, 1993).

Spectral Doppler echocardiography

Spectral Doppler studies were conducted using the transducer in high pulse repetition frequency (HPRF) mode, with ultrasound emitted at a frequency of 2.5 MHz. As for colour flow mapping studies low intensity velocity signals could be rejected (reject) and all other signals could be amplified by a user specified control (gain). These controls were set to ensure that the waveforms were clearly visible with minimal artefacts. A low velocity filter was also available, which allowed low velocity, high intensity signals, such as those emanating from slowly moving intracardiac structures, to be filtered from the display. During spectral Doppler studies the low velocity filter was set at 0.1 $m.s^{-1}$. Sample volume length was fixed at 2.5 mm. The sample volume was always positioned using the colour flow image to assess the area of fastest flowing blood. Once spectral studies commenced, the colour flow Doppler image was frozen, allowing the transducer to be dedicated to the acquisition of Doppler information (Long, Bonagura and Darke, 1995).

The Vingmed system uses fast Fourier transform spectral analysis to provide quantitative velocity determination. The frequencies of velocities occurring within the sample volume are recorded using a grey scale display. The brightest white line in any velocity envelope represents the modal velocity within the sample volume. The maximum magnitude and phase of the velocities recorded could be modified by moving the zero baseline of the spectral display. The maximum positive velocity that could be registered using a single sample volume in HPRF mode was 1.5 $m.s^{-1}$. By adding additional sample volumes, higher velocities could be recorded, but range ambiguity was introduced (see page 14). For most transoesophageal studies in anaesthetised horses aortic blood flow velocity was less than 1.5 $m.s^{-1}$, so adjustment of the scale

was unnecessary. The horizontal sweep time was also adjustable but was pre-set at 4 s for all Doppler studies. This sweep speed allowed at least one complete cardiac cycle to be included on the ultrasound screen. Accurate alignment with aortic blood flow was assumed from the clarity of the audible signal and when a complete velocity envelope containing minimal spectral dispersion was obtained.

Data Recording by the Vingmed CFM 700

Echocardiographic studies were recorded on VHS video tape by a Panasonic AG 6200 video recorder. Still photographs were taken using a freeze frame video recorder[26]. A base apex ECG was recorded during all studies and was displayed with the ultrasound data at the bottom of the ultrasound monitor (Figure 2). Pre-gelled silver-silver chloride adhesive electrodes[27] were used to obtain the base apex ECG, one recording electrode being fixed to the right hemithorax at the cardiac apex, a second one in the right jugular furrow half way up the neck, and an earth electrode high on the right thoracic wall.

Transoesophageal Probe Insertion

Within 15 minutes of induction of anaesthesia, with the horses in lateral recumbency, the transoesophageal probe was inserted into the uppermost nostril and advanced through the ventral nasal meatus into the pharynx. Once the probe reached the pharynx, the endotracheal tube was removed. One operator then placed a hand into the pharynx through the horse's mouth, which was held open using a Varnell's gag. From this position the end of the probe could be guided into the oesophagus and advanced at the nares by a second operator. The endotracheal tube was then reintroduced and it's cuff inflated. As soon as the airway was secure, 60 mls of lubricating fluid was introduced through the lubrication tubing. The probe was then advanced down the oesophagus until the endoscopic controls reached the nostrils.

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[26] Polaroid UK Limited, Ashley Road, St Albans, Herts,UK.
[27] F60, Skintact ECG pads, HA West Ltd, 41, Watson Crescent, Edinburgh, UK.

Blind introduction of the transoesophageal probe into the oesophagus was abandoned after inadvertent transtracheal ultrasonography was performed in 3/8 horses during pilot studies. The probe entered the larynx despite the anaesthetised horse swallowing and the presence of a 25 or 30 mm endotracheal tube in it's trachea. The images obtained in these horses were indistinguishable from those obtained from the oesophagus. In retrospect difficulty advancing the probe unless the endotracheal tube cuff was first deflated and constant leakage of anaesthetic gases were signs of probe malpositioning, that went unrecognised at the time of the study. Affected horses then experienced high body temperatures, lethargy and coughing for 3 - 5 days after the procedure. Endoscopy of affected animals revealed inflamed tracheal mocosae and the presence of food material in the airway. In the next batch of studies when the first horse swallowed the probe, the endotracheal tube was removed and its position was checked by introducing a hand through the horse's mouth and palpating the probe in the pharynx; it could clearly be felt entering the larynx. Inadvertent transtracheal placement of a transoesophageal echocardiography probe has been reported in a 74 year old human patient with neurological deficits (Fagan, Weiss, Castello and Labovitz, 1991); this individual also suffered inhalational pneumonia after the procedure. The same workers then examined transtracheal echocardiography in an anaesthetised dog, and observed that the image quality obtained was "virtually indistinguishable from that obtained by the transoesophageal approach". Whilst inadvertent tracheal intubation is a rare complication of human transoesophageal echocardiography, it occurred commonly when oesophageal echocardiography was performed in anaesthetised horses. Since it is feasible to advance the probe by hand into the oesophagus of an adult horse, the introduction procedure was modified. Interestingly tracheal introduction had not occurred previously when the anaesthetised horses swallowed the original probe which had a flexible end.

The transoesophageal ultrasound probe was positioned, by slowly withdrawing it, until a reference view of the aorta, the left ventricular outflow tract, and the pulmonary artery (Figure 4) was obtained. The probe occasionally had to be rotated to bring this image into view.

Echocardiographic data measurement

Data from echocardiographic studies were measured by a single observer (L. Young) from the video tape. Software within the CFM 700 provides two electronic calipers and a series of automated measurement menus. During video playback the calipers are calibrated for the ultrasound image by entering a digital calibration code (Figure 2). The calipers have been shown to measure velocity with an accuracy of 0.01 $m.s^{-1}$, time with an accuracy of 0.01 s and distance with an accuracy of 0.01 cm (Vingmed operating manual[28]). In spectral Doppler mode the caliper can be guided to any point on the display, using a tracker ball, and the integral software determines the velocity represented by the vertical height of the caliper above the zero baseline. Use of two calipers allows the difference in velocity and time between two points on the display to be determined.

In these studies to determine maximum aortic velocity (V_{max}), one caliper was positioned at the peak of a single aortic velocity spectrum (Figure 5). To determine maximum aortic acceleration (dv/dt_{max}) one caliper was positioned on the baseline at the start of ejection, and the line adjoining it to the second caliper was placed parallel to the maximum upstroke of the velocity spectra and positioned at the vertical level of the peak velocity. Pre-ejection period (PEP) was calculated from the horizontal distance between one caliper placed at the start of the 'Q' wave of the ECG and the other positioned at the onset of aortic flow. Ejection time (ET) was measured similarly, but the first caliper was transferred to the point on the baseline when aortic flow ceased. The area under the Doppler spectrum (velocity time integral, VTI) was measured by manually tracing

[28] Vingmed CFM 700: Operating Manual, Vingmed Sound, co. Sonotron Ltd, Bedford, England, UK.

the brightest white line, or modal value, of the velocity envelope using the tracker ball. The software within the spectral Doppler menu then measured the area below the trace to the nearest 0.01 cm.

Anatomic measurements from 2-D images were made using a separate measurement menu. When the anatomical structure was aligned perpendicular to the ultrasound beam the first caliper was placed on the endocardial surface closest to the transducer (leading edge) and the second caliper was placed on the leading endocardial edge of the distant wall. Although use of this technique results in a measurement which incorporates the thickness of one wall, in vivo studies have shown it is preferable, because the first echo from the surface closest to the transducer is easiest to identify and measure accurately (Wyatt, Haendchen, Meerbaum and Corday, 1983). When tissue interfaces are aligned parallel to the ultrasound beam, considerable lateral broadening of the echo always occurs (Feigenbaum, 1993). According to the studies by Wyatt, Haendchen, Meerbaum and Corday (1983) errors in width measurement in these circumstances are minimised when measurement is made from the middle of each band of echoes corresponding to the anatomical boundaries.

INTRACARDIAC AND INTRA-ARTERIAL PRESSURE MEASUREMENT

Micromanometers

Left ventricular and aortic pressure measurements were made using 2 strain gauge transducers[29] mounted on a 150 cm long woven Dacron catheter with a 2.64 mm outside diameter (size 8F). One manometer was sited at the distal end and one 12 cm more proximal. Sensitivity of the strain gauge transducers was 5 $\mu V.V^{-1}.mmHg^{-1}$ and their frequency response exceeded 12 kHz. The bridge excitation voltage from each manometer was monitored via a high gain amplifier[30]. The output from each high gain

[29]Gaeltec Ltd, Dunvegan, Isle of Skye, Scotland, UK.
[30]Series 5000, No 5248. Lectromed Ltd, Unit 26, The Business Centre, Avenue One, Letchworth Garden City, Hertfordshire, England, UK.

amplifier was recorded simultaneously by one channel of a four channel chart recorder[31] and a data acquisition system on a Macintosh IIvi microcomputer[32].

Data acquisition using the Macintosh IIvi

The analogue outputs from the micromanometers were connected to channels 1 and 2 of a 16-bit analogue to digital converter[33], which had 8 differential input channels. The connections between the input/output board and the micromanometers were standardised in all studies (Table 1)

Table 1: Standardised connections between micromanometers and A-D input channels.

Location	Channel
Left Ventricle	1
Aorta	2

The Macintosh IIvi was upgraded by addition of a maths coprocessor, and its random access memory (RAM) was increased from 5 to 8 MB. Calibration of micromanometers, data acquisition and analysis were performed using a series of programmes written using Labview 2.2.1 software[34]. During data acquisition, each channel was scanned alternately at a frequency of 50 HZ

Labview 2.2.1.

Labview 2.2.1 has the power of traditional programming languages, but the lines of code and syntax are replaced by graphical objects in a 'windows' environment.

[31]Multitrace 4, Lectromed Ltd, Unit 26, The Business Centre, Avenue One, Letchworth Garden City, Hertfordshire, England, UK.
[32]Macintosh II VI, Scotsys, Ltd, The Apple Centre, Rigshead Industrial Park, Bellshill. Scotland,UK.
[33]Lab NB-MIO-16, National Instruments UK, 21, Kingfisher Court, Hambridge Road, Newbury, Berkshire, England, UK..
[34]Labview, National Instruments Corporation, 6504 Bridge Point Parkway, Austin, Texas, USA.

The application programmes created in Labview are called virtual instruments (VIs). Labview programmes are hierarchical in structure, the final VI being built up of several linked, but discrete subVIs.

The front panel is the user interface to the VI. It is built with a combination of controls and indicators. This is illustrated by Figure 6 which shows the front panel of the application programme, 'DVCal levels', written for calibration of the strain gauge transducers.

Front panel indicators simulate instrument output devices, and display data generated when the programme is executed. When a VI is used as a subVI, the controls and indicators receive data from, and return data to, the VI at the next level in the hierarchy.

Labview 2.2.1 has a library of standard VIs capable of performing a wide variety of functions, which can be integrated into user defined VIs. For the present studies standard VIs controlled the analogue to digital converter, saved and retrieved data from hard disc and performed mathematical calculations and charting functions. Purpose written VIs calculated heart rate and systolic and diastolic blood pressures.

Using the Labview interface, three discrete programs were developed for invasive haemodynamic studies; the first was used for calibration of manometers (DVCal levels), the second, for real time acquisition of four channels of pressure data, and on-line analysis of mean, systolic, diastolic pressures and heart rate (DVpoly), and the third, for off-line analysis of stored data (DV compute bp,hr,etc).

Micromanometer calibration

Each transducer was calibrated against 100 mmHg, using a mercury manometer, before being inserted and again on removal. In the present studies after removal from the horse, zero for both transducers lay within 2.5 mmHg of the pre-

insertion zero with 95% confidence. Recorded pressures were not adjusted when baseline drift occurred because of the difficulty of knowing when the drift started and whether it was linear. Maximum drift detected during these studies was +3 mmHg to -2 mmHg for the proximal manometer, and +2.5 mmHg to -3.5 mmHg for the distal manometer.

Catheterisation technique

An arterial sheath introducer[35] was placed in the raised right carotid artery using the percutaneous Seldinger technique (Grossman, 1992). The sheath had a side arm and proximal haemostasis valve, allowing the internal catheter to be removed, without invoking serious haemorrhage. The dacron catheter was advanced through the introducer until the pressure traces recorded indicated the distal transducer was located in the left ventricle, and the proximal transducer in the aorta (Figure 7). Pressure data was displayed throughout each study on the chart recorder and on the screen of the microcomputer.

In human medicine fluroscopy is used to image the catheters and facilitate their introduction into the heart (Grossman, 1992). In horses it has been suggested that cardiac catheters can be advanced blindly into the heart (Muir, Skarda and Milne, 1976; Carlsten, Kvart and Jeffcott, 1984). However at the end of an early study, a woven Dacron catheter could not be withdrawn through the arterial sheath in Horse 3. Radiography revealed that it had become kinked (Figure 8). The catheter was removed by first removing the arterial sheath, followed immediately by the catheter. Considerable haemorrhage resulted, but there were no long-term adverse effects to the horse. The catheter was irreparably damaged. In the next series of studies in horses 2 and 4, the proximal micromanometer entered the left ventricle first. Two-dimensional echocardiography was performed and a bend in the body of the catheter, proximal to the micromanometers, was visible within the left ventricle. If the catheter was withdrawn,

[35]Haemaquet, 9F. Bard Ltd, Forest House, Brighton Road, Crawley, West Sussex, England, UK.

or advanced, at the introducer, it did not uncurl, but the bend moved vertically within the heart. Continued withdrawal resulted in the distal micromanometer entering the aorta (Figure 9). To correct the problem, the body of the catheter was rotated in the introducer, whilst 2-D transthoracic echocardiography was performed. If a long axis view of the left ventricular outflow tract and aorta were obtained from either right or left hemithorax (Long, Bonagura and Darke, 1992), the catheter loop became visible: The image was then used to determine the direction of rotation and the amount of withdrawal of the catheter. Once the free end of the bent catheter was pivoted away from the intraventricular septum, there was sufficient room in the ventricle for it to uncurl. Once this orientation was achieved, the catheter straightened when it was pulled backwards at the arterial sheath. It could then be removed uneventfully from the horse.

In subsequent studies the catheter was inserted into the left ventricle under ultrasonographic scrutiny. A long axis view of the aorta and left ventricular outflow tract was obtained using either transthoracic or transoesophageal ultrasonography. The catheter was advanced through the arterial sheath until the distal micromanometer became visible on the ultrasound image just above the aortic valve (Figure 10). The final advance of the catheter was then made to coincide with ventricular systole. If the distal micromanometer failed to enter the left ventricle, becoming lodged in the sinus of Valsalva, the catheter was withdrawn slightly and repositioned in the centre of the vessel, and the procedure was repeated. To compensate for the natural tendency of the end of the catheter to enter the sinus of Valsalva, it was often necessary to rotate catheter within the arterial sheath, as it was advanced. When the catheter passed into the ventricle the distal micromanometer could be visualised in the left ventricular outflow tract (Figure 11).

Occasionally the catheter was already bent when it was first seen at the sinus of Valsalva. The cause of the bend was unclear, since the insertion technique was apparently the same. One possibility is that the end of the catheter entered one of the

brachiocephalic arterial branches, proximal to the aortic valve which could not be visualised using ultrasound. If the body of the catheter was advanced from the arterial sheath this would force the body of the catheter to bend if the distal end was lodged. Introduction of more catheter might free the fixed extremity, so that the catheter would be advanced bend-first down the aorta. When a catheter had bent in this way there was insufficient room in the aorta to straighten it, so the bend was deliberately advanced into the left ventricle. The catheter was then uncurled in the ventricle using the technique described above. On five occasions during the straightening process, rotation of the catheter caused the distal transducer to enter the left atrium, evidenced by a left atrial pressure trace on the chart recorder. From this position the catheter could always be straightened. The uncurling process was monitored by transthoracic echocardiography using a right parasternal long axis view of the aorta. Transoesophageal echocardiography was not suitable for this purpose as the left ventricle was too far from the ultrasound crystal to allow the whole chamber to be visualised.

Real Time Data acquisition and charting

At the start of each study session the scales and offsets for each micromanometer obtained from the calibration program were manually entered into the corresponding control of 'DV poly', the program written for data acquisition. When the program was initiated the user was prompted to define a folder on the hard disk of the Macintosh 11vi, all files generated during that study were then stored within it. The program had the capacity to acquire data from four channels, allowing two additional channels of pressure data to be collected if required.

A double buffered data acquisition system was used to allow uninterrupted acquisition of data from the four channels. Use of a buffer carries with it the risk that data will be overwritten if the application programme is unable to access it sufficiently regularly. If this occurs DV poly returns an error message, registered by an indicator on the front panel. Data was not overwritten during the course of these studies.

DV Poly retrieved micromanometer data in 5 second blocks from the buffer. These voltages were immediately converted into mmHg, using the previously defined scales and offsets. Using purpose written VIs the mean, systolic and diastolic pressures from each channel were calculated and displayed on a corresponding front panel chart (Figure 12). The calculations were performed on the blocks of data, extracted from the buffer, and results from the previous 15 minutes were continuously displayed on each chart. A scroll facility allowed data from the entire study to be accessed at the request of the operator. DV Poly also contained an on-line algorithm to calculate heart rate. The instantaneous value of heart rate was also displayed.

The duration of each recording epoch, was set using a control on the front panel of the program. In these studies it was 20 s, ensuring that data from at least 10 cardiac cycles were available for analysis. Data were stored permanently on disk only when the operator recruited a subVI of the main program by activating a front panel control. When the store facility was activated the data were stored in a file which was automatically identified using a label from the internal clock of the microcomputer. This label included the date and the running time of the program, in hours, minutes and seconds. To allow visual appraisal of the saved data, after the data had been written to disk, the subVI displayed each channel on the Macintosh monitor. The subVI also displayed a synopsis of the saved data from each channel on the front panel of DV Poly. This allowed the operators to monitor trends in the data and to ensure that it had been recorded at all time points specified in the procedure protocol.

Measurement of pressure data

The programme 'DV compute bp, hr etc' calculated the systolic, mean and diastolic pressures from the four channels averaged from the 20 s of data recorded on the microcomputer hard disk (Figure 13). Mean pressure from each channel was calculated by a standard library VI, which measured the arithmetic mean of all the data points constituting a 20 s sample from each channel. The algorithm to calculate systolic

and diastolic pressures detected the maxima and minima of the pressure waveforms by scanning the data to determine when the rate of change of pressure is zero. To avoid detection of false maxima such as the dichrotic notch on the aortic pressure, the algorithm only accepted an end point after a pre-determined change in pressure had occurred. These values could be set by the operator. Their default values were 20 and 10 mmHg for the left ventricle and aortic pressure data respectively. For data obtained during anaesthesia it was sometimes necessary to reduce one or both of these limits so that the analysis programme could detect all the maxima and minima of a wave-form. Heart rate was calculated from the number of maxima detected on channel 1 (the left ventricular channel).

An additional standard library VI was used as a subroutine to differentiate left ventricular pressure data from channel 1. The maxima and minima of the resultant trace were then determined by the purpose written VI used for systolic and diastolic blood pressure. The average value of the maxima over the 20 s period was the isovolumic index of left ventricular contractility (LV dp/dt_{max})

To ensure that all maxima and minima had been correctly identified, as the programme analysed each channel sequentially, it plotted the waveform in a full screen window (Figure 14). Also plotted were the maxima (red crosses), minima (blue crosses) and horizontal lines representing the calculated mean (green), systolic (red) and diastolic (blue) blood pressures. This ensured that all computer-generated data could be visually appraised before being accepted. The programme automatically paused at this screen for 10 seconds for each channel, but this period could be extended by activating an on-line pause option.

Occasionally e.g. when a micromanometer was opposed to a valve, it was necessary to perform maxima and minima detection manually by using two electronic cursors and increasing the scale of both axes (Figure 15). If visual inspection of the

intermediate window for any channel showed errors in detection of end points the manual system was also employed. Manual determination was required most often to obtain the maxima of the differentiated left ventricular pressure waveform. In anaesthetised horses myocardial depression by halothane reduced the amplitude of the waveform, so that maxima were not always detected reliably by the software. As the automated facility detected left ventricular end systolic pressure ($LV_{es}P$) the cursors were also used to measure the end diastolic left ventricular pressure ($LV_{ed}P$).

Files corresponding to each data point in a study were analysed sequentially. Once analysis of each study session was completed the programme was terminated. The programme then prompted for a result file to store the results of the automated analysis as a text-delimited spreadsheet. The data was stored in chronological order of analysis, each row of the spreadsheet corresponding to an individual Labview file from a single data collection point. The appropriate time identification label was also stored in the first column of the spreadsheet next to the analysed data. The text-delimited file was then read into a commercial spreadsheet programme[36], missing values of $LV_{ed}P$, were then entered and other computed values corrected if manual measurement had been employed.

STATISTICAL METHODS

All statistical manipulations were performed using a commercial software package, Statgraphics Version 6[37] on a personal computer. Data was checked for normality using a normal probability plot. If data showed deviation from normal non-

[36] Microsoft Excel Version 5, Microsoft Ltd, Microsoft Place, Wharfedale Road, Winnersh Triangle, Wokingham, Berkshire, England, UK.
[37] Statgraphics, The Bloomsbury Software Co. Ltd, 3 - 6, Alfred Place, London. UK

parametric statistical analyses were performed. Specific statistical methods and tests are detailed in the appropriate chapters.

FIGURES FOR CHAPTER 2

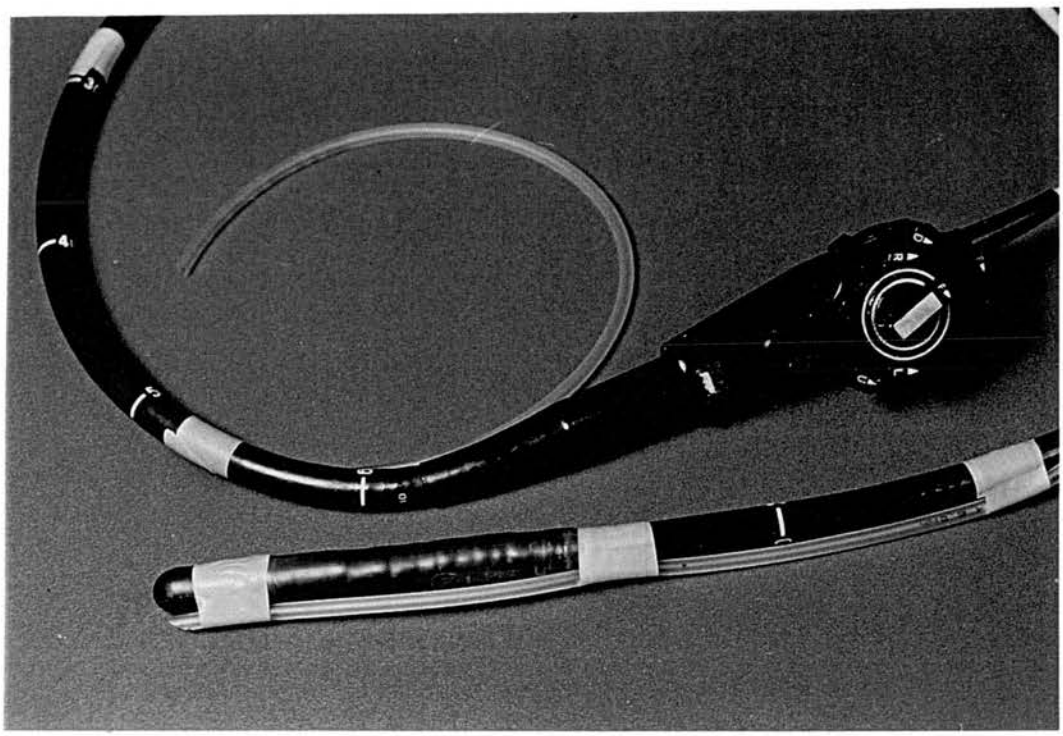

Figure 1: Equine transoesophageal probe.

A 3.0 MHz, mechanically steered, annular phased array transducer, mounted at the distal end of a 160 cm human colonoscope.

Note that the steering system of the colonoscope was locked and the flexibility of its distal end was reduced by the application of heat shrink material. The oesophagus was lubricated by means of 'Lubrel' delivered through the added external tubing

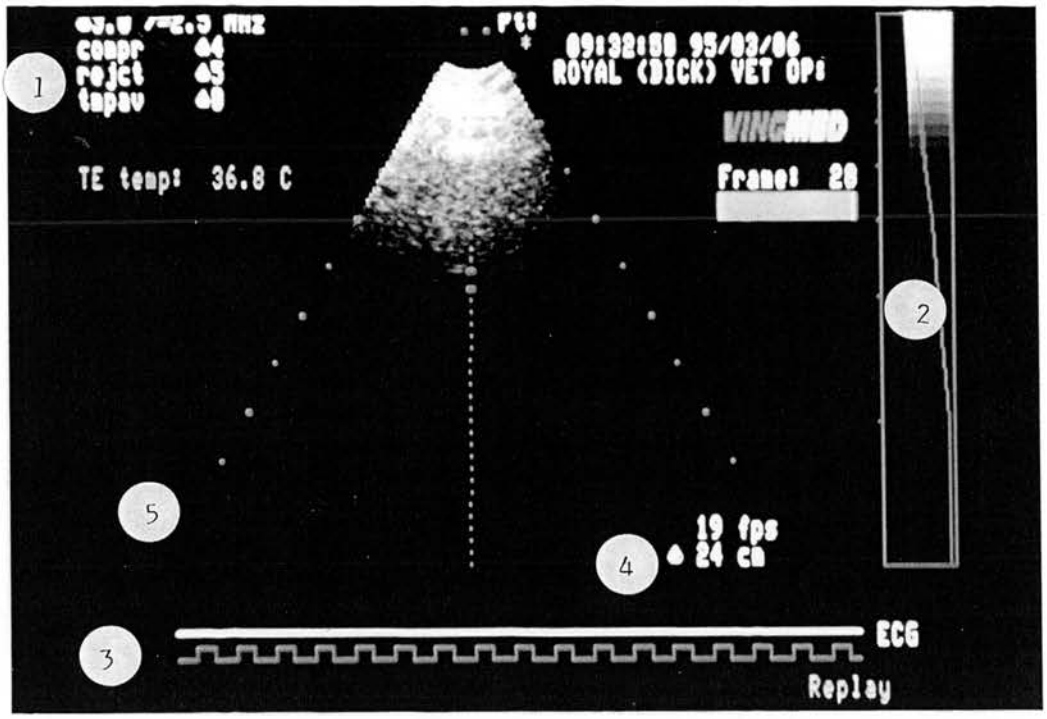

Figure 2: The screen of the vingmed CFM 700 as it appears for 2-D transoesophageal ultrasonography

1. Displayed in the left upper corner are the pre-set controls (compression, reject and temporal averaging) The temperature of the transoesophageal probe is registered below
2. On the far right is a diagrammatic ramp illustrating the settings of the adjustable gain at the five depth stages.
3. The ECG and frame update traces are displayed at the bottom of the screen. The far right hand corner of the trace indicates the frame being displayed in 2-D imaging modes
4. The imaging depth and the frame rate indicator are at the bottom right of the image sector.
5. The calibration code for calibration of measurement menus during video playback of stored data is displayed in this position

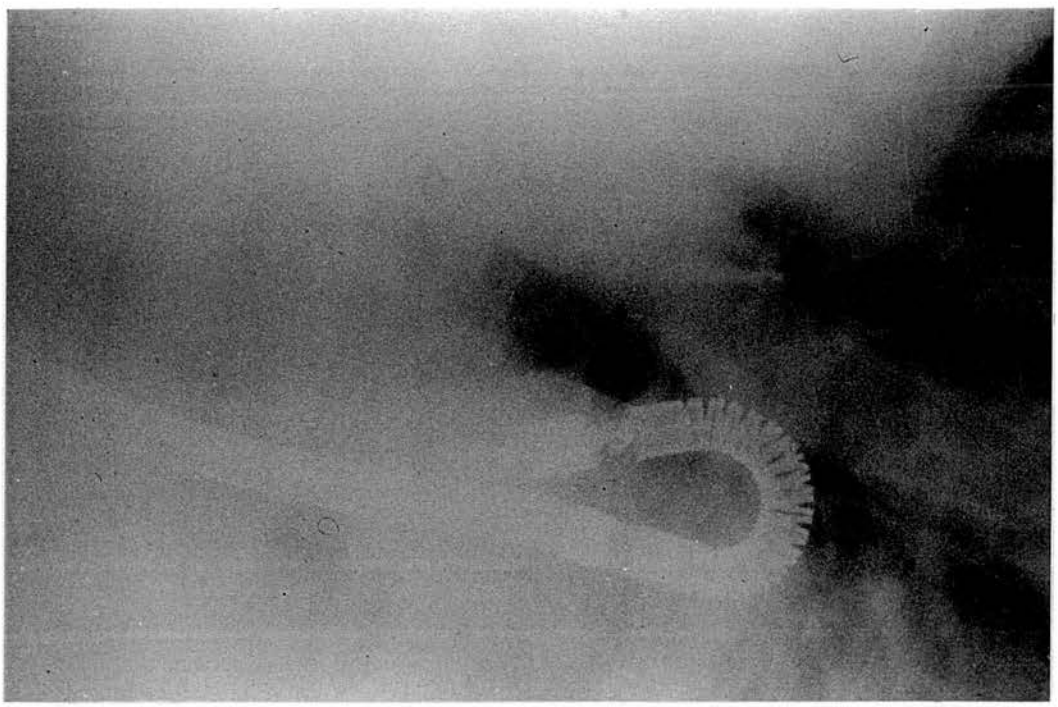

Figure 3: Lateral radiograph of the caudo-dorsal thorax of horse 1

A 'U' bend in the transoesophageal echocardiography probe is clearly visible against the air filled lung.

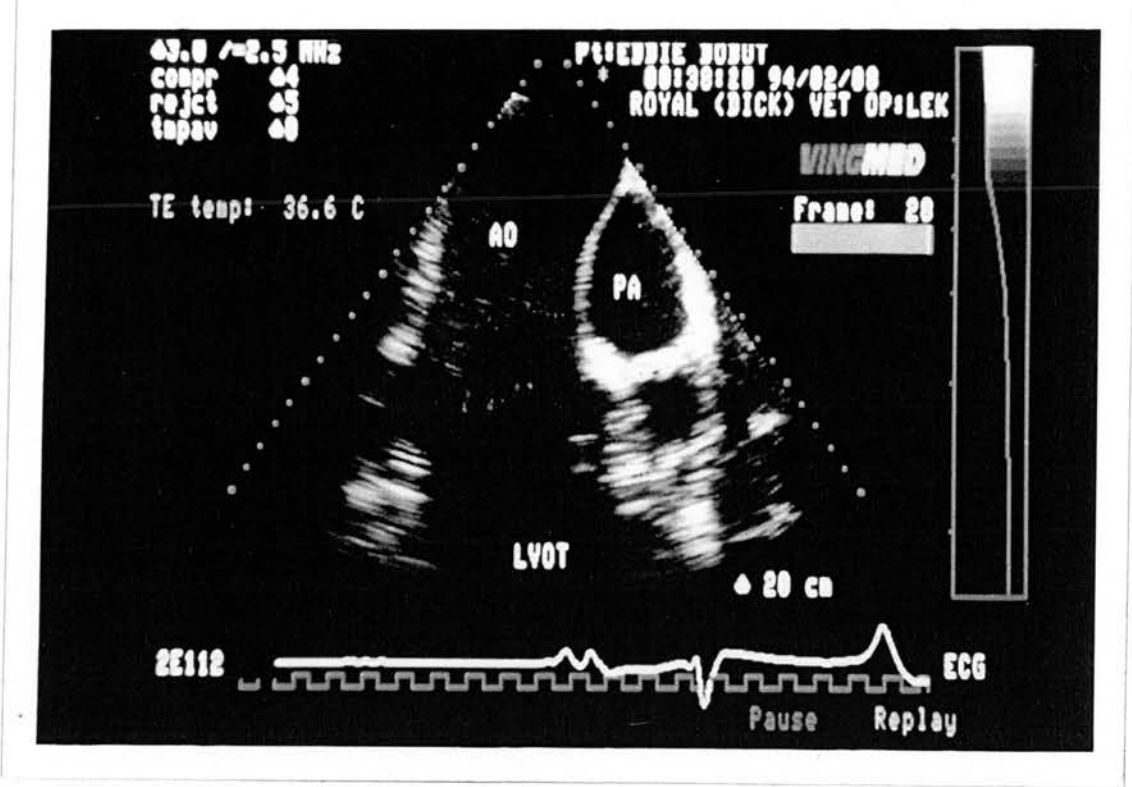

Figure 4: Reference 2-D image obtained by transoesophageal echocardiography

Showing the long axis of the aorta and the left ventricular outflow tract.

PA = pulmonary artery LVOT = Left ventricular outflow tract
AO = Aorta

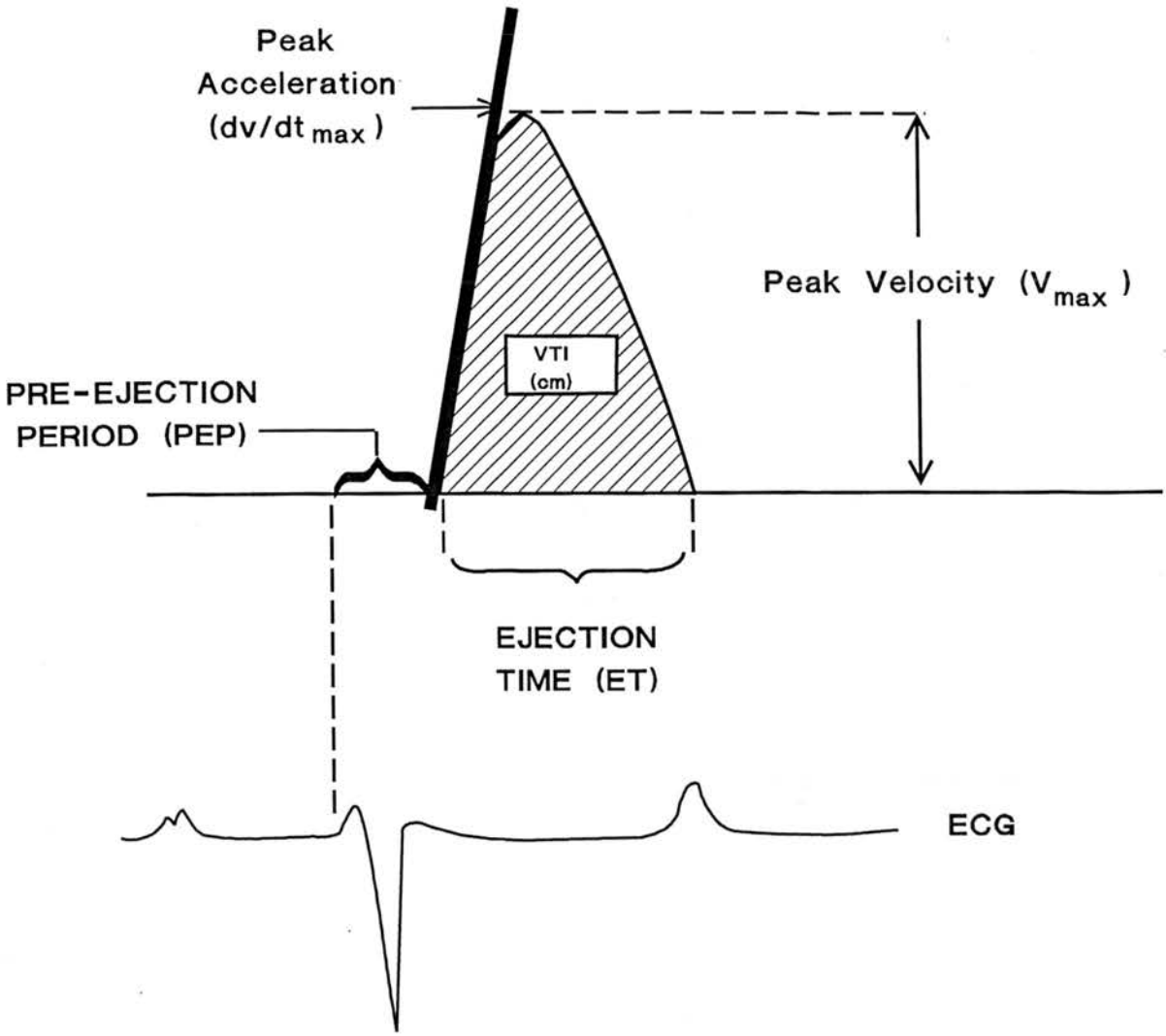

Figure 5 : Diagram representing the indices of left ventricular function, outflow velocities and systolic time intervals measured from aortic velocity spectra recorded by transoesophageal Doppler echocardiography.

Peak velocity (V_{max}) is measured in ms^{-1}. Peak acceleration (dv/dt_{max}) in ms^{-2}, is measured from the gradient of the line drawn parallel to the maximum upstroke of the spectral envelope. The line begins at the start of ejection and stops at the vertical height of the maximum velocity. The area under the curve (VTI) is measured in cm, and is derived by integrating under a line traced around the brightest line of the spectral envelope (the modal velocity). Pre-ejection period (PEP) is measured from the start of the 'Q' wave of the ECG to the start of ejection, Ejection time (ET) is time between the start and the end of ventricular ejection. Both PEP and ET are measured in seconds.

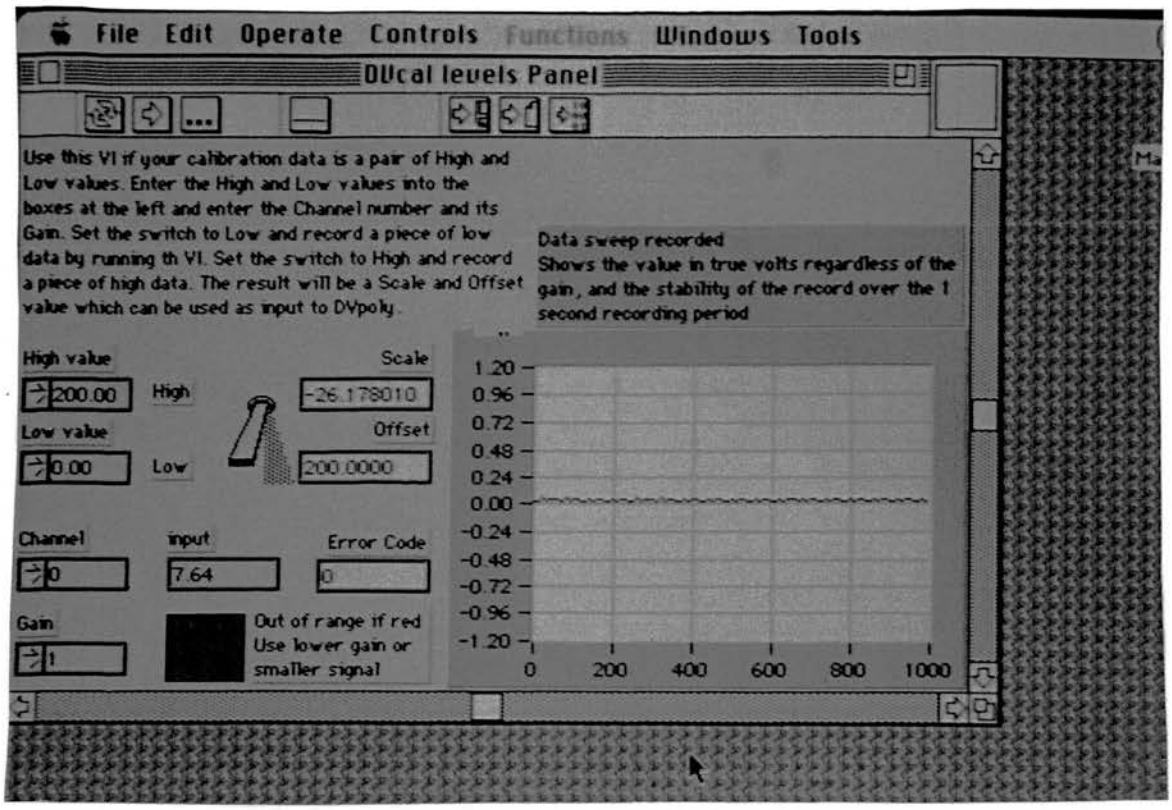

Figure 6: Front panel of calibration program

The front panel of 'DV Cal Levels' as it appears on the screen of the Macintosh IIvi. The virtual instrument (VI) is used for calibration of the micromanometers. The high and low digital indicators are set by the operator, to supply the numeric values of the calibration pressures for each micromanometer. They are used by the VI to calculate a scale and offset for each transducer. The input channel control selects which transducer (1 or 2) is being calibrated. The analogue to digital converter has a programmable gain, which can be adjusted using a front panel control. This facility was not employed here and the control was set at 1, it's default value

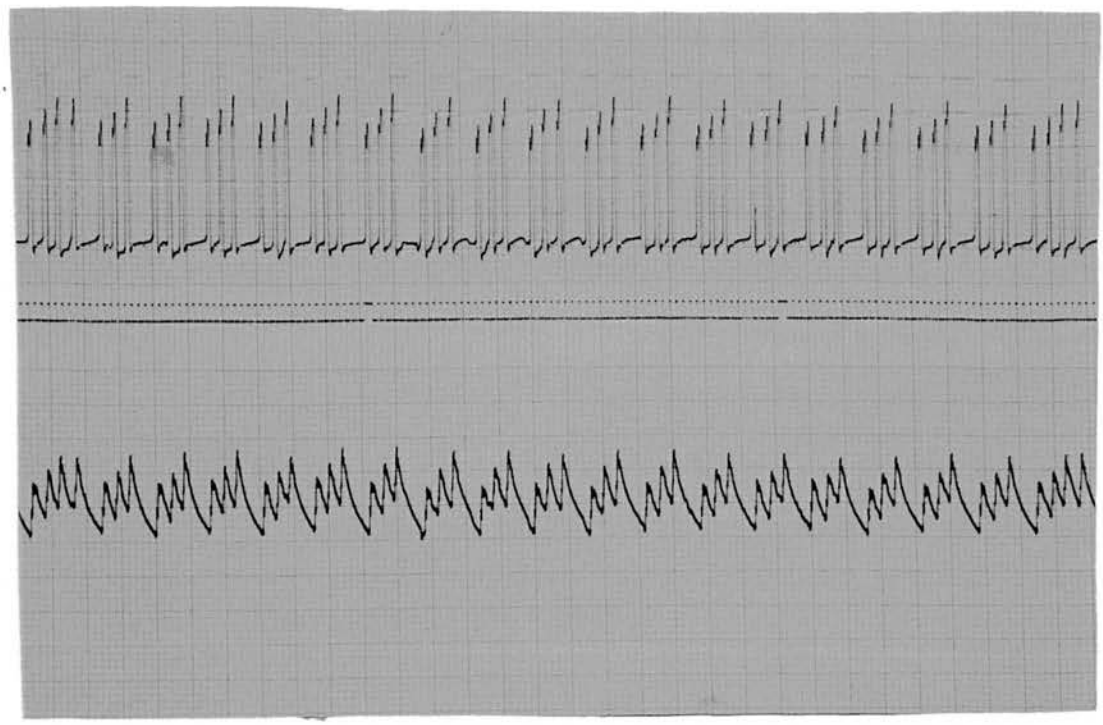

Figure 7: Characteristic left ventricular and aortic pressure waveforms

Pressure measured from two micromanometers sited in the left ventricle (upper) and aorta (lower) of a standing horse (Horse 1).

The horse is exhibiting 1 : 3 second degree atrioventricular block, a common finding in normal Thoroughbred horses. There is a progressive increase in systemic arterial pressure with conducted beats, which results in baroreceptor activation and increased vagal tone. In this animal after 3 conducted beats vagal tone is sufficient to block the next beat at the atrioventricular node.

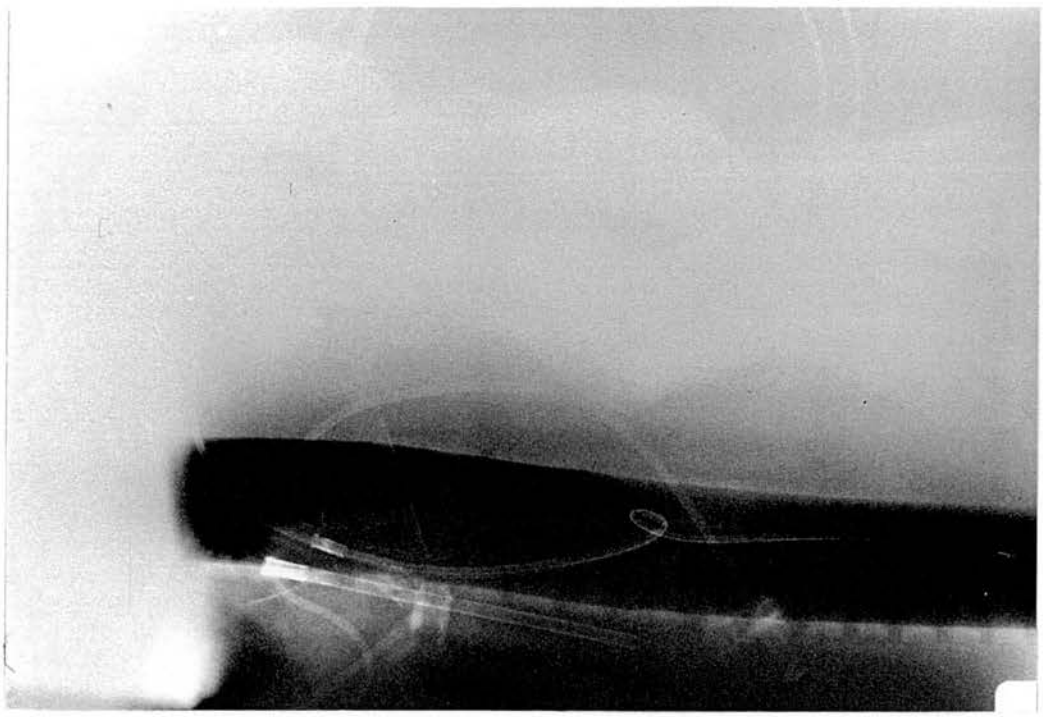

Figure 8: Lateral radiograph of neck of Horse 3.

A kink in the micromanometer tipped catheter within the carotid artery is visible against the air-filled trachea. The kink prevented withdrawal of the catheter from the arterial sheath introducer.

The catheter was removed by first removing the arterial sheath, followed immediately by the catheter. Considerable haemorrhage resulted, but there were no long-term adverse effects to the horse. The catheter was irreparably damaged.

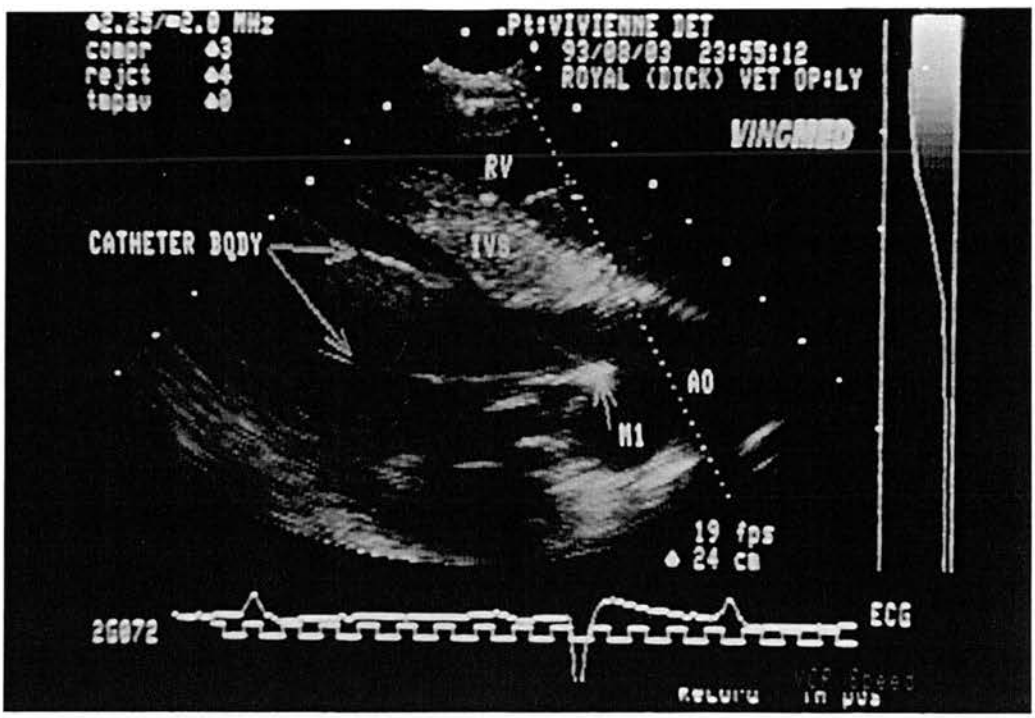

Figure 9: Right parasternal long axis view, showing bend in woven dacron catheter.

The distal strain gauge transducer is hyperechoic and is visible as a bright white spot at the level of aortic valve (M1).

AO = Aorta RV = Right ventricle
IVS = Intraventricular septum

The woven dacron catheter has entered the left ventricle with a bend. The strain gauge transducer at the end of the woven dacron catheter is in the aorta, whilst the transducer mounted 9 cm more proximal on the catheter body is in the left ventricular outflow tract. A portion of the curled catheter body can be seen above the aortic micromanometer entering the left ventricle. Such errors in catheter positioning can be reduced by ultrasonographic monitoring.

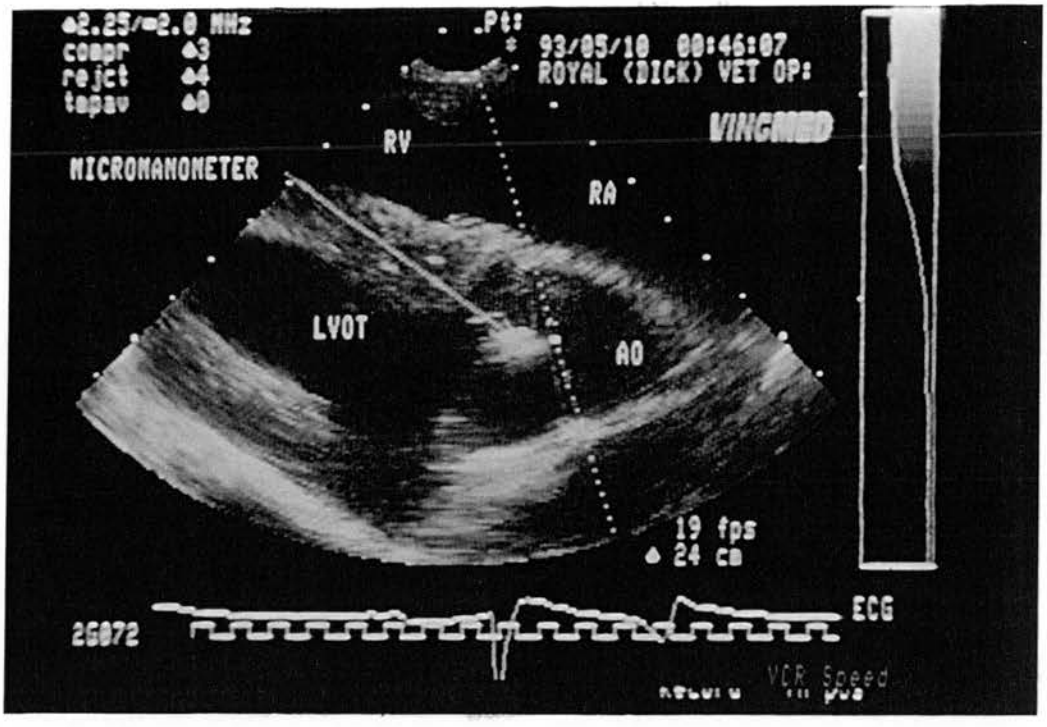

Figure 10: Right parasternal long axis view showing distal strain gauge transducer positioned above the aortic valve

LVOT = Left ventricular outflow tract
RA = Right atrium
AO = Aorta
RV = Right ventricle

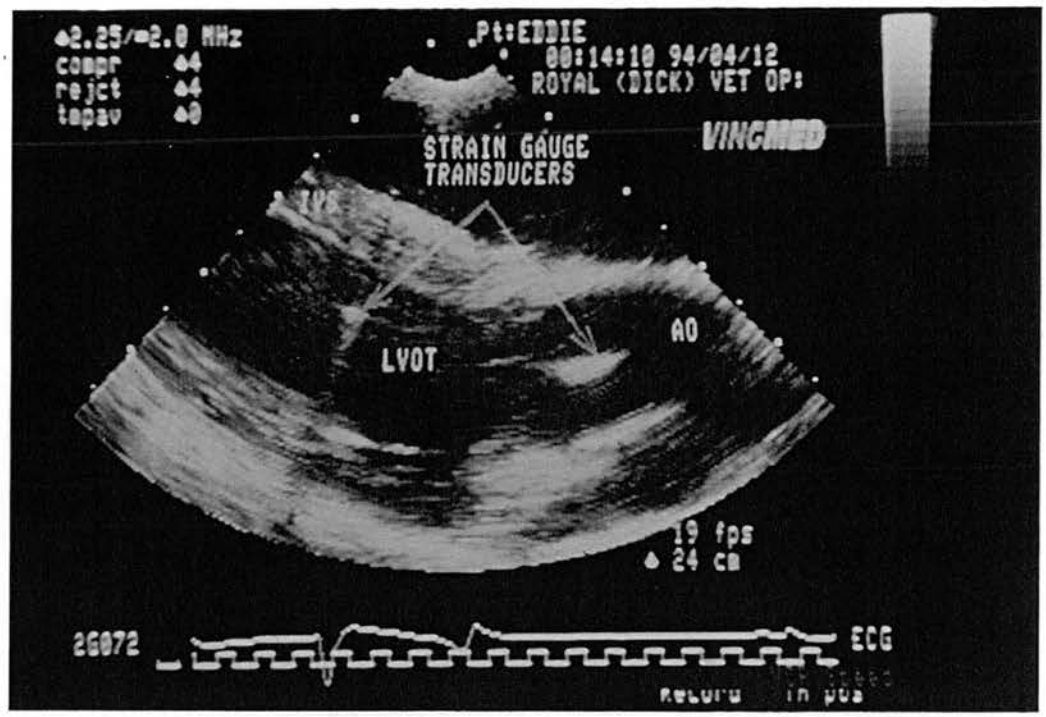

Figure 11: Right parasternal long axis view showing correctly positioned strain gauge transducers.

The strain gauge transducers are now correctly positioned on either side of the aortic valve. The woven dacron catheter was advanced through the arterial sheath during systole and the distal micromanometer has crossed the aortic valve.

LVOT = Left ventricular outflow tract AO = Aorta
IVS = Intraventricular septum

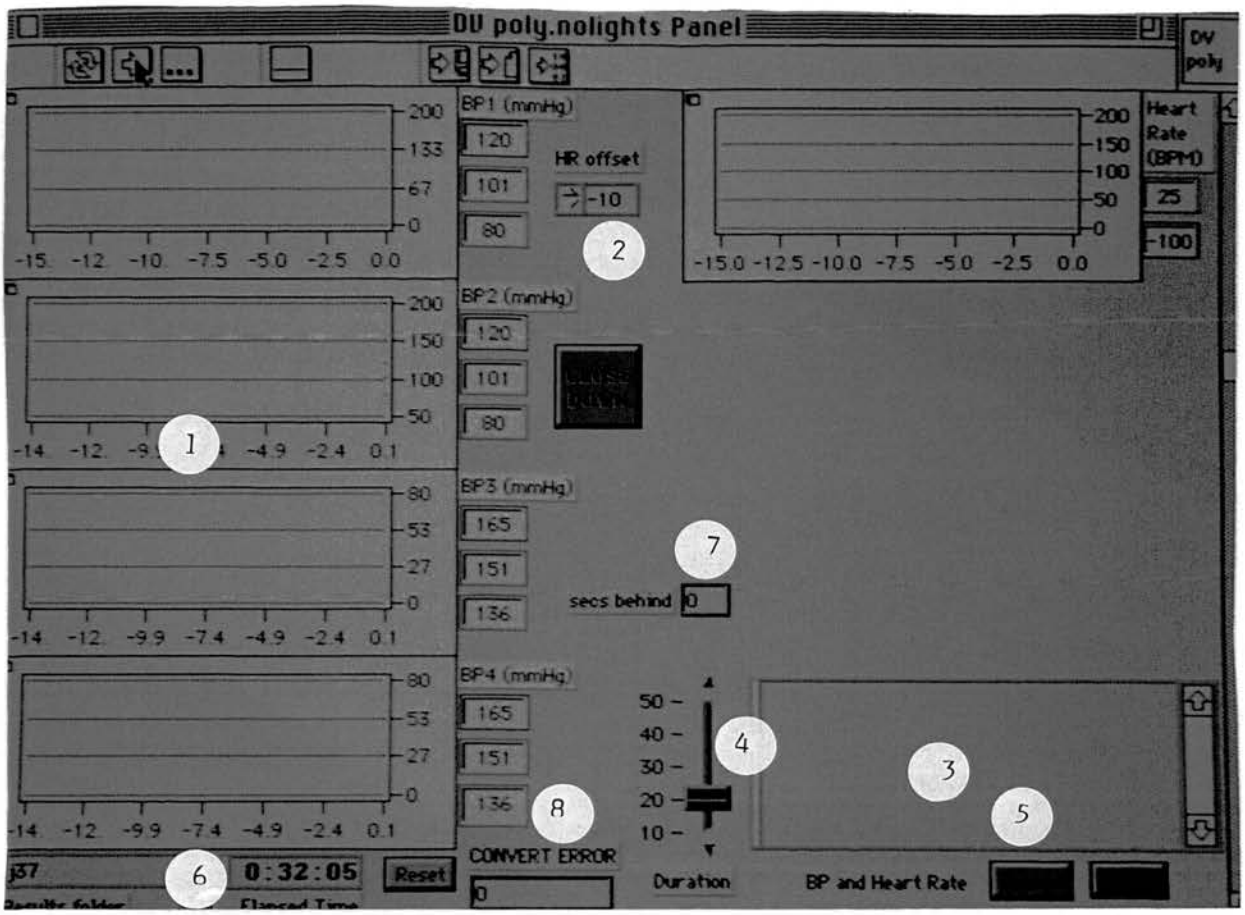

Figure 12: Front panel of real time data acquisition program, 'DV Poly'

1. Charts used to plot heart rate and mean, systolic and diastolic pressures from four strain gauge transducers. Each chart displays up to 15 minutes of real time data (a scrolling facility to access the entire data is also available). The instantaneous pressure or heart rate is also shown by the digital indicators on the left of each chart.
2. Digital control 'Hr offset' which determines the pressure change in mmHg that must occur before the programme counts a maximum value from the peaks of the pressure wave-form from which to calculate heart rate.
3. Empty summary chart which is used to store summary statistics from pressure data saved to hard disc during program execution.
4. Slide control used to set duration of data recording periods.
5. Button to activate record facility.
6. Digital indicator showing instantaneous running time of program. Used to time and label data acquisition in all studies.
7. Indicator showing number of seconds of pressure data still stored in the circular data buffer.
8. Alarm indicator which alerts the operator to overwriting of data in the circular buffer

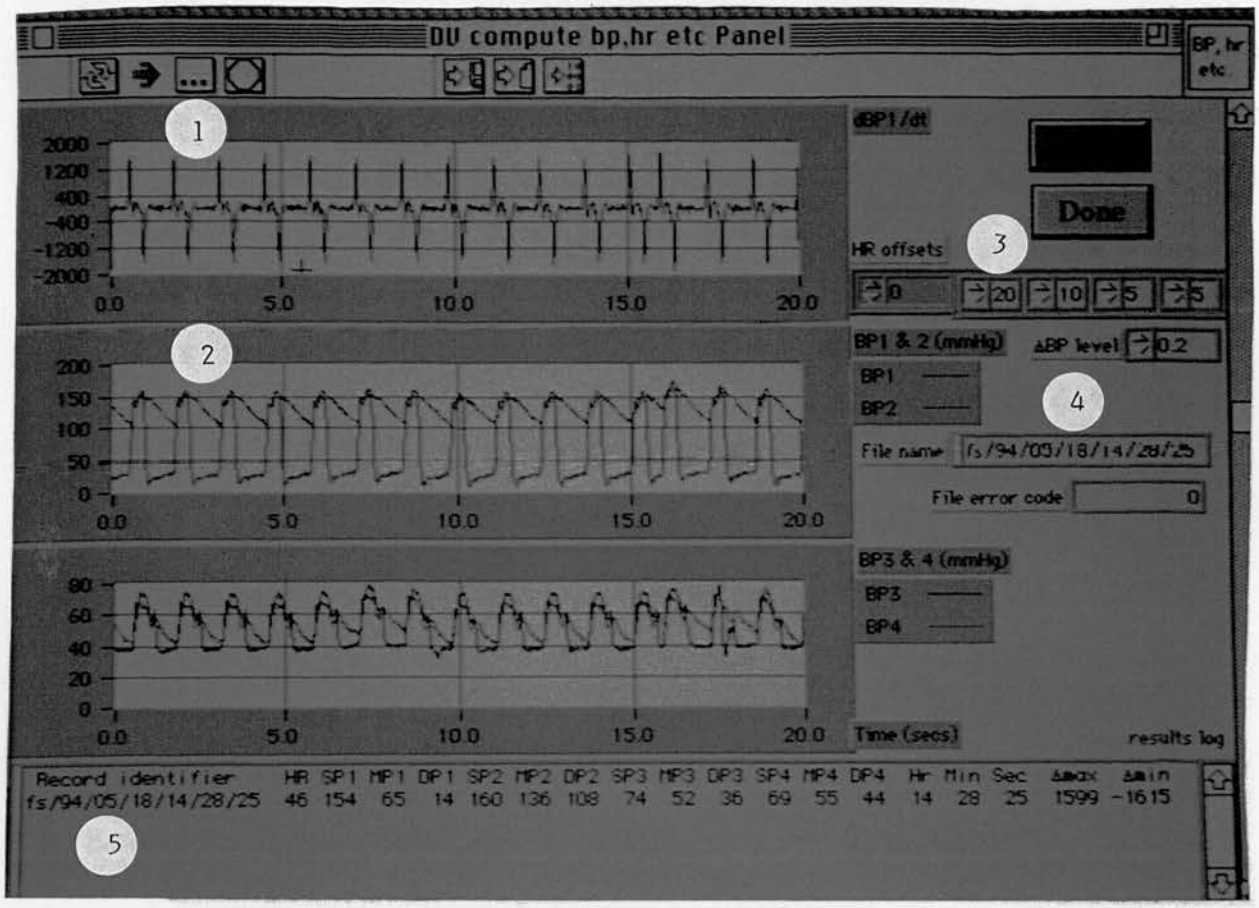

Figure 13: Front panel of data analysis programme, 'DV compute bp, hr etc'

1. Chart showing first derivative of left ventricular pressure over recording period. The data is obtained by differentiation of channel 1 by a standard library VI, used as sub VI in the analysis program hierarchy
2. Charts showing 2 channels of pressure data plotted for recording period. In this case the upper chart displays pressures from micromanometers in the left ventricle (blue) and the aorta (red) of horse 4. The lower traces are derived simultaneously from manometers in the right ventricle (black) and the pulmonary artery (purple)
3. Offsets for maxima and minima detection are set individually for each of the channels using a digital control array.
4. The file name of the record being analysed is identified by this indicator. During acquisition data from each 20 s recording period were stored as an individual Labview file in a user specified folder by 'DV poly'. Individual files are identified by labels, corresponding to the actual date and time the data was recorded.
5. The calculated data, for each channel can be written to a text delimited tab file, which is displayed as a chart.

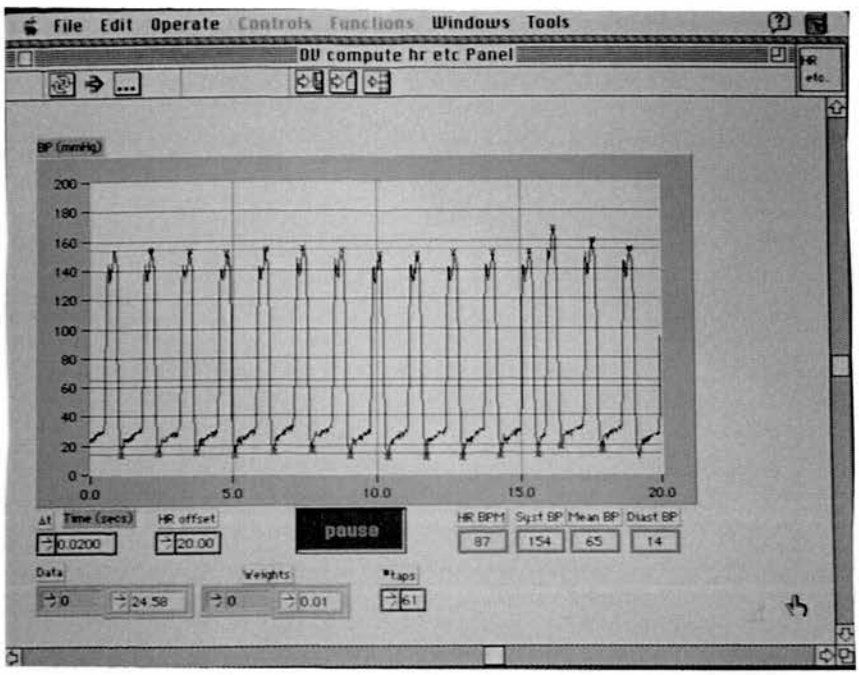

Figure 14: Intermediate window from the analysis program 'DV compute bp hr etc'.

During execution the analysis program pauses on data from each channel sequentially. On a chart showing the raw pressure data, the program superimposes the maxima (red crosses) and minima (blue crosses), detected using it's subVI. These derived points are used by the program to calculate the average pressure for each recording period. The resultant calculated value for mean (green), systolic (red) and diastolic (blue) pressure are also drawn on the chart for visual inspection.

Data shown on the left has been recorded from a micromanometer sited in the left ventricle of horse 4. There was a premature ventricular contraction after 15 seconds.

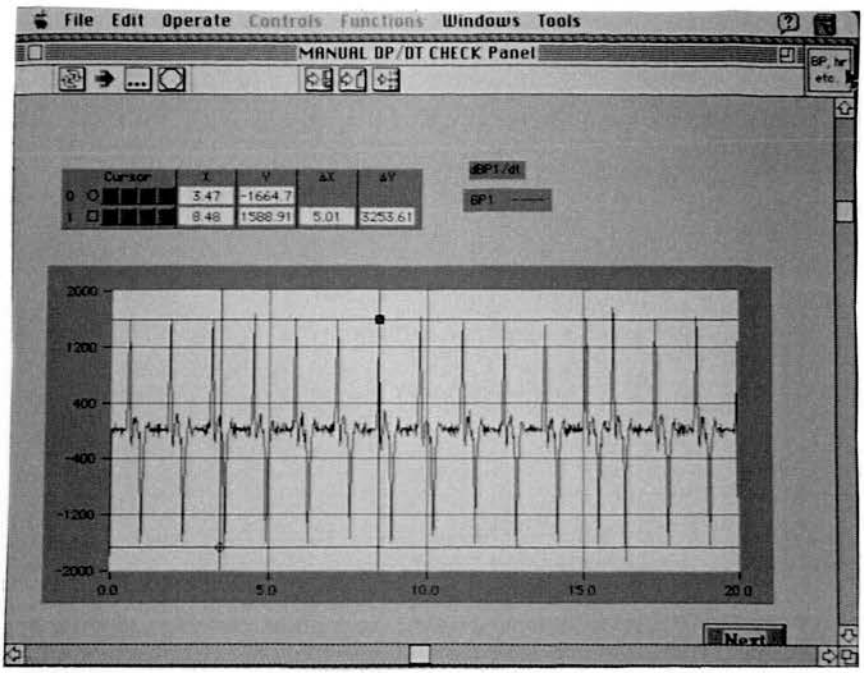

Figure 15: Labview 2.2.1 charting cursors.

Use of integral cursors within the analysis program allows waveforms to be measured manually if necessary.

The cursors are shown here, being used to measure the maximum and minimum values of the first differential of left ventricular pressure from Horse 6.

Chapter 3:

ASSESSMENT OF THE REPEATABILITY OF DOPPLER INDICES OF LEFT VENTRICULAR SYSTOLIC PERFORMANCE

AIMS

The indices of cardiac performance derived from Doppler echocardiography have been demonstrated to be non-invasive safe methods of assessing cardiovascular disease and responses to treatment in humans (Ihlen, Amlie, Myhre, Forfang and Larsen, 1985; Elkayam, Gardin, Berkley, Hughes and Henry, 1983). Transoesophageal echocardiography has potential to be a useful technique in anaesthetised horses for monitoring cardiac output and other indices of left ventricular performance. For the technique to be able to monitor an individual horse and to establish an individual's response to treatment, it is necessary to determine the reliability of the technique for detecting serial changes in cardiac performance. Before this can be achieved it is necessary to determine the day to day, or anaesthetic to anaesthetic, changes in cardiac performance for a single individual, as well as the range of values that may be encountered in different individuals. The purpose of this study was to assess the anaesthetic to anaesthetic variability of the transoesophageal Doppler-derived indices of cardiac performance in normal horses. To reduce other sources of variation throughout the study animal management and anaesthetic regimes were standardised. Similar studies were not available for other more commonly used measurements including arterial and intracardiac pressure, heart rate and cardiac output measured by thermodilution. The study additionally assessed the repeatability of measurements of heart rate, arterial blood pressure, and the invasive index of myocardial contractility, maximum rate of rise of left ventricular pressure ($Lvdp/dt_{max}$), in the same group of Thoroughbred horses.

MATERIALS AND METHODS

General anaesthesia and instrumentation

The eight thoroughbred horses described in Appendix 1 were the subjects of this study. Each horse was anaesthetised and instrumented for transoesophageal echocardiography as described previously (see page 47). Once the reference 2 dimensional (2-D) long axis view of the left ventricular outflow tract and aorta had been obtained (Chapter 2: Figure 4), colour flow Doppler echocardiography was performed. Using the keyboard tracker-ball the sample volume for high pulse repetition frequency (HPRF) Doppler echocardiography was then positioned in the centre of the vessel just above the valve in the area with the fastest blood flow shown by the colour flow map. Faster flowing blood was indicated by a paler red coloration in the colour flow map (Figure 16), or a blue coloration which occurred when the Nyquist limit (blood flow velocity > 0.6 $m.s^{-1}$) had been exceeded (Figure 17). HPRF Doppler studies were then performed with the 2-D imaging facility frozen so that the transducer was dedicated to the acquisition of Doppler information. The Doppler spectra were displayed continuously on the screen of the echocardiograph and were recorded onto video tape during data collection.

Left heart catheteration was performed and a calibrated strain gauge transducer was placed in the ascending aorta and left ventricle (see page 53). General anaesthesia was maintained with halothane at an end-expired concentration of 0.9%. The constant end-tidal halothane concentration was maintained for 45 minutes before data were collected. Intermittent positive pressure ventilation was performed by a mechanical ventilator to maintain arterial $PaCO_2$ between 35 to 45 mmHg. Each horse was anaesthetised on four separate occasions and 1 month elapsed between each anaesthetic episode. The allocation of horses to each group of anaesthetic episodes designated by numeric codes 1 - 4 was randomised to minimise any effects of ageing or training on cardiovascular function.

On the day following the first anaesthetic episode in each horse, nasal and pharyngeal endoscopy was performed to check for evidence of oesophageal damage caused by the transoesophageal echocardiography probe.

Data collection and measurement

Mechanical ventilation was stopped at each measurement point. Because intermittent positive pressure ventilation had maintained normocapnia in the horses, spontaneous breathing had ceased, so data were always recorded during apnoea. Twenty seconds of pressure data from each strain gauge transducer was stored on the hard disk of the Macintosh computer. This was then analysed off-line using the analysis programme described previously (see page 56). The average mean, systolic and diastolic pressures for the aortic transducer and the average left ventricular systolic pressure and heart rate were computed by the programme. The left ventricular end-diastolic pressure was measured manually using electronic calipers (see page 57). The left ventricular pressure waveform was differentiated to obtain maximum rate of rise of left ventricular pressure ($Lvdp/dt_{max}$).

All Doppler derived data was measured from the video taped images by a single observer by manual planimetry using electronic calipers. Measurements from the spectra comprised; velocity time integral (VTI), maximum acceleration (dv/dt_{max}), maximum velocity (V_{max}), left ventricular ejection time (ET) and pre-ejection period (PEP) (Chapter 2: Figure 5). Five consecutive velocity spectra, coinciding with the period of blood pressure data acquisition, were averaged for each anaesthetic episode. Cardiac output was calculated using the equation:

$$\text{Cardiac output} = \text{VTI} \times \text{aortic cross sectional area} \times \text{heart rate}$$

Aortic cross sectional area was calculated using the equation:

$$\text{Aortic cross sectional area} = 3.14 \times (\text{radius})^2$$

Aortic radius was measured from a 2-D standard transoesophageal image, of the sino-tubular junction (Figure 18). In this view both walls are imaged with lateral resolution so that the diameter measurement was performed from centre to centre of both aortic wall images (Hatle and Angelsen, 1985a). To obtain the diameter, three measurements were taken during systole from three consecutive cardiac cycles and an average figure obtained. These 2-D images were recorded onto video tape immediately before the spectral Doppler recordings.

Statistical analysis

Differences between anaesthetic episodes and horses were assessed using analysis of variance. When the f ratio was significant ($p < 0.05$) an estimate of the day to day variability and within horse variability was determined by calculating the intraclass correlation coefficient, using the method described by Sokal and Rohlf (1969). In this method the added variance between groups, s_A^2, is first calculated using the equation:

$$s_A^2 = \frac{s_B^2 - s_W^2}{n}$$

s_A^2 = measure of the variability between individual horses. (an estimate of the variance due to error-free variability of different horses)

s_B^2 = the between group mean square (measure of the variance between horses)

s_W^2 = the within group mean square (measure of the variance in individual horses)

n = number of horses

The intraclass correlation coefficient (r_I) is calculated from the equation

$$r_I = \frac{s_A^2}{s_W^2 - s_A^2}$$

The intraclass correlation coefficient represents the fraction of the overall variability of the measurement that arises due to variability between individual horses.

It therefore varies from 0 to 1. The more repeatable is a measurement in an individual the closer r_I is to 1.

The coefficient of variation was calculated for each variable from pooled data by dividing the mean value by the standard deviation and expressing the result as a percentage. 95% confidence intervals for the error-free (or true) value of a measured variable in a single subject was calculated using the methods described by Moulinier, Venet, Schiller, Kurtz, Morris and Sebastian (1991). The square root of s_W^2 is used to obtain the standard deviation within individuals.

$$\text{95\% confidence interval for a single measurement} = 2 \times s_w$$

s_w = standard deviation within individuals.

This value was then expressed as a percentage of the mean. The percentage difference between two measurements in a single individual must therefore exceed the 95% confidence interval, if the observed difference reflects a real change ($p < 0.05$).

RESULTS

The probe was placed in the oesophagus successfully in each horse on every occasion. The stiffened distal portion of the colonoscope made access to the ventral meatus difficult in horses 2 and 4 and inadvertent introduction into the middle meatus resulted in nasal haemorrhage on five occasions in horses 2, 4 and 8. Haemorrhage was of limited extent and duration, and had always stopped before the horse recovered from anaesthesia. If the probe entered the middle meatus, increased resistance to its passage was detected before reaching the pharynx, the probe was then withdrawn and re-introduced into the ventral meatus. On the day after each study all horses had mild serous nasal discharge from the nostril that had housed the transoesophageal echocardiography probe. Endoscopy revealed slight mucosal reddening of the ventral nasal meatus but there was no evidence of inflammation along the length of the

oesophagus. The nasal discharge had ceased within 48 hours of recovery from anaesthesia except in one animal (Horse 3) on one occasion. Radiography of Horse 3 at this time revealed a fluid line in the left maxillary sinus and endoscopy showed evidence of nasal mucosal inflammation. Clinical and radiographic signs had resolved after 7 days of antibiotic treatment.

Once the oesophageal probe was fully inserted the reference 2-D view of the left ventricular outflow tract and aorta was obtained within 5 minutes. The image was obtained after between 130 - 145 cm of scope had been inserted in all horses: the depth was repeatable for each individual. A long axis view of the left atrium and left ventricular inflow was also observed, but this was not specifically studied.

Spectral Doppler recordings taken from aortic blood flow were of uniform high quality, only minor adjustment or rotation of the probe being required to maintain clear audible signals and velocity spectra (Figure 19).

Table 2 shows the pooled data for all measured variables. Analysis of variance revealed significant differences between horses for heart rate, V_{max}, and VTI. Intraclass correlation coefficients were calculated for these variables. No significant differences between anaesthetic episodes were found for any of the measured variables.

Table 3 shows data from each anaesthetic episode averaged for each horse, the coefficient of variation indicates the variability of cardiovascular function of individual horses. In Table 4 the data is averaged for all horses for each anaesthetic episode, the coefficients of variation therefore reflect the variability between horses. Graphs 1a to 13a (Appendix Chapter 3, Page 230) are box and whisker plots of all the measured variables plotted for individual anaesthetic episodes and Graphs 1b to 13b (Appendix Chapter 3, Page 230) are similar plots, but the variables are grouped for individual horses.

Table 2: Mean values and coefficients of variation of measured haemodynamic variables derived from pooled data (seven anaesthetised Thoroughbreds in four separate anaesthetic episodes). NA= not applicable (p>0.05) **CI** = confidence interval, **n** = number of measurements.

	Mean (n=28)	Coefficient of Variation	95% CI as % of mean value	Intraclass correlation coefficient
Heart rate (**b.p.m**)	28	14%	20%	0.43
LV systolic pressure (**mmHg**)	77	15%	31%	NA
LV end-diastolic pressure (**mmHg**)	22	25%	47%	NA
Maximum aortic velocity V_{max} (**m.s^{-1}**)	0.84	11%	23%	0.75
Maximum aortic acceleration dv/dt(**m.s^{-2}**)	5.12	23%	22%	NA
Pre-ejection period PEP (**s**)	0.23	12%	17%	NA
Ejection time (ET) (**s**)	0.51	9%	15%	NA
Velocity time integral VTI (**cm**)	24.8	14%	19%	0.47
Cardiac output (**L.min^{-1}**)	27.8	14%	24%	NA
Aortic systolic pressure (**mmHg**)	78	18%	35%	NA
Aortic mean pressure (**mmHg**)	66	20%	42%	NA
Aortic diastolic pressure (**mmHg**)	55	22%	45%	NA
LV dp/dt_{max} (**mmHg.s^{-1}**)	246	26%	52%	NA

Table 3: Mean values of measured haemodynamic variables in individual horses from 4 separate episodes of 0.9% end-tidal halothane anaesthesia (values in parenthesis indicate coefficient of variation).

	H1	H2	H3	H4	H5	H6	H7
Heart rate (**b.p.m**)	28.0 (14%)	26.7 (8%)	29.7 (6%)	37 (7%)	28.2 (5%)	27.5 (14%)	30.5 (8%)
LV systolic pressure (**mmHg**)	75.0 (12%)	76.2 (19%)	73.5 (15%)	82.0 (15%)	67.5 (16%)	76.5 (11%)	86.3 (15%)
LV end-diastolic pressure (**mmHg**)	19.5 (15%)	26.7 (17%)	24.7 (17%)	23.8 (16%)	19.5 (32%)	18.8 (26%)	20.6 (26%)
Maximum aortic velocity V_{max} ($m.s^{-1}$)	0.93 (8%)	0.86 (5%)	0.75 (8%)	0.80 (14%)	0.84 (5%)	0.87 (8%)	0.86 (15%)
Maximum aortic acceleration dv/dt ($m.s^{-2}$)	5.91 (37%)	5.62 (18%)	4.64 (17%)	5.1 (13%)	4.74 (14%)	5.71 (22%)	4.14 (14%)
Pre-ejection period PEP (**s**)	0.22 (18%)	0.21 (14%)	0.24 (4%)	0.22 (9%)	0.24 (13%)	0.22 (9%)	0.26 (8%)
Ejection time (ET) (**s**)	0.49 (8%)	0.56 (11%)	0.48 (13%)	0.51 (2%)	0.53 (6%)	0.50 (6%)	0.48 (8%)
Velocity time integral VTI (**cm**)	26.8 (10%)	29.5 (12%)	21.1 (9%)	23.7 (13%)	26.2 (11%)	24.8 (5%)	21.3 (7%)
Cardiac output ($L.min^{-1}$)	27.6 (13%)	29.06 (10%)	23.0 (11%)	32.4 (8%)	27.1 (10%)	28.1 (14%)	26.7 (17%)
Aortic systolic pressure (**mmHg**)	77 (19%)	75 (21%)	76 (17%)	84 (19%)	67 (21%)	76 (12%)	89 (13%)
Aortic mean pressure (**mmHg**)	64 (20%)	63.2 (30%)	65 (18%)	72 (24%)	58 (22%)	66 (13%)	77 (14%)
Aortic diastolic pressure (**mmHg**)	53 (22%)	51.8 (32%)	54 (20%)	61 (27%)	47 (23%)	54 (14%)	65 (16%)
LV dp/dt_{max} ($mmHg.s^{-1}$)	238 (32%)	225 (24%)	242 (18%)	289 (33%)	206 (29%)	278 (17%)	244 (22%)

Table 4: Mean values of measured haemodynamic variables in seven anaesthetised Thoroughbreds after 60 minutes of 0.9% end-tidal halothane concentration in each of four anaesthetic episodes (values in parenthesis indicate coefficient of variation)

	Episode 1	Episode 2	Episode 3	Episode 4
Heart rate (**b.p.m**)	31 (14%)	29 (14%)	28 (13%)	30 (14%)
LV systolic pressure (**mmHg**)	76 (15%)	76 (14%)	73 (12%)	82 (19%)
LV end-diastolic pressure (**mmHg**)	21 (29%)	23 (13%)	21 (26%)	23 (30%)
Maximum aortic velocity V_{max} (**m.s^{-1}**)	0.82 (12%)	0.89 (9%)	0.88 (5%)	0.78 (12%)
Maximum aortic acceleration dv/dt (**m.s^{-2}**)	4.69 (16%)	5.89 (31%)	5.18 (10%)	4.74 (19%)
Pre-ejection period PEP (**s**)	0.22 (14%)	0.24 (12%)	0.24 (13%)	0.24 (4%)
Ejection time (ET) (**s**)	0.51 (8%)	0.51 (10%)	0.48 (6%)	0.53 (11%)
Velocity time integral VTI (**cm**)	24.6 (14%)	25.1 (16%)	24.8 (10%)	24.5 (19%)
Cardiac output (**L.min^{-1}**)	28.4 (9%)	28.6 (17%)	26.6 (18%)	27.0 (11%)
Aortic systolic pressure (**mmHg**)	78 (18%)	76 (19%)	75 (15%)	82 (20%)
Aortic mean pressure (**mmHg**)	68 (20%)	64 (21%)	62 (20%)	72 (22%)
Aortic diastolic pressure (**mmHg**)	55 (22%)	53 (22%)	51 (20%)	61 (24%)
LVdp//dt_{max} (**mmHg.s^{-1}**)	257 (26%)	237 (34%)	234 (18%)	257 (26%)

DISCUSSION

The present study shows that transoesophageal echocardiography is well tolerated in anaesthetised Thoroughbred horses and although the number of two dimensional images obtained was limited compared to human studies, a long axis view of the left ventricular outflow tract and aorta was always obtained. Nasal haemorrhage was an undesirable complication of probe insertion in 3 animals. Horse 2 was consistently the most difficult to intubate, although haemorrhage did not result on every occasion. The mare was not the smallest animal of the group, but she did have a long face with slightly roman nose that tapered to the nares (Figure 20). This problem had not been experienced before the distal end of the transoesophageal echocardiography probe was stiffened. The reduction in flexibility presumably reduced access to the ventral meatus by limiting the operator's ability to manipulate the tip of probe in the nostril, a problem which seemed to be accentuated in certain animals because of upper airway anatomy. This difficulty could probably be eliminated if the probe was redesigned.

The mild serous nasal discharge which occurred consistently after transoesophageal echocardiography was not considered to be a serious complication in these healthy Thoroughbred horses. Nosocomial sinusitis is well recognised in human patients after nasotracheal intubation (Rouby, Laurent and Gosnach, 1994). There is still controversy whether poor sinus drainage, or the trauma associated with the tube are primary causes for the maxillary sinusitis that invariably occurs in humans. The maxillary sinus is an ideal location for resistant infections because it is shielded from full antibiotic penetration, and can thus provide a source of bacteria for septicaemia in critically ill humans (Heffner, 1994). Radiographic evidence of unilateral sinusitis was obtained from Horse 3, and its presence cannot be ruled out in the other horses, certainly evidence of mechanical trauma to the nasal mucosa was demonstrable in the

horses 24 hours after transoesophageal echocardiography. In this study all the symptoms were short-lived and were considered to be of little clinical consequence, however it is possible that a larger series would reveal that significant sinusitis did occur especially in the presence of other upper respiratory tract pathogens.

The axial alignment of the aorta and left ventricular outflow tract with the ultrasound beam in the reference long axis transoesophageal view was ideal for Doppler echocardiography. High quality velocity spectra, which were suitable for derivation of ejection phase indices of left ventricular function, were readily obtained using high pulse repetition frequency Doppler insonation.

Management of the horses in the study was controlled with respect to diet, exercise and environment. Anaesthetic technique was standardised, and intraoperative arterial blood gas tensions were maintained within fixed limits. The effects of these sources of variance on the measured haemodynamic variables within each study, should therefore have been minimised. All measured variables showed marked variation, indicated by coefficients of variation greater than 10% and wide 95% confidence intervals (Table 2). Since variation in a biological measurement made on a particular animal on different occasions dictates it's sensitivity for detecting serial changes, allowance must be made for this when the measurement is to be used to detect responses to treatment. Variation between individuals also influences the normal range of a measurement, and must be defined, if the measurement is to be used to help define disease or abnormal function. For physiological data these two sources of variation can be of differing relative importance. When haemodynamic data is considered, the situation is complex. If the heart rate of a group of horses is measured by auscultation considerable variation will be detected. Auscultation is expected to measure heart rate with almost 100% accuracy, so that the observed variation must reflect differences between individual horses. If the horses are ausculated on a second occasion, it is unlikely that each horse will have the same heart rate as on the first examination, the

magnitude of this variation within individuals describes the variable's repeatability. The ability of auscultation to measure these heart rates correctly on each occasion indicates the reliability of the auscultatory technique. With any measurement technique, measurement errors can also contribute additional sources of variation to biological data, so reliability is an important consideration for new methods.

In this study significant differences in measured variables between individual horses was assessed using analysis of variance. Statistically significant differences were detected in heart rate, V_{max}, and VTI. The use of intraclass correlation coefficient, r_I, has been used as an index of measurement technique reliability (Landis and Koch, 1977). It provides a number between 0 - 1, for which 1 which indicates perfect repeatability. Moulinier, Venet, Schiller, Kurtz, Morris and Sebastian (1991) reported a very similar study of day to day reliability of Doppler derived VTI measurements in 7 conscious human volunteers kept under tight environmental control. They used transthoracic echocardiography to obtain the aortic velocity spectra and also measured heart rate and arterial blood pressure. If the same calculation for the correlation coefficient, r_I described by these workers is used on data from the present study the values obtained for heart rate are very similar (0.60 for conscious humans compared to 0.57 for anaesthetised horses). The value obtained for VTI was considerably higher in the human study (0.87 cf. 0.51), indicating that VTI measurement varies little between days in conscious humans, whilst there was relatively more variation between different anaesthetic episodes for horses. These workers presented similar findings for systolic and diastolic arterial blood pressure ($r_I = 0.85$) indicating that there is also minimal day to day variation of blood pressure. This contrasts with findings in the present study in anaesthetised horses when analysis of variance failed to reveal significant differences between individual animals, because variation between anaesthetic episodes was so great. It was therefore inappropriate to calculate an intraclass correlation coefficient for the equine blood pressure data (Sokal and Rohlf, 1969), making direct comparison with

the human study impossible. However the 95% confidence intervals for a single blood pressure measurements can be compared for the two species; in conscious humans this value was less than 10%, compared to 35% and 45% for systolic and diastolic aortic pressure measurements in anaesthetised horses. If the errors in blood pressure measurement technique are similar in both studies it must be concluded that general anaesthesia in horses interferes with normal homeostatic control of arterial blood pressure.

In the present study, heart rate, V_{max}, and VTI were the only variables for which significant differences were detected between individual horses. The source of this variation is more clearly illustrated in Table 3 and throughout Graphs 1 - 13 (Appendix Chapter 3, Page 230). If Graphs 1a and 1b are examined two horses (1 and 6) show much higher individual variation in heart rate than the rest of the group. Horse 1 was noted to have second degree atrioventricular block and a heart rate of 22 during anaesthetic episode 2. In the other three episodes the horse was in normal sinus rhythm with a mean rate of 30 beats per minute. Dysrhythmias have important effects on all indices of myocardial performance and in this horse second degree atrioventricular block was probably responsible for the very high coefficients of variation of dv/dt_{max} and $LVdp/dt_{max}$. Examination of the raw data revealed this to be the case, aberrant high values for dv/dt_{max} and $LVdp/dt_{max}$ were also present during anaesthetic episode 2. In Horse 6 the high coefficient of variation was not associated with a single anaesthetic episode. Marked variation of heart rate between horses is illustrated by Horse 4 which maintained a higher heart rate in all anaesthetic episodes. Left ventricular end-diastolic pressure showed the highest variation of all pressure measurements. The reason for this is unclear, measurements were always taken during apnoea, so respiratory effects should not be responsible. Left ventricular end-diastolic pressure has been used as an index of preload for normally compliant ventricles. The value of 47% for the 95% confidence interval for a single measurement of left ventricular end-diastolic pressure

(Table 2) indicates that this variable must be used with caution for assessing the effects of treatment on preload in individual anaesthetised horses.

The main source of error in the measurement of linear velocity by Doppler echocardiography arises from poor alignment of the ultrasound beam with the direction of blood flow (Hatle and Angelsen, 1985b; Angelsen and Brubakk, 1976). The measured velocity of blood flow is proportional to the cosine of the angle between the direction of blood flow and the insonating beam. If this angle is less than 18° this will give a maximum error of +/- 5% in velocity measurement. The standard 2-D image obtained by transoesophageal echocardiography in horses suggested that alignment with aortic flow in two dimensions was good (Figure 18). Alignment in the other plane is difficult to assess but the clarity of the audible signals indicated that the beam was well aligned to blood flow and these are the criteria accepted in human in-vivo studies (Hatle and Angelsen, 1985a). It is therefore considered unlikely that poor alignment provided a significant source of error in the present study.

Although operator errors associated with measurement of the Doppler-derived indices are a possible source of error in this study, most variation was associated with variables derived from aortic and left ventricular pressure measurement. The high fidelity micromanometers and recording system used in these studies were calibrated frequently and are considered to have measured pressure accurately. The greatest coefficient of variation and widest 95% confidence intervals were found in the index of left ventricular contractility, $LVdp/dt_{max}$. It might be expected that a similar amount of physiological variation would occur in the indices of ventricular performance derived simultaneously from Doppler echocardiography. In this study however the coefficient of variation and 95% confidence intervals were narrower for the Doppler-derived variables than for those obtained by cardiac catheterisation. Doppler indices of ventricular performance are ejection phase indices, occurring after the aortic valve has opened. In contrast $LVdp/dt_{max}$ is an isovolumic index of left ventricular contractility.

Marked variation in aortic diastolic pressure in these anaesthetised horses may explain the poorer repeatability of $LVdp/dt_{max}$. Reduction in aortic diastolic pressure is known to influence $LVdp/dt_{max}$ since the aortic valve opens before maximum tension has been produced by the contracting myocardium (Borow, Neumann, Marcus, Sareli and Lang, 1992; Wallace, Skinner and Mitchell, 1963). Marked variation in left ventricular end-diastolic pressure, and therefore ventricular preload, also occurred in these studies which would be expected to influence all the indices of cardiac performance (Bedotto, Eichhorn and Grayburn, 1989). The increased variability associated with the isovolumic index in the present study suggests that it may be more sensitive to changes in afterload and preload than the indices derived from transoesophageal Doppler echocardiography. Alternatively the relative increase in variability of $LVdp/dt_{max}$ may reflect increased measurement error rather than true physiological variation.

Maximum aortic acceleration showed much higher coefficient of variation than the peak velocity (V_{max}). This is in agreement with a study performed in experimental dogs (Wallmeyer, Wann, Sagar, Czakanski, Kalbfleish and Klopfenstein, 1988). Gardin, Dabestani, Martin, Alfie, Russel and Henry (1984) attributed a similar finding in humans to technical difficulties in defining dv/dt_{max} from the velocity spectra. Peak velocity is much easier to identify and small errors in identifying dv/dt_{max} are magnified by differentiation.

In summary it appears that indices of cardiac performance derived from Doppler echocardiography can be obtained reliably in anaesthetised horses using transoesophageal echocardiography. At first sight the repeatability of the indices may be considered disappointing when compared to similar studies performed in conscious humans. However this difference may be attributable to changes in homeostatic control of cardiovascular function imposed by general anaesthesia, rather than reflecting true species differences, or inadequacy in the measurement techniques. In conscious humans blood pressure data was strongly repeatable between days for given individuals

in marked contrast to the situation in anaesthetised horses. In humans blood pressure is kept under tight physiological control (Haites, McLennan, Mowat and Rawles, 1984) and unpublished work in horses suggests that the situation is similar for both arterial blood pressure and Doppler-derived indices of cardiac performance when horses are conscious. The poor repeatability detected when the same animals were anaesthetised could arise because the anaesthetic techniques were sufficiently different on each occasion to change haemodynamic function. This situation cannot be ruled out, but on a practical level the anaesthetic procedures in these studies were standardised within the limits of currently available expertise and equipment. An alternative explanation may be that general anaesthesia interferes with the normal homeostatic regulation of cardiovascular performance in anaesthetised horses.

FIGURES FOR CHAPTER 3

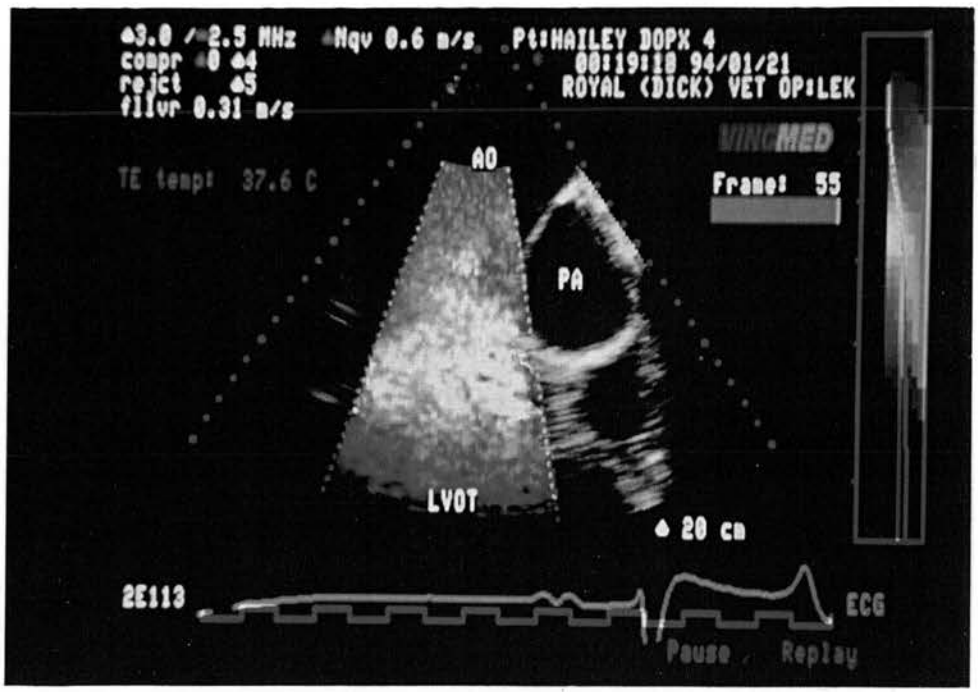

Figure 16: Colour Doppler echocardiography study of the aorta.

The red colour shows flow from left ventricular outflow tract to aorta during systole. The lighter shades of red indicate a central core of faster flowing blood in the centre of the vessel. For high pulse repetition frequency pulsed Doppler studies the sample volume was positioned in the centre of the central core above the aortic valve.

The timing of this frame is represented by the ECG in the far right of the figure.

AO = aorta LVOT = left ventricular outflow tract

PA = pulmonary artery

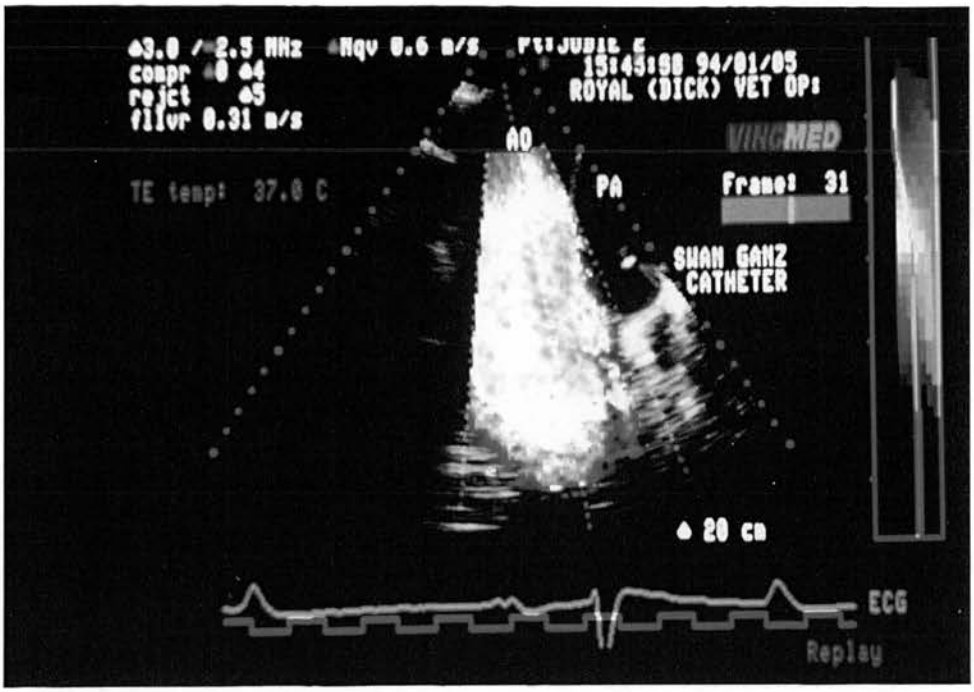

Figure 17: Colour Doppler echocardiography study of the aorta.

Systolic frame showing blood flow from left ventricular outflow tract to aorta. In this frame velocity of blood flow has exceeded the Nyquist limit of 0.6 ms^{-1} as a result velocity has been coded in shades of blue as if it were moving in the opposite direction.

AO = aorta LVOT = left ventricular outflow tract

PA = pulmonary artery

In this example which is taken from a later study, the bright echo in the lumen of the pulmonary artery is caused by reflection from the balloon of a Swan Ganz catheter, inserted during comparative studies with thermodilution (chapter 4)

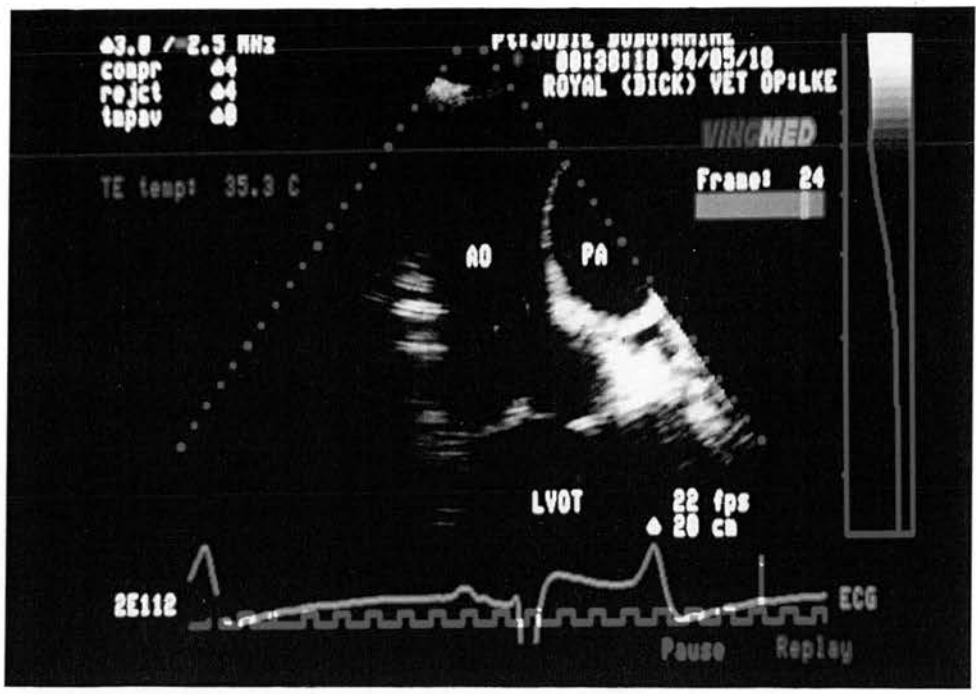

Figure 18: Reference 2-D image of aorta and left ventricular outflow tract from transoesophageal echocardiography

The long axis of the aorta is parallel to the ultrasound beam which results in lateral broadening of the aortic walls.

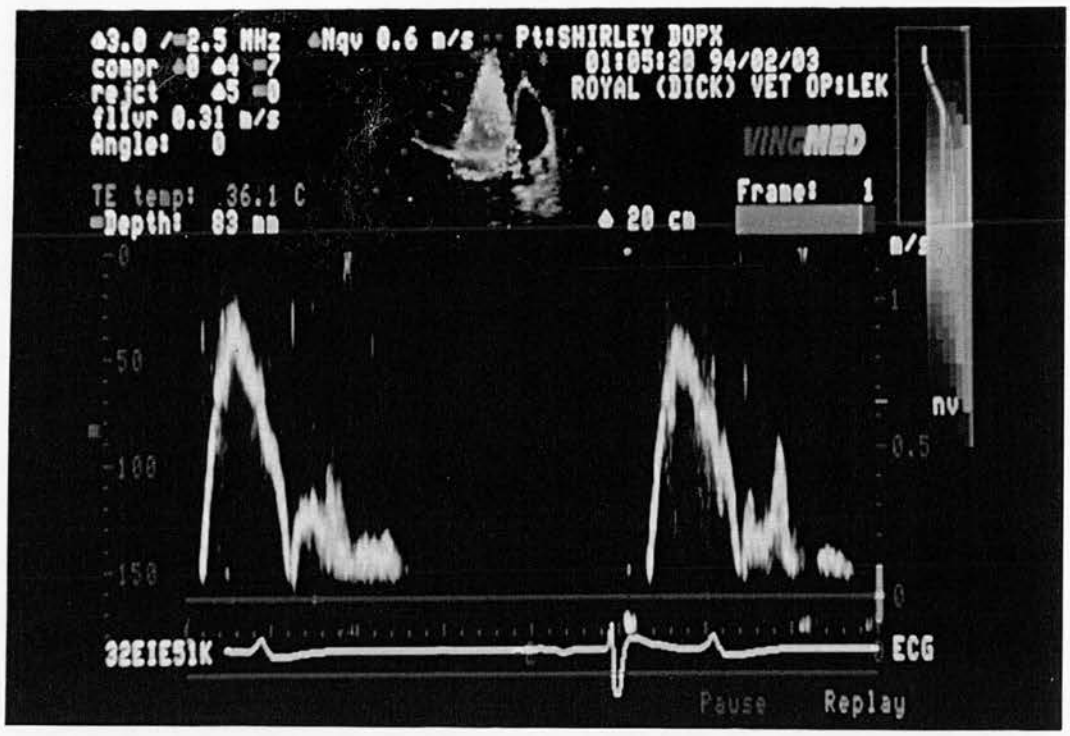

Figure 19: Typical appearance of an HPRF Doppler study of aortic blood flow in an anaesthetised horse

The colour flow study of the aorta and left ventricular outflow tract, used to position the Doppler sample volume, was always frozen during spectral Doppler studies. The shrunken frozen image is displayed above the velocity information.

The velocity scale in ms^{-1} is depicted on the right hand axis. Because blood is flowing towards the transducer it is plotted above the baseline.

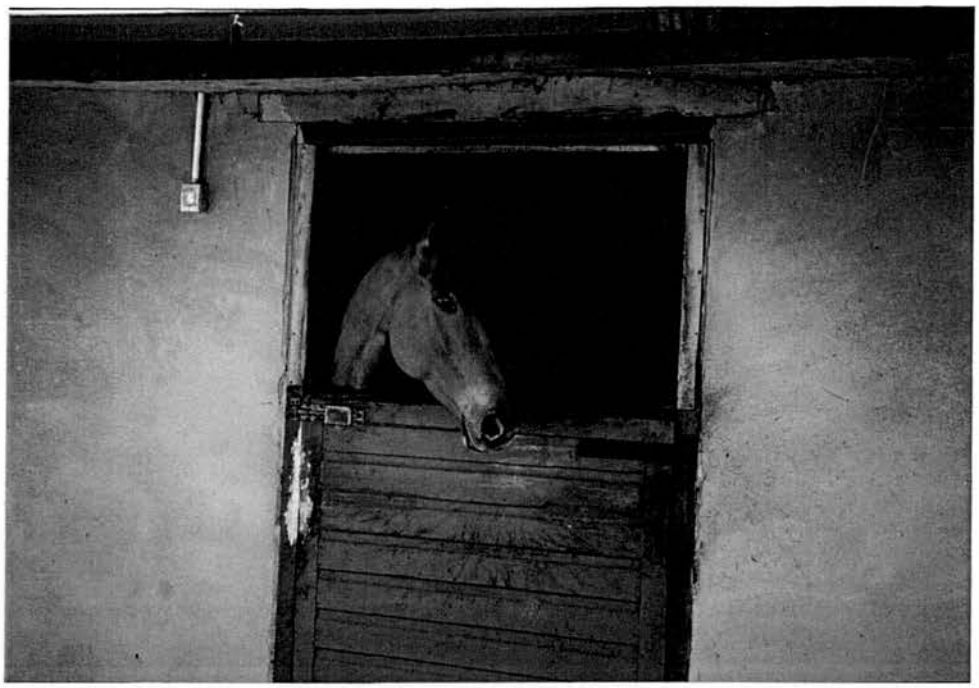

Figure 20: Horse 3, Vivienne.

This horse was consistently the most difficult to intubate, the transoesophageal echocardiography probe always tended to enter the middle, rather than ventral nasal meatus.

The horse was the largest of the group of mares, so the problem is not one of body size. The mare has a long narrow head which tapers towards the nostrils and this may be a guide to the confirmation of the nasal meatus.

CHAPTER 4:

COMPARISON OF CARDIAC OUTPUT MEASUREMENTS FROM TRANSOESOPHAGEAL DOPPLER ECHOCARDIOGRAPHY WITH THOSE OBTAINED BY THERMODILUTION

INTRODUCTION

Transoesophageal Doppler echocardiography provides a non-invasive alternative for measurement of cardiac output in anaesthetised horses. Ideally if a new measurement technique is proposed it should be compared to a standard method which measures the variable with known accuracy (Bland and Altman, 1986). Unfortunately no such standard exists for cardiac output measurement in the intact animal (Schuster and Nanda, 1984). The thermodilution or dye dilution methods have gained widest acceptance in clinical practice and both have been employed in horses (Dunlop, Hodgson and Chapman, 1992; Muir, Skarda and Milne, 1976; Hillidge and Lees, 1975; Fisher and Dalton, 1959). Thermodilution is generally favoured over dye dilution because use of a thermal indicator ensures that multiple measurements can be made in a single individual without indicator accumulation compromising accuracy. The potential for allergic reactions to the dye and the necessity to withdraw blood from the patient are also factors which have encouraged more widespread use of thermodilution (Schuster and Nanda, 1984).

Measurement of cardiac output by thermodilution

In this technique a known volume of cold fluid is injected into the right atrium. A temperature sensor positioned in the pulmonary artery registers the change in temperature caused by dilution of the thermal indicator with the blood. Measurement of cardiac output by thermodilution was first described in anaesthetised dogs by Fegler (1954). A flow directed pulmonary arterial catheter to facilitate thermodilution measurements was subsequently developed by Swan, Ganz, Forrester, Marcus,

Diamond and Chonnette (1970). The catheter contained two lumens, one opening at the distal extremity and the other 10 cm more proximal. The proximal lumen allowed thermal indicator to be administered into the right atrium through the same catheter as housed the thermistor. The distal lumen allowed measurement of pulmonary artery pressure and facilitated sampling of mixed venous blood. The catheter was introduced into clinical use in humans a year later by the same group (Forrester, Ganz, Diamond, McHugh, Chonnette and Swan, 1972). These balloon-tipped, flow-directed catheters are now used extensively for thermodilution measurements in human medicine and have become known as Swan Ganz catheters.

In the thermodilution technique temperature changes in the pulmonary artery are recorded by an analogue computer. The computer measures the area under the blood temperature curve after the thermal injectate has been administered. Cardiac output (CO) is then determined using the following equation:

$$CO = \frac{(\text{Blood Temp} - \text{Injectate Temp}) \times \text{Injectate Volume}}{\text{Integral of the dilution curve}}$$

Temperature is measured in °C
Integral is measured in degree minutes
Volume is measured in mls
Cardiac output is measured in $L.min^{-1}$

The thermodilution technique relies upon accurate measurement of injectate and blood temperature, small errors in either measurement have very large effects on calculated cardiac output. To minimise measurement errors the pulmonary artery temperature must be measured directly, not estimated from rectal temperature, and the injectate temperature should be measured directly by a calibrated thermal sensor placed in the injectate fluid (Levett and Replogle, 1979).

There is conflicting evidence to the relative merits of using iced versus room temperature fluids in the medical literature. Traditionally injectate, cooled to between 0

- 4 °C was recommended as thermal indicator (Sorensen, Bille-Brahe and Engell, 1976; Weisel, Berger and Hechtman, 1975). A large temperature difference between injectate and blood results in increased amplitude of dilution curve. Physiological fluctuations in pulmonary artery temperature, superimposed on the temperature changes caused by cold fluid injection cause relatively greater errors when the curve is of low amplitude (Elkayam, Berkley, Azen, Weber, Geva and Henry, 1983). However there are practical and theoretical problems associated with use of iced injectate which may in themselves cause inaccuracies and counteract the improved signal to noise ratio of the temperature curve. When cold fluids are used the temperature of the injectate can be reduced in the catheter before reaching the right atrium, heat being lost to the surrounding blood and tissues. Such indicator loss is an error inherent in the thermodilution technique, since it is impractical to measure injectate temperature directly at the site of administration. As the temperature differential between injectate and blood is increased by lowering the injectate temperature, the greater is the loss of thermal indicator by this route and the greater the measurement errors (Meisner, Glanert, Steckmeier, Gams, Hagl, Heimisch, Sebening and Messmer, 1973). Second handling and measuring the temperature of iced indicators is more difficult. When fluid has been stored at room temperature, temperature measurement is easily performed and usually truly reflects the temperature of all the fluid in the injectate. In contrast Levett and Replogle (1979) showed that at least 60 minutes are required before a 5 cc syringe containing 5% dextrose solution reaches the same temperature as a surrounding ice bath. The time required for larger volumes (> 40 mls) needed in horses has not been evaluated, but the long equilibration time needed would undoubtedly cause practical difficulties when multiple measurements were to be made.

Both lowering injectate temperature, or increasing its volume will increase the amount of thermal indicator and augment the temperature change registered. If the volume of injectate is increased, the signal to noise ratio of the curve is improved, and

acceptable "dilution curves" can be obtained from room temperature injectate in human patients. In fact clinical studies in humans failed to demonstrate greater reproducibility, or accuracy, in cardiac output measurements when 10 mls of room temperature injectate were used instead of 10 mls of an iced solution (Pearl, Rossenthall, Nielson, Ashton and Brown, 1986; Elkayam, Berkley, Azen, Weber, Geva and Henry, 1983). Use of large injectate volumes probably explains why adequate thermodilution curves have been obtained in adult horses when room temperature saline was used as a thermal indicator (Long, Young, Jones, Darke and Utting, 1992). Although this finding contradicts the findings of Muir, Skarda and Milne (1976), who demonstrated decreased correlation of thermodilution with dye dilution when room temperature injectate was used in horses, this discrepancy can probably be explained by the difference in the reported ambient temperature of the two studies (27 °C for Muir, Skarda and Milne, 1976, and 12 - 15 °C for Long, 1993).

Errors in measurement of cardiac output by thermodilution can also be caused by inadequate mixing of injectate and blood, a situation which results in an irregular thermodilution curves (Pavek, Pavek and Boska, 1970). As a result it is recommended that the shape of the dilution curve should be inspected before any associated measurement is accepted (Levett and Replogle, 1979).

Cardiac output is traditionally calculated from the mean of three individual thermodilution measurements obtained within a period of a few minutes. It has been demonstrated that the variability of the measurement is minimised when this approach is adopted (Elkayam, Berkley, Azen, Weber, Geva and Henry, 1983; Stetz, Miller, Kelly and Raffin, 1982). The optimal timing of thermodilution estimates within the respiratory cycle is also subject to some controversy (Snyder and Powner, 1982). Blood temperature in the pulmonary artery is known to fluctuate with respiration (Alfonso, Herrick, Youmans, Rowe and Crumpton, 1961). This is illustrated by the baseline variations in the early part of the lower trace of Figure 21. The trace is derived

from a thermistor sited in the pulmonary artery of an anaesthetised horse. The inspiratory cycle of the mechanical ventilator in this case results in an overall increase in intrathoracic pressure which elevates the baseline of the upper pulmonary artery pressure trace in Figure 21. From these traces it can be appreciated that the baseline fluctuations in pulmonary artery pressure coincide with those of pulmonary arterial blood temperature. To minimise the effect of this unstable baseline on cardiac output measurements in the present studies the horses were mechanically ventilated and estimates were always obtained during apnoea after the mechanical ventilator was switched off.

The true accuracy of thermodilution for measuring absolute flow remains in doubt. Mackenzie, Haites and Rawles (1986) demonstrated that during conditions of pulsatile flow three commercially available cardiac output computers agreed better with each other than with absolute flow. From this they concluded that factors resulting in lack of accuracy with pulsatile flow affected all computers similarly. Transition from continuous to pulsatile flow in the Mackenzie, Haites and Rawles model doubled the confidence intervals for a single measurement for each computer. All the computers substantially overestimated absolute flow during pulsatile flow conditions. The authors explain this by consideration of the time base of the flow calculation. A true estimate of flow will only be obtained if the time base used for the integration comprises a whole number of cardiac cycles. If the sample starts and ends during a period of diastole or static flow, cardiac output will be underestimated, the reverse occurring if computation starts and ends during systole, a high flow period. Individual computers also differ in the method used to integrate under the thermodilution curve, especially in defining the tail of the curve. The shorter the time base used for integration the greater will be the sampling errors during pulsatile flow conditions. Arrythmias provide an additional source of error, and the high incidence of second degree atrioventricular block and

sinus arrhythmia in thoroughbred horses can increase sampling errors for thermodilution measurements in this species.

Despite widespread acceptance in clinical medicine studies evaluating the accuracy of the thermodilution technique are lacking. Apart from the study performed by Mackenzie, Haites and Rawles (1976) most in vitro studies have utilised continuous flow models, which are likely to overestimate the accuracy and repeatability of the technique. Accuracy of the technique in a high flow, low frequency, pulsatile model, corresponding to the situation in horses not been addressed. Jarvis, Woliner and Steffey (1992) evaluated a commercial thermodilution computer at flows between 8 and 50 $L.min^{-1}$ in an artificial circulation. However use of a continuous flow pump in their model means their results may not represent the in-vivo situation. The majority of in-vivo studies have evaluated the technique against estimates of cardiac output by dye dilution in both humans (Ganz, Donoso, Marcus, Forrester and Swan, 1971) and horses (Dunlop, Hodgson and Chapman, 1992; Muir, Skarda and Milne, 1976). However both techniques are indicator dilution methods, and are therefore subject to similar errors, calling the validity of this comparison into question (Stetz, Miller, Kelly and Raffin, 1982). Despite these technical limitations many authors conclude that provided that the sources of error are fully appreciated and the technique is standardised, the thermodilution method provides as reasonable a means of cardiac output measurement as the other techniques available (Schuster and Nanda, 1984; Levett and Replogle, 1979), and therefore can be used as a reference method (Stetz, Miller, Kelly and Raffin, 1982).

Aims of Chapter 4

Cardiac output estimations made by transoesophageal echocardiography were compared to those obtained using thermodilution in anaesthetised horses over a range of cardiac output. For each Doppler derived estimate two separate comparisons were made; the first using a thermodilution estimate derived simultaneously and the second

using a composite mean of three thermodilution measurements made in quick succession. Spectra were obtained using both continuous wave (CW) and high pulse repetition frequency Doppler (HPRF) echocardiography and both techniques were compared to thermodilution.

MATERIALS AND METHODS

Horses and preparation

The eight thoroughbred horses described in Appendix 1 were the subjects of this study. Each horse was anaesthetised and instrumented for transoesophageal echocardiography as described previously. General anaesthesia was maintained with halothane at an end expired concentration of 0.9%. Intermittent positive pressure ventilation was performed by a mechanical ventilator to maintain arterial $PaCO_2$ between 35 to 45 mmHg.

Once positioned on the operating table two percutaneous catheter introducer sets[38] were inserted into the horse's right jugular vein, using the percutaneous Seldinger technique (Grossman, 1992). A 150 cm long thermodilution catheter[39] (OD = 2.31 mm) was inserted through one introducer until pressure recordings from it's distal port indicated that it was situated in the pulmonary artery. Pressure waveforms were derived by connecting the distal catheter lumen, via a fluid line, to a disposable strain gauge transducer[40]. The strain gauge transducer was connected to an amplifier within the cardiac output computer whose output was displayed on one channel of a two channel chart recorder[41] (Figure 21).

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[38] Haemaquet, 9F. Bard Ltd, Forest House, Brighton Road, Crawley, West Sussex, England, UK.
[39] Columbus Instruments, 950N North Hague Avenue, Columbus Ohio, USA.
[40] DTX Plus Transducer, Viggo-Spectramed, Faraday Road, Dorcan, Swindon, Wiltshire, UK.
[41] Multitrace 2, Lectromed Ltd, Unit 26, The Business Centre, Avenue One, Letchworth Garden City, Hertfordshire, England, UK.

The thermodilution catheter was equipped with a proximal port, but high internal resistance to flow precluded it's use for thermal indicator administration. A separate introducer catheter was made for this purpose from a 200 cm length of polyethylene tubing[42] (OD = 1.6 mm). The atrial end of the catheter was sealed closed by heat from a Bunsen burner. Five holes (D = 0.5 mm) were then pierced along the final 4 cm of catheter body, using a hot 14 gauge intravenous needle. The open end of the tubing was forced over the body of 14 gauge intravenous needle. The hub of the needle was then connected to the pressure injector. A test injection of 45 mls of fluid was then made through the catheter using the pressure injector to ensure that flow occurred evenly through the side holes and that injection was completed within 3 seconds. The catheter was then sterilised using ethylene oxide.

The catheter was pre-filled with heparinised saline (5 IU per ml) and introduced into the right atrium by advancing it down the second percutaneous introducer set. For location in the right atrium the polyethylene catheter was connected to the pressure transducer, and advanced down the introducer until a characteristic right ventricular pressure waveform was obtained. It was then withdrawn until the pressure trace indicated it had just re-entered the right atrium. With the catheter in position a test injection with 45 mls of 0.9% saline was carried out whilst observing a two dimensional (2-D) image of the right atrium obtained by transthoracic echocardiography. Correct catheter placement was confirmed by the sudden short-lived appearance of multiple echogenic speckles in the right atrium, coinciding with injection. These echoes were caused by microbubbles present in the injectate. This simple technique to provide echogenic contrast is widely used in clinical echocardiography to diagnose atrial septal defects and right to left intracardiac shunts (Carlsten and Nilfors, 1986). At intervals throughout each study (before each new batch of measurements

[42] 800/200/225, Portex, Arterial Medical, Arterial House, 313 Chase Road, South Gate, London, UK.

began) the contrast technique was repeated to confirm that the atrial catheter was still correctly positioned.

MEASUREMENT OF CARDIAC OUTPUT

Thermodilution technique

A Cardiomax II model 85 cardiac output computer[43] was used to measure cardiac output by thermodilution. Blood temperature was measured directly from the thermistor situated on the indwelling pulmonary arterial catheter.

For the Cardiomax II a calorific difference of at least 100 calories is necessary to obtain dilution curves that are adequate for integration[44]. Calorific difference was calculated from the equation:

Calorific difference = (Blood Temp - Injectate Temp) x Injectate Volume

Blood temp and injectate temp are measured in °C
Injectate Volume is measured in mls
Calorific difference is measured in calories

Previous work using the same instrument demonstrated that satisfactory dilution curves could be obtained from standing horses when 45 mls of room temperature saline was injected using a pressure injector through a separate catheter in the right atrium (Long, Young, Jones, Darke and Utting, 1992). This combination of injectate temperature and volume exceeds the minimum calorific difference specified by the manufacturers of the Cardiomax II. The pressure injector was driven by compressed air at an operating pressure of 30 pounds per square inch (psi) which ensured that the charge of 45 mls of injectate was delivered within 3 seconds, as recommended by Ganz and Swan (1972). The dilution curves were displayed on the second channel of the two channel chart recorder allowing visual inspection of each curve. Only measurements

[43] Columbus Instruments, 950N North Hague Avenue, Columbus Ohio, USA.
[44] Cardiomax II Model 85, Operators instruction manual, Columbus Instruments, 950N North Hague Avenue, Columbus Ohio, USA.

from dilution curves with a characteristic fast attack slope and a slower return to baseline were accepted (Figure 21: lower trace). Cardiac output estimations derived from curves which did not satisfy these criteria were excluded.

Injectate temperature was measured using a calibrated platinum thermistor supplied with the Cardiomax II. The probe was placed in an upturned plastic 50 ml syringe case which contained 0.9% saline solution. The syringe case was fixed to the front of the computer unit, which was stored in the operating room throughout the studies. The bags containing 0.9% saline, used as thermal indicator, were also stored at the same temperature. The injectate temperature was not measured directly by the thermistor but equilibration of both injectate fluid and the saline surrounding the platinum probe with ambient temperature was assumed. During these studies the ambient temperature varied between 14.4 and 19.2 °C.

Doppler echocardiographic technique

Data from HPRF and CW transoesophageal echocardiographic studies were measured by a single observer from video-taped images of aortic blood velocity spectra. Cardiac output was calculated from aortic velocity spectra using the equation:

Cardiac output = VTI x aortic cross sectional area x heart rate

VTI = Area under the velocity spectra (velocity time interval)

Area under individual velocity envelopes (VTI) was measured by manually tracing the spectra using the keyboard track-ball. The resultant area was digitised by software within the echocardiograph. The modal velocity or brightest line in the velocity envelope, was used to delineate the area beneath spectra derived from HPRF studies (Figure 22), whilst maximum velocity was used for CW envelopes (Figure 23). Doppler signals from 5 consecutive cardiac cycles were measured for each cardiac output estimation and the mean velocity time interval and heart rate for the group of five

cycles was then calculated. Heart rate was calculated from the 5 corresponding RR intervals from the electrocardiogram of the ultrasonograph.

Aortic cross-sectional area

Cross sectional area of the aorta was calculated using the equation:

$$\text{Aortic cross sectional area} = 3.14 \times (\text{radius})^2$$

Three separate estimates of aortic radius were obtained by measuring the diameter from three different 2-D echocardiographic images of the aorta. The first was obtained at the sino-tubular junction from a standard 2-D transoesophageal image (Figure 24). In this view the anatomical boundaries of the vessel are parallel to the ultrasound beam, resulting in considerable lateral broadening and poor lateral resolution (Feigenbaum, 1993). According to the recommendations of Hatle and Angelsen (1985a) the diameter was measured perpendicular to its long axis by a line joining the middle of the band of echoes corresponding to the vessel walls.

Since optimal resolution of anatomical structures occurs when the ultrasound beam is perpendicular to the acoustic interface (Feigenbaum, 1993), two further estimates of vessel diameter were obtained from transthoracic echocardiography. A parasternal long axis view of the aorta was obtained from the right axilla using the 2.35 MHz probe (Long, Bonagura and Darke, 1992). The diameter of the vessel was measured above the sinuses of Valsalva by a leading edge to leading edge method (Figure 25). The final measurement was obtained from a similar right parasternal view, angled slightly to bring the left ventricular outflow tract into long axis (Figure 26). The diameter of the aortic valve annulus was then measured from its trailing edge to leading edge. This methodology was employed because these interfaces were usually best defined for caliper placement.

To obtain each diameter, three measurements from each site were taken during systole from three consecutive cardiac cycles and an average figure obtained. The 2-D images needed for the measurements were recorded onto video tape immediately before each study period. Three separate cardiac output calculations were then made using the three estimates of vessel area for every Doppler echocardiographic recording.

Timing of cardiac output measurements

Mechanical ventilation was discontinued before each cardiac output measurement, the ventilator was switched off in the expiratory pause just after an inspiratory cycle was complete. Injection of thermal contrast was initiated by pressing the pressure injector foot pedal, to coincide with the second 'p' wave of the ECG after the ventilator was stopped. The record facility of the VHS video recorder on the Vingmed CFM 700 was was also activated. Spectral Doppler data were recorded until a complete thermodilution curve had been traced on the two channel chart recorder, or at least five complete spectra had been recorded. Provided the dilution curve was acceptable the computed thermodilution cardiac output value was labelled with a time in hours, minutes and seconds. The time coincided with the end of the injection of cold contrast indicated by the sound of the pressure injector barrel refilling, it was read from the internal clock of the echocardiograph. Since this time was also recorded onto the video tape with the velocity spectra it ensured that the measurements made later from Doppler data were simultaneous with the corresponding measurement by thermodilution.

According to the manufacturers instructions at least 60 seconds were allowed to elapse between consecutive thermodilution measurements. The insonation mode of the Doppler echocardiograph was changed from HPRF to CW and a second thermodilution cardiac output measurement was made to coincide with recording of resultant velocity spectra. The final, third thermodilution measurement was made without a corresponding Doppler recording.

In the study two separate comparisons between CW and HPRF derived cardiac output estimations and thermodilution measurements were made. Both HPRF and CW spectra were paired with a thermodilution measurement obtained simultaneously. This was used to provide the instantaneous value for the first comparison (instantaneous). For each pair of HPRF and CW spectra a total of three thermodilution cardiac output values were available (1 simultaneous with HPRF, 1 with CW, and 1 taken in isolation). The three thermodilution estimates were always obtained within four minutes of each other. The three measurements were then averaged to give a mean value, which was used for the second of the comparisons of thermodilution with both HPRF and CW techniques (mean of 3 thermodilution).

Study protocol

A group of five sets of three thermodilution measurements with associated Doppler recordings constituted a set of data for each horse at each cardiac output level. After the first group of 5 sets was complete the cardiac output was increased by the continuous infusion of the β_1 adrenoreceptor agonist, dobutamine[45], at 2 $\mu g.kg^{-1}.min^{-1}$ through a pre-placed jugular catheter. After fifteen minutes cardiac output estimations were repeated. The infusion rate was then increased to 4 $\mu g.kg^{-1}.min^{-1}$, and after a further 15 minutes, the final set of cardiac output data were collected. At the start of each data acquisition period 2-D images were recorded from transoesophageal and transthoracic echocardiography. This allowed vessel area to be determined at each level of cardiac output. If the dobutamine infusion produced any disturbance to cardiac rhythm that was considered to be a risk to the horse, the infusion was discontinued and the procedure was terminated.

Statistical analysis

Cardiac output estimates by Doppler echocardiography were plotted against the thermodilution estimate. The resultant scatter plots allowed the linear relationship

[45] Dobutamine hydrochloride, Dobutrex, Eli Lilley & Co, Basingstoke, UK.

between the two set of variables to be assessed as recommended by Bland and Altman (1986). Separate plots for all 3 calculations of cardiac output by Doppler echocardiography obtained from each vessel area and each mode of insonation (HPRF and CW) were produced (Appendix Chapter 4: Graphs 1a - 12a, Page 244). The Doppler estimates were plotted against both the instantaneous thermodilution cardiac output measurement and the mean of three consecutive measurements. Linear relationships between the variables were assessed by calculation of the product-moment correlation coefficient (r). Agreement between the two techniques was assessed using the methods of Altman and Bland (1983). This technique is used when both measurement methods are subject to individual errors and neither measures the variable absolutely. The best estimate of the 'true' value is considered to be the mean of the two techniques. The difference between the two measurements is then plotted against the mean value. Visual appraisal of the resultant plot may then indicate any relationship between the measurement error and the true value. The bias of the Doppler technique was calculated from the mean of the differences between Doppler and thermodilution measurements, 95% confidence intervals for the bias were also determined. The limits of agreement of the two techniques as defined by Bland and Altman (1986) were calculated by adding or subtracting twice the standard deviation of the differences between techniques to the calculated bias. To allow comparison of these results with those from previous studies the differences between the two methods were expressed as a percentage of the thermodilution method. The mean and standard deviation of the percentage differences were then calculated.

The three measurements of aortic diameters were compared with each other before and after dobutamine, using a Kruskal-Wallis test. A probability of < 0.05 was considered to indicate a significant difference or change in the data. Where significant differences were found a paired Wilcoxon test was used to examine differences between individual measurements or treatments .

RESULTS

A total of 95 comparisons of cardiac output estimations from Doppler and thermodilution techniques were made using the various measurement methods and both insonation modes. Only five estimates were taken from Horse 6, since supraventricular tachycardia (rate 186 bpm) commenced 10 minutes after starting the 2 $\mu g.kg^{-1}.min^{-1}$ infusion of dobutamine. In Horse 7 atrial fibrillation occurred during infusion of 2 $\mu g.kg^{-1}.min^{-1}$ dobutamine, the heart rhythm then returned to normal sinus rhythm during recovery from anaesthesia. Estimations made in this study were not included in the analysis, as the study was repeated after 1 month. Supraventricular tachycardia (rate >150 bpm) occurred in Horses 4, 5 and 8 during infusion of 4 $\mu g.kg^{-1}.min^{-1}$ dobutamine, before cardiac output estimates had been made, thus only ten data points are included from each horse.

The range of cardiac outputs measured by thermodilution during the study was between 14.1 and 65.4 $L.min^{-1}$. Graphs 1a to 12a (Appendix Chapter 4, Page 244) are scatter plots of the cardiac output estimations derived from Doppler echocardiography against those obtained by thermodilution. Product moment correlation coefficients are detailed in Table 5. There was a significant linear correlation between all Doppler derived cardiac output estimates (both CW and HPRF modes) and thermodilution measurements (both instantaneous and the mean of three consecutive measurements). Estimations of cardiac output by Doppler echocardiography showed closer correlation with thermodilution measurements when the HPRF insonation mode was employed. The best linear relationship, $r = 0.94$, was achieved when aortic diameter was obtained by transthoracic echocardiography measured at the sino-tubular junction using the leading edge method and the comparison was made with simultaneous thermodilution measurements.

Graphs 1b to 12b show the differences in the cardiac output estimations plotted against the mean of the two techniques. In these figures individual data points are coded using each horse's numeric. From these plots the differences between techniques are most pronounced for data from Horses 4 and 8. Summary statistics of the differences between techniques are given in Table 6. The 95% confidence intervals for the mean (or bias) of the differences and the limits of agreement of the techniques are shown in Table 7. Estimates of cardiac output by Doppler echocardiography tended to overestimate those obtained by thermodilution. This is shown by the positive 95% confidence intervals for the bias of the two techniques in all comparisons, except when the aortic annulus diameter is used to estimate cardiac output from HPRF waveforms. Overall the limits of agreement between the two techniques were narrower and the bias was less when the HPRF insonation mode was used to obtain the Doppler spectra. The limits of agreement are wider for both modes of insonation when the vessel diameter is obtained from a transthoracic image of the aortic valve annulus. Limits of agreement are similar when comparisons with Doppler techniques are made using either a single simultaneous thermodilution measurement or a mean of three consecutive measurements. The closest agreement between the two techniques was obtained when the instantaneous thermodilution measurement was compared to the Doppler estimate made from HPRF waveforms, and the vessel diameter was measured from a transthoracic image using the leading edge method.

The differences between measurements by Doppler and thermodilution did not increase with increasing cardiac output (Graphs 1b to 12b, Pages 245 - 256). Summary statistics of the differences expressed as a percentage of the thermodilution measurement are detailed in Table 8.

Aortic diameter at the sino-tubular junction measured from transthoracic echocardiography was significantly greater than the same diameter from transoesophageal echocardiography and the aortic annulus diameter from transthoracic

echocardiography. The aortic diameter at the valve annulus was significantly less than all other estimates (Table 9). There were no significant changes to any of the aortic measurements with either dobutamine at 2 $\mu g.kg^{-1}.min^{-1}$ or 4 $\mu g.kg^{-1}.min^{-1}$ (Table 10).

Table 5 : Product - moment correlation coefficients and probability values for the relationship between transoesophageal Doppler estimations of cardiac output and those obtained by thermodilution. N = number of estimates, r = correlation coefficient, Graph refers to figure number of the appropriate scatter plot of Doppler against thermodilution measurements in Appendix Chapter 4.

High pulse repetition frequency mode

2-D measurement	N	r	p	Graph
<u>Instantaneous thermodilution</u>				
Leading edge (transthoracic)	95	0.94	0.00000	1a
Centre wall (transoesophageal)	95	0.93	0.00000	2a
Valve annulus (transthoracic)	95	0.90	0.00000	3a
<u>Mean of 3 thermodilution</u>				
Leading edge (transthoracic)	95	0.93	0.00000	4a
Centre wall (transoesophageal)	95	0.93	0.00000	5a
Valve annulus (transthoracic)	95	0.90	0.00000	6a

Continuous wave mode

2-D measurement	N	r	p	Graph
<u>Instantaneous thermodilution</u>				
Leading edge (transthoracic)	95	0.90	0.00000	7a
Centre wall (transoesophageal)	95	0.89	0.00000	8a
Valve annulus (transthoracic)	95	0.89	0.00000	9a
<u>Mean of 3 thermodilution</u>				
Leading edge (transthoracic)	95	0.91	0.00000	10a
Centre wall (transoesophageal)	95	0.92	0.00000	11a
Valve annulus (transthoracic)	95	0.90	0.00000	12a

Table 6: Summary statistics of differences between cardiac output measurements by Doppler echocardiography and those obtained by thermodilution in eight anaesthetised horses. S.D. = standard deviation of differences, MIN = maximum underestimation of thermodilution estimate, MAX = maximum overestimation of thermodilution estimate. All values are in litres per minute. Total number of estimates = 95.

High pulse repetition frequency mode

2-D measurement	mean	S.D.	MIN	MAX
<u>Instantaneous thermodilution</u>				
Leading edge (transthoracic)	3.7	3.7	-10.8	13.3
Centre wall (transoesophageal)	1.1	4.2	-12.4	10.2
Valve annulus (transthoracic)	-0.9	5.2	-17.3	8.9
<u>Mean of 3 thermodilution</u>				
Leading edge (transthoracic)	3.3	3.9	-10.8	13.7
Centre wall (transoesophageal)	0.7	4.2	-12.4	10
Valve annulus (transthoracic)	-1.3	5.3	-17.3	8.1

Continuous wave mode

2-D measurement	mean	S.D.	MIN	MAX
<u>Instantaneous thermodilution</u>				
Leading edge (transthoracic)	7.2	5.3	-8.4	22.7
Centre wall (transoesophageal)	4.1	4.7	-15.4	17.9
Valve annulus (transthoracic)	1.4	4.8	-16.1	11.5
<u>Mean of 3 thermodilution</u>				
Leading edge (transthoracic)	7.1	5.0	-5.0	19.8
Centre wall (transoesophageal)	4.0	4.4	-10.2	15.0
Valve annulus (transthoracic)	1.3	4.8	-12.2	10.2

Table 7: Confidence intervals for the bias (mean difference between techniques) and limits of agreement between Doppler and thermodilution methods of cardiac output measurement. Limits of agreement are mean difference +/- 1.96 x the standard deviation of the difference. All values are in litres per minute. Total number of estimates = 95.

High pulse repetition frequency mode

2-D measurement	Bias	95% confidence interval of mean	Limits of agreement
<u>Instantaneous thermodilution</u>			
Leading edge (transthoracic)	3.7	3.0 - 4.5	-3.7 - 11.1
Centre wall (transoesophageal)	1.1	0.2 - 1.9	- 7.3 - 9.5
Valve annulus (transthoracic)	-0.9	-2.0 - 0.2	- 11.3 - 9.5
<u>Mean of 3 thermodilution</u>			
Leading edge (transthoracic)	3.3	2.5 - 4.1	-4.5 - 11.1
Centre wall (transoesophageal)	0.7	-0.2 - 1.6	-7.7 - 9.1
Valve annulus (transthoracic)	-1.3	-2.4 - 2.1	-11.9 - 9.3

Continuous wave mode

2-D measurement	Bias	95% confidence interval of mean	Limits of agreement
<u>Instantaneous thermodilution</u>			
Leading edge (transthoracic)	7.2	6.1 - 8.3	-3.4 - 17.8
Centre wall (transoesophageal)	4.1	3.1 - 5.0	-5.4 - 13.5
Valve annulus (transthoracic)	1.4	0.4 - 2.4	-8.1 - 10.9
<u>Mean of 3 thermodilution</u>			
Leading edge (transthoracic)	7.1	6.1 - 8.1	-2.9 - 17.1
Centre wall (transoesophageal)	4.0	3.0 - 4.9	-4.9 - 12.8
Valve annulus (transthoracic)	1.3	0.3 - 2.3	-8.2 - 10.8

Table 8: Difference between Doppler derived estimates of cardiac output and those obtained by thermodilution, expressed as a percentage of the thermodilution measurement. Total number of estimates = 95.

High pulse repetition frequency mode

2-D measurement	Mean % difference	Maximum % overestimation	Maximum % underestimation
Instantaneous thermodilution			
Leading edge (transthoracic)	18	65	15
Centre wall (transoesophageal)	8	56	22
Valve annulus (transthoracic)	1	49	32
Mean of 3 thermodilution			
Leading edge (transthoracic)	16	68	17
Centre wall (transoesophageal)	6	58	23
Valve annulus (transthoracic)	0	41	33

Continuous wave mode

2-D measurement	Mean % difference	Maximum % overestimation	Maximum % underestimation
Instantaneous thermodilution			
Leading edge (transthoracic)	31	94	18
Centre wall (transoesophageal)	19	75	33
Valve annulus (transthoracic)	9	51	38
Mean of 3 thermodilution			
Leading edge (transthoracic)	30	81	16
Centre wall (transoesophageal)	19	70	25
Valve annulus (transthoracic)	9	51	38

Table 9: Median, maximum and minimum values in cm of aortic diameters obtained from transthoracic and transoesophageal 2-D echocardiography in 8 horses during 0.9% end tidal halothane anaesthesia.

Vessel Diameter	Leading edge (transthoracic)	Centre wall (transoesophageal)	Annulus (transthoracic)
Median	7.23^{bc}	$7.\ 10^{ac}$	6.61^{ab}
Maximum	7.74	7.58	7.20
Minimum	6.70	6.53	6.30

[abc] significantly different measurement of aortic diameter from that obtained at other sites ($p < 0.01$ using a Kruskal-Wallis test) :

[a] different from vessel diameter measured from transthoracic echocardiography using the leading edge to leading edge method.

[b] different from vessel diameter measured from transoesophageal echocardiography using the Centre wall to Centre wall method.

[c] different from aortic valve annulus diameter measured from transthoracic echocardiography using the trailing edge to leading edge method.

Table 10: Median value (range in parentheses) of aortic diameter (cm) before and during dobutamine infusion. Kruskal-Wallis test revealed no significant differences in any vessel diameters during the infusion periods. P values are recorded in right hand column. 1 = 0.9% halothane, 2 = 0.9% halothane after 15 minutes infusion of 2 $\mu g.kg^{-1}.min^{-1}$ dobutamine, 3 = 0.9% halothane after 15 minutes infusion of 4 $\mu g.kg^{-1}.min^{-1}$ dobutamine

Vessel Diameter	1	2	3	p value
Leading edge aorta (transthoracic)	7.23 (6.70 - 7.74)	7.17 (6.70 - 7.64)	7.20 (6.76 - 7.51)	0.52
Centre wall (transoesophageal)	7.10 (6.53 - 7.58)	7.07 (6.48 - 7.50)	7.16 (6.48 - 7.65)	0.95
Aortic valve annulus (transthoracic)	6.61 (6.30 - 7.2)	6.58 (5.64 - 7.20)	6.68 (5.64 - 7.20)	0.91

DISCUSSION

Estimations of cardiac output by Doppler echocardiography showed a close linear relationship with measurements obtained by thermodilution. The correlation between the Doppler technique and thermodilution in the present study is higher than that determined for man in similar studies using transoesophageal echocardiography. In the human studies blood flow across the mitral and pulmonary valves, not the aortic valves, were most commonly used to obtain velocity spectra for measurement of VTI (Gorcsan, Diana, Ball and Hattler, 1992; Muhiudeen, Kuecherer, Lee, Cahalan and Schiller, 1991; LaMantia, Carter, Davis and Ezekowitz, 1990; Ellis, Runyon-Hass, Lichtor and Roizen, 1967). Mitral and pulmonary blood flows were chosen because of superior alignment with the ultrasound beam from an oesophageal transducer. The poor correlations obtained in these studies (0.65 - 0.80) may reflect difficulties in measurement of the mitral and pulmonary valve areas (Sahn, 1985). In biped species the descending aorta runs parallel to the oesophagus, therefore it is difficult to align aortic blood flow and ultrasound from an oesophageal transducer. One group of workers compared cardiac output calculations from human aortic blood flow profiles obtained by transoesophageal echocardiography with measurements by thermodilution (Perrino, Fleming and LaMantia, 1990). Due to the wide angle of incidence between the beam and the descending aorta, the device had to be calibrated by calculating a constant from a second transcutaneous Doppler transducer placed in the suprasternal notch. Although these workers obtained a correlation of 0.91 between the two techniques and limits of agreement within 26% of the mean cardiac output, the technique is not widely used, probably due to the cumbersome calibration process (Perrino, Fleming and LaMantia, 1991).

In horses the anatomical relationship of aorta and oesophagus differs from humans and a transducer within the oesophagus can be aligned perfectly with the

ascending aorta. This probably explains why the agreement and linear relationships obtained by transoesophageal techniques in horses is better than for previously reported human studies. The correlations obtained in the equine transoesophageal studies are similar to those obtained in numerous human studies using transthoracic echocardiography (Dubin, Wallerson, Cody and Devereux, 1990; Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984; Nishimura, 1984; Huntsman, Stewart, Barnes, Franklin and Colocousis, 1983). Cardiac output estimations using transthoracic Doppler echocardiography are now widely used in human medicine (Haites, McLennan, Mowat and Rawles, 1984), and it is generally accepted that the estimates derived from Doppler echocardiography agree as well with the standard methods (Fick principle, thermal and dye dilution) as the standard methods agree with themselves (Schuster and Nanda, 1984).

Similar studies have been performed in standing horses when cardiac output estimations from aortic velocity spectra derived by transthoracic echocardiography were compared with measurements made by thermodilution (Long, Young, Jones, Darke and Utting, 1992). Overall the linear relationship and limits of agreement of the two techniques were consistently worse from the transthoracic studies in standing horses than was found in the present transoesophageal studies in anaesthetised horses. Poor alignment with aortic blood flow would consistently underestimate volumetric flow, but have little effect upon the limits of agreement. In the previous transthoracic studies in standing horses the narrowest limits of agreement were -12.89 - 11.83 $L.min^{-1}$ (Long, 1993) compared to -3.70 - 11.10 $L.min^{-1}$ from the present studies. Both these values were obtained when vessel area was calculated using an aortic diameter obtained from a transthoracic 2-D image. Since the technique of vessel area measurement was common to both Doppler methods, the narrower limits of agreement in the transoesophageal study must reflect more consistent alignment with blood flow in individual horses. The reference long axis 2-D image obtained from transoesophageal echocardiography that

was used to guide placement of the Doppler sample volume was obtained repeatably in every horse and the image did not appear to vary between individuals. Marked inter-subject variation in correlation between transthoracic Doppler measurements of cardiac output and those from the thermodilution and Fick methods has been reported previously in humans (Christie, Sheldahl, Tristani, Sagar, Ptacin and Wann, 1987). This variability remained when flow area was removed from the calculation of cardiac output. Other workers have also noted variation in alignment between ultrasound beam and aorta in individual patients during transthoracic echocardiography (Angelsen and Brubakk, 1976; Sequeira, Light, Cross and Raftery, 1976). Within-subjects measurement error also occurs in transthoracic echocardiography as the transducer must be re-aligned with blood flow for each measurement. In transoesophageal echocardiography, once in position, the transducer remains stationary in the oesophagus.

Further errors may have occurred due to movement of conscious horses; small movements between the transducer and the thoracic wall, e.g. associated with ventilation, have a marked effect on the position of the sample volume which is located 18 cm from the skin surface. Although large changes in alignment would be obvious to the operator from visual and audible changes in the spectra, small alterations in angulation may have been more difficult to detect. In the present transoesophageal studies the spectra were recorded from the oesophagus of an anaesthetised horse during apnoea. This should have eliminated the alignment errors caused by motion and may explain the narrower limits of agreement associated with the transoesophageal technique.

There is a high prevalence of dysrhythmias in conscious horses; sinus arrhythmia, second degree atrioventricular (AV) block and sinus blocks are common (Hamlin, Klepinger, Gilpin and Smith, 1972). Blocked beats will increase the loss of thermal indicator causing overestimation of cardiac output by thermodilution. This may

have resulted an errors in the previous transthoracic studies. In the present study Horses 4 and 8 had marked sinus arrhythmia during infusion of dobutamine. These animals appeared most frequently as outlying points in graphs 1b - 12b (Appendix Chapter 4, Page 244), Since the time base of a single thermodilution measurement is short, it is possible for cardiac output to be over or underestimated, depending at what stage in the arrhythmia the measurement is made (Mackenzie, Haites and Rawles, 1986). In many of the human studies it is stated that patients who were not in normal sinus rhythm were excluded from the study groups (Gorcsan, Diana, Ball and Hattler, 1992; Ryan, Page, Bouchier-Hayes and Cunningham, 1992). Such stringent exclusion criteria cannot be applied to adult Thoroughbred horses. In the present study data were only excluded from the one horse which developed iatrogenic atrial fibrillation. However it is possible that other more benign rhythms such as mild sinus arrhythmia or second degree atrioventricular block may have affected the accuracy of both the thermodilution and Doppler echocardiographic techniques in both the present and previous studies.

In the previous studies using the transthoracic approach in standing horses (Long, 1993) the best correlation coefficient, lowest bias and narrowest limits of agreement between techniques were obtained when the ascending aortic diameter was measured by the leading edge method. This method of measurement of vessel diameter also gave the closest agreement with thermodilution in the present transoesophageal study. Similar correlation coefficients and limits of agreement and a lower bias between thermodilution and transoesophageal-derived Doppler measurements were obtained when aortic diameter was measured from a 2-D transoesophageal image. It can be concluded therefore that transoesophageal echocardiography provides a suitable 2-D image for derivation of aortic area for cardiac output determinations in anaesthetised horses. This is convenient, as the same transducer can be used for acquisition of data for both flow and cross-sectional area.

In the present study estimates of cardiac output derived from the aortic diameters obtained by both transthoracic and transoesophageal echocardiography overestimated cardiac output when compared with thermodilution, a finding which has previously been reported in human studies (Ryan, Page, Bouchier-Hayes and Cunningham, 1992; Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984).

Mathematical considerations dictate that the vessel should be measured at the same anatomical location as the flow velocity. However in humans and dogs the flow velocity has been shown to be constant at different centre-line positions in the aorta (Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984; Fisher, Sahn, Friedman, Larson, Valdez-Cruz, Horowitz, Goldberg and Allen, 1983), indicating that velocity measured by Doppler echocardiography is relatively insensitive to the vertical location of the Doppler sample volume. A study in thoracotomised dogs confirmed this hypothesis, the vertical position of the sample volume making no significant difference to the agreement between aortic flow by pulsed Doppler echocardiography and the volumetric flow produced by the roller pump providing the artificial circulation (Brubakk and Givold, 1985).

It has been suggested that because the left ventricle ejects through a narrow valve orifice into a much larger aortic root, the inelastic aortic annulus effectively restricts flow to its cross sectional area, and the area through which most of the flow occurs is less than the anatomical aortic root area. As a result the area of the aortic valve annulus has been proposed to provide the best estimate of the true flow area (Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984). This hypothesis may explain why, in the present studies, when the aortic annulus measurement was used to derive aortic diameter, the value of cardiac output obtained, more closely approximated that derived from the thermodilution technique. Despite this, the correlation between techniques was poorer and the limits of agreement more widely separated than when the sino-tubular junction measurement was used. This probably

reflects greater difficulties in imaging the aortic annulus compared to the sino-tubular junction in individual horses. Errors in measurement of vessel diameter are magnified because the derived radius is then squared in the calculation of flow area. Poorly aligned or inconsistent images of the vessel which cause inaccurate diameter measurements will cause large errors in flow calculation. In the present studies although the calculations using measurements of the aorta at the sino-tubular junction considerably overestimated cardiac output measured by thermodilution, the narrower limits of agreement and closer linear relationship with the thermodilution technique render the use of the sino-tubular junction area preferable in anaesthetised horses.

An in-vitro study in thoracotomised dogs (Loeber, Goldberg, Marx, Carrier and Emery, 1987) showed that the areas of both aorta and pulmonary artery could vary during systole by up to 12%. This is in contrast to the inelastic fibrous aortic valve annulus the area of which is fixed during systole (Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984). If the same situation occurs in the intact animal, errors would be introduced into the flow calculation depending on the time in systole that vessel diameter was measured. However in the study by Loeber, Goldberg, Marx, Carrier and Emery (1987) the area changes only occurred under extreme conditions of preload and afterload, so the significance of this effect in an anaesthetised horse is unclear. The time that the maximum diameter occurs within the systolic cycle is also contoversial; some workers demonstrated that it occurred early in systole coincident with the upstroke of the pressure tracing (Greenfield and Patel, 1962). As a result Stewart, Jiang, Mich, Pandian, Guerrero, and Weyman (1985) concluded that most volumetric flow should occur when the aortic area is at its maximum dimension. In their dog model Loeber, Goldberg, Marx, Carrier and Emery (1987) showed that maximal vessel distension occurred in mid - late systole, but because maximal distension was transient Goldberg, Allen, Marx and Donnerstein (1988) suggested that it is unnecessary to measure the area at the point of maximal distension specifically. In

human cardiology it has become a convention to derive aortic area from a single systolic diameter measurement (Stewart, Jiang, Mich, Pandian, Guerrero and Weyman, 1985), and since the pulmonary artery is subject to greater cyclic variation it is recommended that an averaged systolic diameter is obtained from 5 randomly selected cardiac cycles (Hatle and Angelsen, 1985a). Since changes in aortic area during systole have not been specifically studied in horses, to minimise any resultant errors during the present study, vessel area was calculated from a mean diameter measured from 3 successive frames during systole in a single cardiac cycle. This process was repeated for two other cardiac cycles to obtain an average diamter measurement.

Stewart, Jiang, Mich, Pandian, Guerrero, and Weyman (1985) demonstrated that the cross-sectional area of aortic, mitral and pulmonary valves increased with increasing volumetric flow. In the present study aortic diameters were measured from 2-D images at each level of dobutamine infusion, but no significant increases in vessel diameter were found. Failure to detect small changes in aortic area may reflect errors in imaging causing failure to obtain true cross-sectional images of the aorta on multiple occasions (Stewart, Jiang, Mich, Pandian, Guerrero, and Weyman, 1985). In the present studies it is also possible that the change in volume flow produced by dobutamine infusion in these horses was too small to produce a measurable change in aortic diameter.

It is generally accepted that inaccuracy in determination of flow area is the major source of error in the Doppler technique (Haites, McLennan, Mowat and Rawles, 1985; Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984). Because of difficulties in its accurate measurement, it has been suggested by some workers that velocity time integral (VTI) alone can be used to reflect changes in stroke volume (Haites, McLennan, Mowat and Rawles, 1985), since a strong relationship has been demonstrated between the two variables (Huntsman, Stewart, Barnes, Franklin and Colocousis, 1983; Sequeira, Light, Cross and Raftery, 1976). The product of VTI and

heart rate (minute distance) has also been proposed as an accurate and repeatable indicator of cardiac output (Moulinier, Venet, Schiller, Kurtz, Morris and Sebastian, 1991; McLennan, Haites, Mackenzie, Daniel and Rawles, 1986). McLennan and coworkers (1986) showed that in vitro the method detected changes in flow rate of 33% with 95% certainty, a sensitivity which is similar to that of the thermodilution technique in vitro under conditions of pulsatile flow. Minute distance derived from Doppler echocardiography has been used to assess responses to medical therapy in human patients (Elkayam, Gardin, Berkley, Hughes and Henry, 1983). In the present studies no statistically significant differences in aortic diameter were found at different cardiac output levels so that omission of vessel area from flow calculations in anaesthetised horses may be worthy of consideration.

Because thermodilution has been shown to overestimate volumetric flow in pulsatile models (Mackenzie, Haites and Rawles, 1986), it is possible that estimates of cardiac output obtained by transoesophageal echocardiography considerably overestimate true flow in horses. Jarvis, Woliner and Steffey (1992) evaluated a commercial thermodilution computer for continuous flows in-vitro between 8 and 50 $L.min^{-1}$. They reported that the technique underestimated true flow when an injectate of 30 - 40 mls was used and volumetric flow exceeded 25 $L.min^{-1}$. If this occurs in-vivo estimates of cardiac output derived from transoesophageal echocardiography may be closer to true cardiac output than the positive bias suggests. Unfortunately Jarvis and coworkers did not evaluate the computer's performance during pulsatile flow, and this may have influenced their result considerably (Mackenzie, Haites and Rawles, 1986). The thermodilution measurement device used in the present studies was different to the model used by Jarvis and co-workers and it has been demonstrated by Mackenzie, Haites, and Rawles (1986) that measurements made by 3 different commercial devices could differ by up to 2 $L.min^{-1}$ during measurement of a 5 $L.min^{-1}$ pulsatile flow.

Continuous wave Doppler echocardiography has been used for computation of aortic flow in humans, using both transthoracic (Huntsman, Stewart, Barnes, Franklin and Colocousis, 1983; Nishimura, 1984) and transoesophageal techniques (Perrino, Fleming and LaMantia, 1990; Gorcsan, Diana, Ball and Hattler, 1992). Most early studies in the medical literature were performed using CW insonation as accuracy of range gated Doppler was poor until the advent of fast Fourier transform analysis (Nishimura, 1984). In human medicine the size of the ultrasound transducer needed for HPRF Doppler studies limited access to the suprasternal window which provided most accurate alignment with aortic blood flow. In the CW mode, maximum velocity is used to obtain the velocity time integral. The spectra produced from CW studies are complex since they are formed from velocity information from all along the depth of the beam. It is therefore possible that the maximum velocity comes from a site other than the aorta. Theoretically though the maximum velocity should occur at the narrowest point in the circulation, which in the case of the aorta should be the valve annulus. It is for this reason that cardiac output calculations from CW spectra usually incorporate aortic area derived from the annulus diameter (Hatle and Angelsen, 1985a). It has been shown that maximum velocity is less sensitive to poor angulation than the modal velocity, used in the HPRF studies (Brubakk and Givold, 1985), and this may explain why some authors found better agreement between Doppler and thermodilution when CW rather than HPRF insonation was used (Fenger, Bertone and Bonagura, 1991). In the present study the magnitude of bias was increased when spectra were derived using CW Doppler echocardiography. Since maximum velocity is used to obtain VTI this is not surprising; although if the flow velocity profile is flat, the spatial mean velocity should be close to spatial maximum velocity in central core of blood flow (Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984). In the present study the limits of agreement between Doppler and thermodilution measurements were wider when the CW mode of insonation was used. The reason for this unclear, since use of the maximum velocity should produce a positive bias, but have no effect on the agreement

between the two techniques. Since the transoesophageal echocardiography probe was not moved between alternate HPRF and CW estimates the wider limits of agreement cannot be attributed to altered alignment. It is possible that in some individuals the CW technique detected a maximum velocity that came from the left ventricular outflow tract or from accelerated flow around the aortic arch.

In this study there was no difference in agreement between the Doppler methods and thermodilution regardless of whether comparison was made with a single thermodilution measurement or a mean of three measurements. This probably reflects the more stable baseline of cardiac output and heart rate in anaesthetised compared to conscious horses (Long, 1993).

Most human studies have compared the Doppler and thermodilution methods in patients in intensive care wards or cardiac catheterisation laboratories, so that agreement has generally been assessed at resting levels. Rose, Nanna, Rahimtoola, Elkayam, McKay and Chandraratna (1984) showed that agreement between Doppler estimates of cardiac output obtained from aortic velocity spectra and thermodilution deteriorated when patients were given dobutamine. In dogs aortic blood velocity becomes turbulent after isoprenaline infusion (Falsetti, Caroll, Swope and Chen, 1977), if this occurs in other species it may explain increased errors in the Doppler technique when inotropic agents are infused. Decreases in the agreement between Doppler and thermodilution techniques after dobutamine infusion was not observed in transoesophageal studies in anaesthetised horses (Appendix Chapter 4: graphs 1b - 12b, Page 244), but increased error has been observed in standing horses after dopamine and dobutamine infusion (Long, 1993).

Conclusions

These studies show that transoesophageal Doppler echocardiography provides a useful alternative to thermodilution for measurement of cardiac output in anaesthetised

horses. This non-invasive technique offers a number of advantages over thermodilution. It avoids the need for cardiac catheterisation and allows continuous and prolonged monitoring of cardiac output to be performed. The best agreement with the thermodilution method was obtained using HPRF Doppler echocardiography to measure aortic blood flow velocity, with aortic area calculated from its diameter measured at the sino-tubular junction.

FIGURES FOR CHAPTER 4

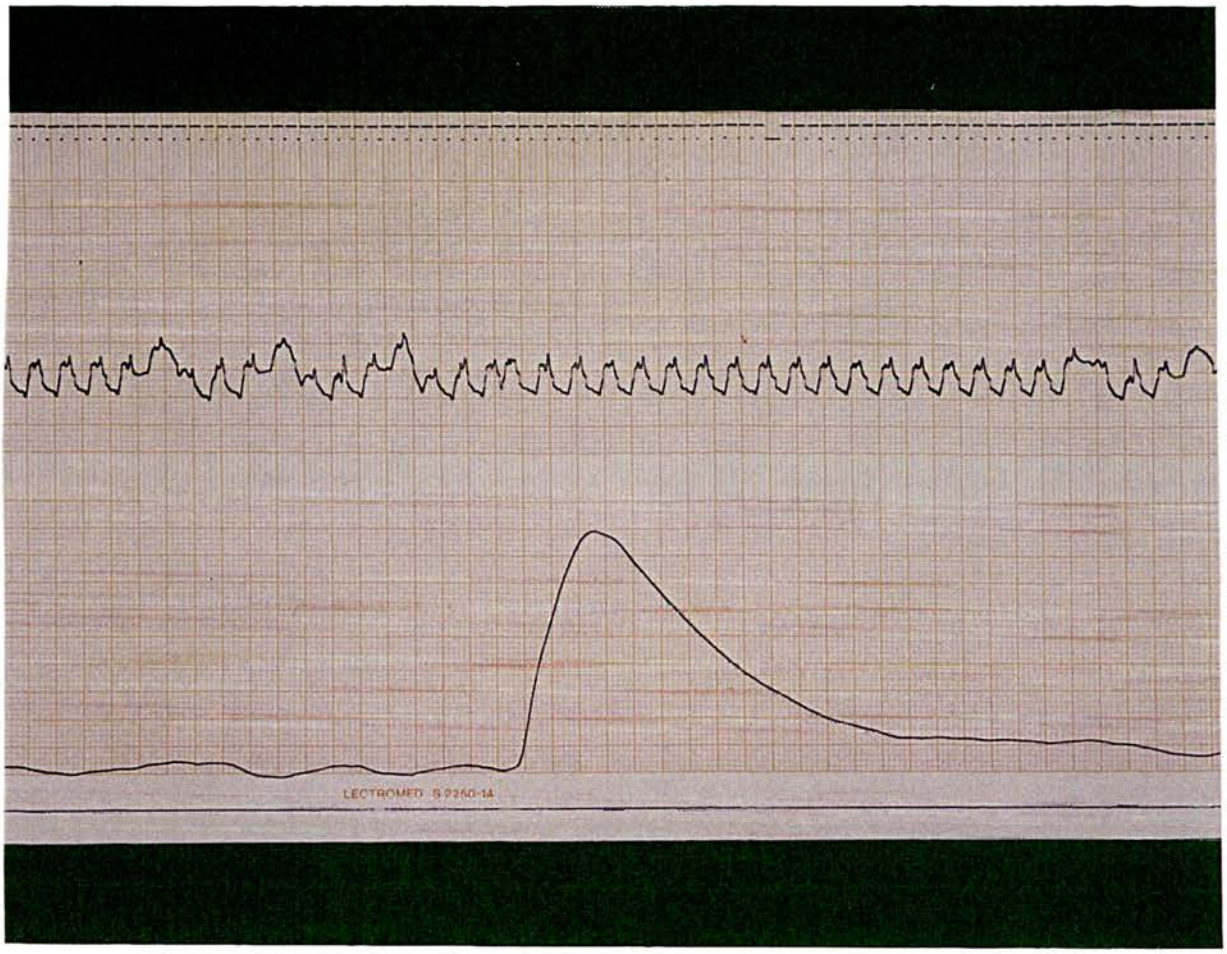

Figure 21: Dilution curve obtained from an anaesthetised horse

The upper trace indicates pulmonary artery pressure measured from the distal port of the thermodilution catheter. Note the baseline fluctuations in pulmonary artery pressure which correspond to the inspiratory cycle of the ventilator.

Mechanical ventilation was stopped immediately before the cardiac output estimations were made, evidenced by the absence of baseline fluctuations in pulmonary artery pressure during the apnoeic period.

The lower trace is taken from the thermistor in the pulmonary artery, whilst a thermodilution measurement is performed. Acceptable dilution curves had a smooth outline, with a characteristically steep ascent and a slower return to baseline.

Note also the small fluctuations in baseline pulmonary artery temperature before and after the indicator curve caused by mechanical ventilation.

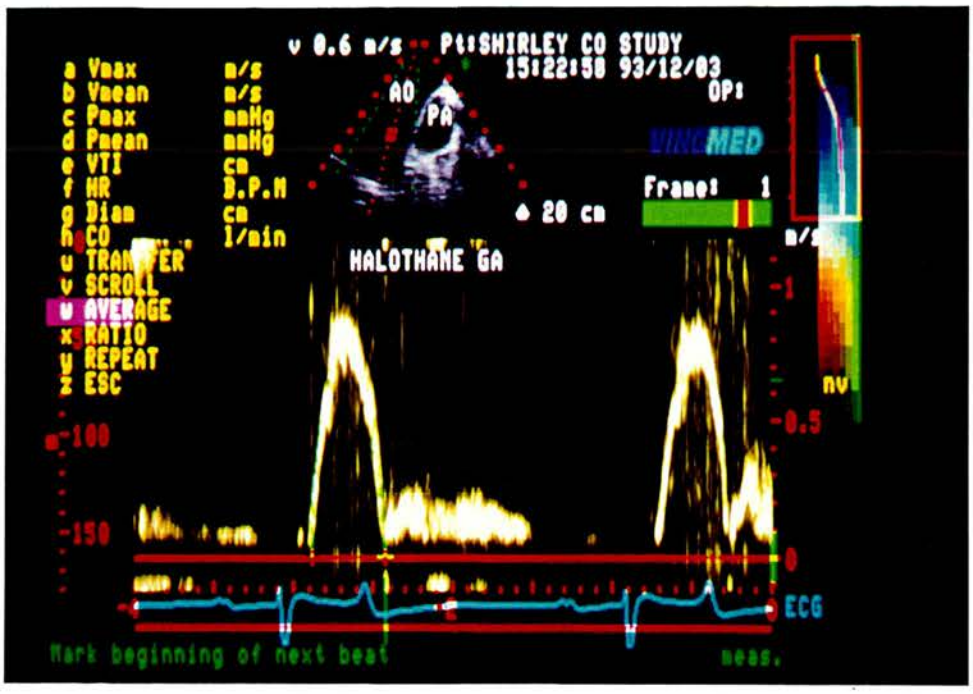

Figure 22: High pulse repetition frequency (HPRF) Doppler study of aortic blood flow velocity obtained by transoesophageal echocardiography

The small 2 D image above shows the Doppler sample volume (two red dots) aligned with the long axis of the aorta (AO). The pulmonary artery (PA) is also imaged in oblique cross section.

The slide was taken when the spectral Doppler measurement menu of the Vingmed CFM 700 was active. The green line around the left hand spectra has been manually traced around the brightest part of the velocity envelope, using the keyboard tracker ball. Note minimal lateral dispersion of the HPRF spectra indicating that flow is laminar at the point of insonation.

The user is prompted to indicate the start of the next spectra, allowing the Vingmed CFM 700 to calculate heart rate, and then complete the left hand panel by inserting the measured and computed values, velocity time interval (VTI), heart rate (HR) and cardiac output (CO). Before calculating CO the user is prompted to input vessel diameter.

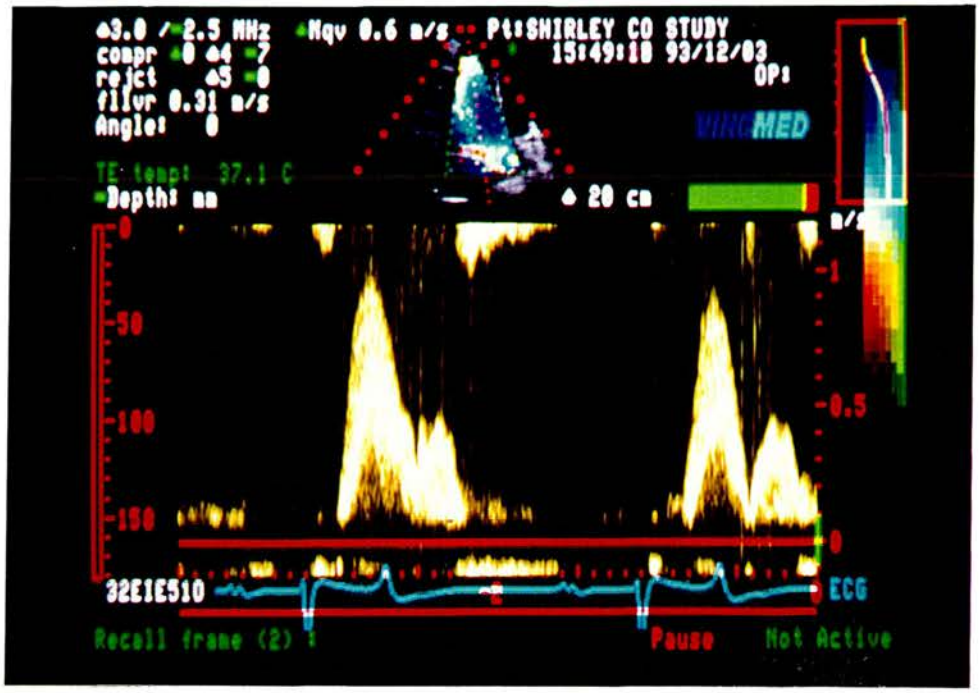

Figure 23: Continuous wave (CW) Doppler study of aortic blood flow velocity obtained by transoesophageal echocardiography

The small 2-D image above shows a colour flow Doppler study of aortic blood flow. Aliasing of the colour flow signal has occurred in the central core of blood at aortic valve level; blood velocity has been coded in blue, as if it were flowing away from the transducer.

Because velocity data is derived from sampling the whole length of the aorta and left ventricular outflow tract, there is increased spectral dispersion compared to the envelopes derived from HPRF insonation in Figure 22.

To derive velocity time integral, the tracker ball is used to trace around the outside of each envelope, thus measuring the area under the maximum velocity, not the modal velocity as in Figure 22.

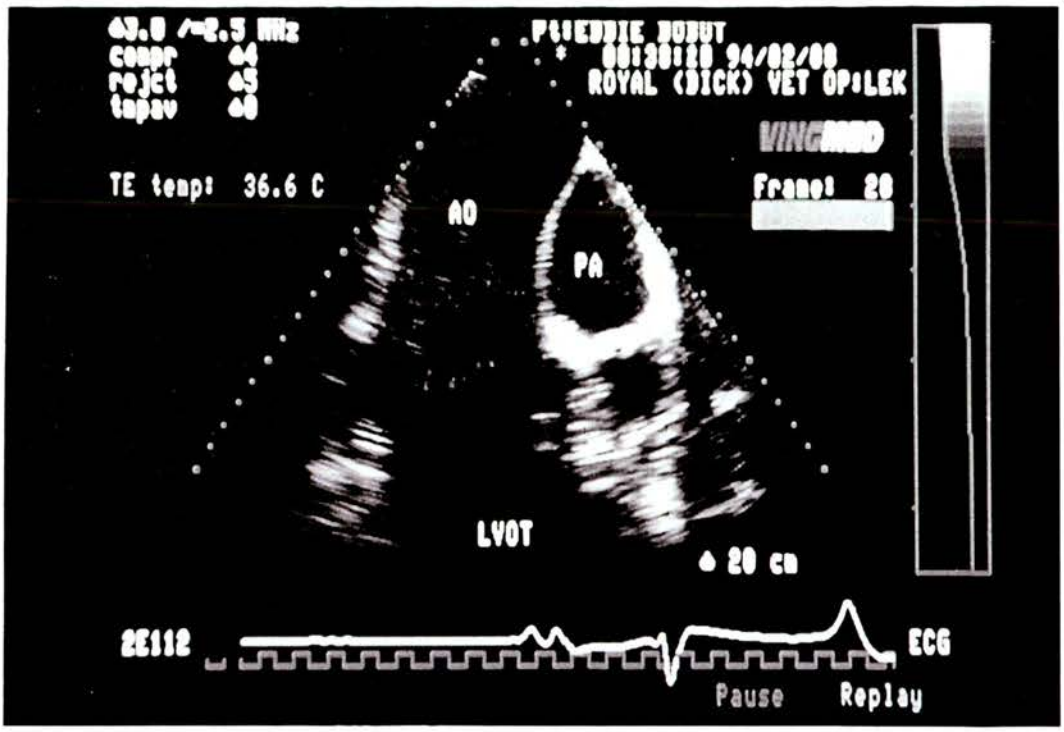

Figure 24: Transoesophageal long axis view of the aorta and left ventricular outflow tract

Standard view used to obtain a transoesophageal derived aortic diameter for cardiac output estimation.

Note the lateral broadening of the echoes from the left lateral wall of the aorta. This occurs when tissue interfaces lie parallel to the ultrasound beam. To measure aortic diameter the calipers were placed in the middle of the echoes representing the anatomical boundaries of the aorta. The vertical level of caliper placement was at the sino-tubular junction at approximately the same level as the Doppler sample volume. The measurement was always made at right angles to the long axis of the vessel.

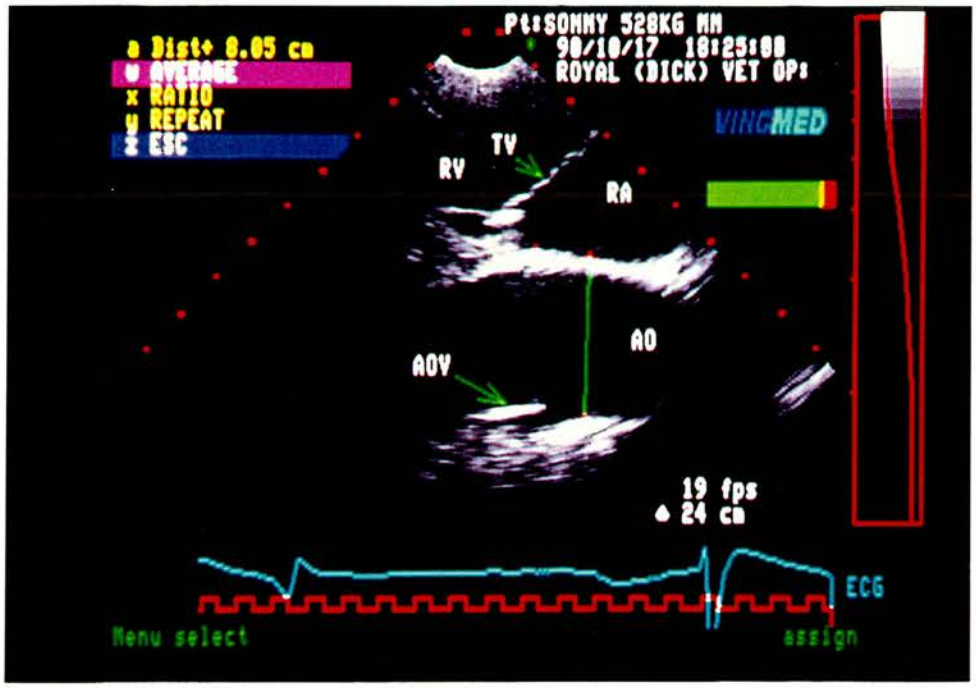

Figure 25: Right parasternal long axis view of the aorta obtained by transthoracic echocardiography

Image used to obtain an aortic vessel diameter from the sino-tubular junction using transthoracic echocardiography.

The green line has been drawn using the electronic calipers of the Vingmed CFM 700. The line indicates the aortic diameter measured by the leading edge to leading edge method. The measurement is made at right angles to the long axis of the aorta.

Note the sharp definition of the vessel walls compared to those in Figure 24. Resolution is improved because the tissue interfaces are now perpendicular to the ultrasound beam.

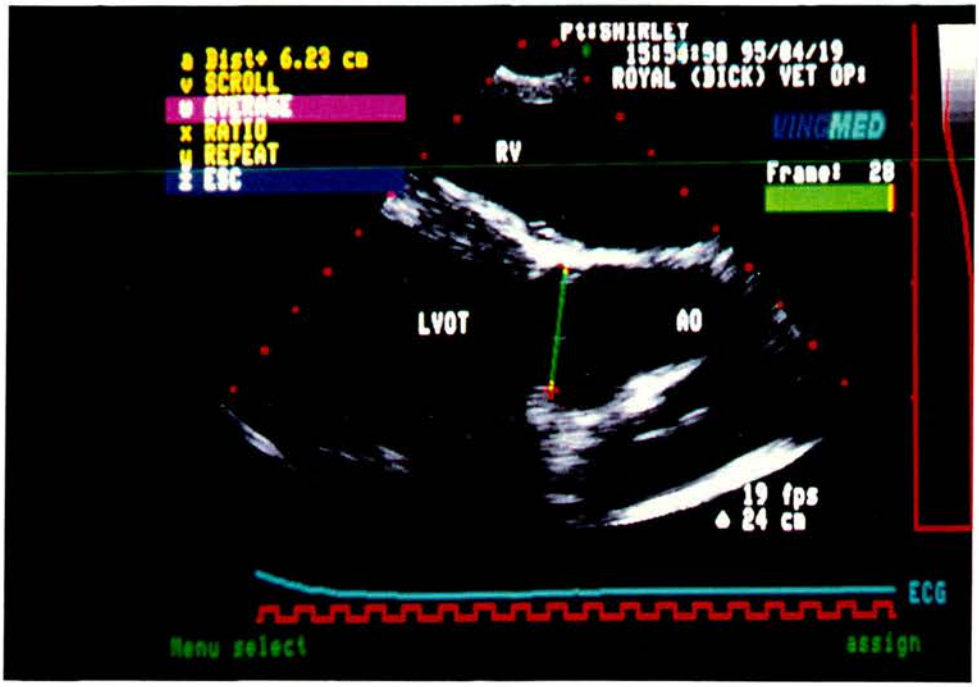

Figure 26: Right parasternal long axis view of the left ventricular outflow tract obtained by transthoracic echocardiography

View used to obtain the aortic valve annulus measurement from transthoracic echocardiography.

The green line drawn using the electronic calipers indicates this measurement. The diameter was measured from the trailing edge of the upper bright echo in the intraventricular septum to the leading edge of the echo at the insertion of the aortic valve into the fibrous annulus.

CHAPTER 5

SENSITIVITY OF DOPPLER DERIVED INDICES OF LEFT VENTRICULAR FUNCTION TO ADMINISTRATION OF INOTROPIC AND VASODILATOR AGENTS IN ANAESTHETISED HORSES.

INTRODUCTION

The data presented in Chapter 3 showed that indices of left ventricular performance derived from transoesophageal echocardiography could be obtained reliably from anaesthetised Thoroughbred horses. The repeatability of these indices was similar to that of the maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$). The studies of Chapter 4 demonstrated that estimates of cardiac output derived from aortic blood velocity spectra agreed well with simultaneous estimates of cardiac output made by thermodilution. This agreement was not affected by administration of dobutamine over a range of cardiac outputs of 15 to 75 $L.min^{-1}$, and it was concluded that the Doppler technique was as sensitive to haemodynamic changes as the invasive method.

Validation of transoesophageal Doppler echocardiography for assessment of left ventricular function in anaesthetised horses depends on demonstration of the sensitivity of Doppler measurements to changes in contractility in the face of changes in preload and afterload. The indices of cardiac performance measured by transoesophageal echocardiography are obtained during left ventricular ejection, and as described by Van den Bos, Elzinger, Westerhof and Noble (1973) they might be expected to be more affected by changes in afterload than indices obtained during isovolumic contraction.

In the following studies afterload and cardiac contractility were manipulated by the administration of three drugs dobutamine, dopexamine and dopamine, and data were recorded from the anaesthetised horses by transoesophageal echocardiography and direct intracardiac pressure recording. The selected drugs possess differing

adrenoreceptor activities, resulting in differing effects on cardiac contractility and loading conditions. In the following paragraphs the actions of adrenoceptors and the receptor affinities of the three sympathomimetic amines studied are reviewed.

MECHANISMS OF ACTION OF SYMPATHOMIMETIC AGENTS

Distribution and actions of β_1 adrenoreceptors

In the earliest classification of adrenoreceptor subtypes all cardiac β adrenoreceptors were classified as subtype β_1, whilst vascular and bronchial β receptors were classified as β_2 adrenoreceptors (Lands, Arnold, McAuliff, Ludicna and Frown, 1967). This simple classification was later modified when radioligand binding studies demonstrated the presence of cardiac β_2 adrenoreceptors (Brodde, 1988). β adrenoreceptors are functionally coupled to adenyl cyclase and by increasing concentrations of cyclic adenosine monophosphate they augment contractility by increasing availability of intracellular calcium (Calvey and Williams, 1982). β_1 adrenoreceptor stimulation increases the rate of change and amplitude of Phase 0 of the cardiac action potential and increases pacemaker firing rate (Smith, Braunwald and Kelly, 1992). β adrenoreceptor agonists also promote extra-systoles, which may result from accelerated closure of the channels carrying the outward potassium currents, and an accelerated repolarisation back to the resting levels, shortening the action potential (Milnor, 1990b). The β_1 subtype of adrenoreceptors have been implicated in the generation of arrhythmias associated with some catecholamines (Opie, 1995; Katz, Lord and Eakins, 1967).

Distribution and actions of β_2 adrenoreceptors

Large numbers of β_2 adrenoreceptors are located in the arterial vascular smooth muscle of skeletal muscle of all species. Stimulation of these receptors results in vasodilation which reduces afterload and increases stroke volume (Lokhandwala and Hegde, 1991). Recent radioligand binding studies have also demonstrated the

coexistence of β_2 adrenoreceptors with β_1 receptors in the human heart (Brodde, 1988). In vitro studies have established that the β_2 cardiac subtype also acts via adenyl cyclase to increase cyclic adenosate monophosphate, and the stimulation of these receptors contribute to the inotropic and chronotropic actions of some catecholamines (Kaumann, Hall, Murray, Wells and Brown, 1991). There is no conclusive evidence that there is similar distribution of β_1 and β_2 subtypes in equine myocardium but a similar distribution has been demonstrated in sheep (Borea, Amerini, Masini, Cerbai, Ledda, Mantelli, Varani and Mugelli, 1992), which suggests that they may occur in other species. There is also evidence that human β_1 adrenoreceptors become selectively down-regulated in patients with severe congestive heart failure, suggesting that utilisation of β_2 adrenoreceptor agonists in therapy of these patients provides a more rational approach to treatment (Lokhandwala and Hegde, 1991; Opie, 1989).

Distribution and actions of α adrenoreceptors

Two subtypes of adrenoreceptors mediating pressor effects have been identified in the vasculature of all species (Berkowitz and Schwinn, 1994). Alpha$_1$ adrenoreceptors are located at the neuroeffector junction and α_2 adrenoreceptors are extra-junctional. Pre-junctional α_2 adrenoreceptors are also situated at noradrenergic nerve terminals where their stimulation results in inhibition of further noradrenaline release (Lokhandwala and Hegde, 1991; Starke and Docherty, 1982).

Distribution and actions of Dopamine 1 (DA_1) adrenoreceptors

DA_1 adrenoreceptors are found predominantly in the arterial smooth muscle of renal, mesenteric, coronary and cerebral vascular beds. DA_1 receptor agonists cause vasodilation which selectively increases blood flow at these sites. In addition activation of renal tubular DA_1 receptors causes natriuresis and diuresis (Brown, Dixon, Farmer, Hall, Humphries, Ince, O'Connor, Simpson and Smith, 1985).

Distribution and actions of Dopamine 2 (DA_2) Receptors

DA_2 receptors are pre-junctional and are located on the terminals of peripheral sympathetic nerves. When stimulated they mediate a reduction of noradrenaline release, which can result in generalised reduction of sympathetic tone throughout the cardiovascular system (Smith and O'Connor, 1988).

MECHANISMS FOR INDIRECT SYMPATHOMIMETIC ACTIVITY

Inhibition of uptake 1

After being released from the adrenergic nerve terminal noradrenaline is in part broken down by a local enzyme catechol-O-methyl transferase, and in part actively taken back into the nerve terminal (uptake 1). If this active uptake is inhibited the active compound noradrenaline persists in the synaptic cleft and causes a sustained sympathomimetic effect which is referred to as being indirect (Smith and O'Connor, 1988).

Tyramine-like activity

Bound noradrenaline is stored in intracytoplasmic vesicles in the noradrenergic nerve terminal. Arrival of action potentials at the terminal unbind the noradrenaline and release it from the vesicles to diffuse out of the nerve terminal. Agents with tyramine-like activity are able to enter the nerve terminal via uptake 1 and then displace endogenous noradrenaline from the storage vesicles (Smith and O'Connor, 1988).

Baroreflex activation

Stimulation of β_2 and DA_1 adrenoreceptors mediating vasodilation, may cause hypotension which reduces the acivity of aortic and carotid sinus baroreceptors. As a result there is increased firing of sympathetic nerves and increased output of noradrenaline from the adrenal medulla which results in vasoconstriction and mild inotropy (Brodde, 1988)

REPORTED CARDIOVASCULAR ACTIONS OF DRUGS ADMINISTERED

Dobutamine

Dobutamine is a synthetic catecholamine that was developed by modifying the chemical structure of isoproterenol (Tuttle and Mills, 1975). The resulting drug had predominantly β_1 activity but its affinity was not solely limited to the β_1 receptor. The commercial preparation is a racemic mixture of two isomers; [+] enantiomer is a potent stimulant of β adrenoreceptors whilst the [-] enantiomer is predominantly a potent α adrenoreceptor agonist (Ruffolo and Yaden, 1982). Radioligand binding studies have shown that β_1 affinity predominates over of β_2, and α_1 predominates over α_2 (Smith, Braunwald and Kelly, 1992; Williams and Bishop, 1981). Stimulation of β_1 receptors in cardiac muscle causes potent positive inotropic effects and a weaker positive chronotropic effect (Vatner, McRitchie and Braunwald, 1974). In the vasculature there is pharmacological and physiological antagonism of the actions of the two stereoisomers at α_1 and β_2 receptors (Williams and Bishop, 1981), resulting in negligible net effects on blood pressure in dogs (Holloway and Frederickson, 1974). When the drug is given to human patients in heart failure, dobutamine causes reduction in systemic vascular resistance, as cardiac output rises and arterial pressure remains relatively unchanged (Leier and Binkley, 1991; Bendersky, Chatterjee, Parmley, Brundage and Ports, 1981; Berkowitz, McKeever, Croke, Jacobs, Loeb and Gunner, 1977). This is in contrast to its effects in anaesthetised horses, when infusion of the drug produced elevation of arterial blood pressure (Donaldson, 1988; Swanson, Muir, Bednarski, Skarda and Hubbell, 1985) and the drug has been advocated as a treatment for intraoperative hypotension in this species (Trim, 1991; Muir and Bendarski, 1983).

Dopexamine

Dopexamine hydrochloride is a synthetic analogue of dopamine (Smith and O'Connor, 1988). It possesses agonist properties at peripheral dopamine receptors (DA_1) and β_2 adrenoreceptors, but has minimal affinity for α or β_1 adrenoreceptors

(Brown, Dixon, Farmer, Hall, Humphries, Ince, O'Connor, Simpson and Smith, 1985). Its stimulant properties at DA_1 receptors and β_2 adrenoreceptors improve renal blood flow and increase cardiac output secondary to afterload reduction (Smith, Hall, Farmer and Simpson, 1987). Mild positive inotropy after dopexamine administration has been attributed to stimulation of cardiac β_2 adrenoreceptors (Smith and O'Connor, 1988), but the work of Brodde (1988) suggested that the predominant mechanisms resulting in enhanced contractility were indirect. Drug induced vasodilation caused activation of aortic and carotid sinus baroreceptors which increased sympathetic nerve outflow. In addition inhibition of uptake 1 potentiated endogenous noradrenaline in the synaptic cleft.

Afterload reduction and concomitant natriuresis by stimulation of renal DA receptors confers specific advantages in the therapy of low output heart failure (Lokhandwala and Hegde, 1991). In humans with congestive heart failure, dopexamine increased cardiac output without undesirable increases in myocardial oxygen consumption (Baumann, Gutting, Pfaferott, Ningel and Klein, 1988; Jaski and Peters, 1988; Dawson, Thompson, Signy, Juul, Turnbull, Jenkins and Webb-Peploe, 1985). Dopexamine has been advocated for use in anaesthetised horses (Muir, 1992b), where studies using specific antagonists have demonstrated its effects are similarly mediated by DA_1 and β_2 adrenoreceptors (Muir, 1992a).

Dopamine

Dopamine is an endogenous catecholamine and is an immediate biosynthetic precursor of noradrenaline (Calvey and Williams, 1982). Dopamine has a mild inotropic effect mediated by weak β_1 adrenoreceptor activity and indirectly by a significant tyramine-like sympathomimetic action (Harrison, Levitt and Udenfriend, 1963). Dopamine also causes vasodilation by direct actions on coronary, cerebral, renal and mesenteric DA_1 adrenoreceptors (Goldberg and Raifer, 1985; Yeh, McNay and Goldberg, 1969). When doses of dopamine are increased vasoconstriction occurs

in the arterioles and veins throughout all vascular beds (Hoffman and Lefkowitz, 1990). This global vasoconstriction is attributable to stimulation of α_1 adrenoreceptors and a direct effect on serotonin receptors in vascular smooth muscle (Gilbert and Goldberg, 1975). In humans and dogs the effects of dopamine on vascular resistance and arterial blood pressure are dose-dependent. At infusion rates below 2 $\mu gkg^{-1}min^{-1}$ the predominant effect is lowered resistance in the renal, mesenteric, cerebral and coronary vascular beds. At between 2 and 5 $\mu gkg^{-1}min^{-1}$ there is a positive inotropic effect; cardiac output and contractility increase with minimal effects on heart rate and either a reduction or no change in peripheral resistance (Goldberg, 1974). With higher infusion rates in humans (5 - 10 $\mu gkg^{-1}min^{-1}$) heart rate, arterial blood pressure and peripheral vascular resistance increase and renal blood flow may decline.

Similar effects were observed when dopamine was infused at 0.5, 2.5 and 5 $\mu gkg^{-1}min^{-1}$ in anaesthetised horses, cardiac output being significantly increased with doses of 2.5 and 5 $\mu gkg^{-1}min^{-1}$ (Trim, Moore and White, 1985). Swanson and coworkers (1985) showed that total peripheral resistance was significantly decreased at 5 $\mu gkg^{-1}min^{-1}$ and had returned to baseline at 10 $\mu gkg^{-1}min^{-1}$. Maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$) and cardiac output (CO) increased with doses of 5 and 10 $\mu gkg^{-1}min^{-1}$ leading these authors to conclude that the haemodynamic effects of dopamine was similar in horses to other species (Swanson, Muir, Bednarski, Skarda and Hubbell, 1985).

AIMS

The main purpose of this study was to determine the sensitivity of Doppler derived indices of left ventricular function during alterations in afterload and inotropy. The studies were designed to test the hypothesis that drug-induced changes in the left ventricle's afterload and contractility would be accurately measured using transoesophageal Doppler echocardiography. Preload also influences ejection phase

and isovolumic indices of cardiac performance and can be manipulated by rapid intravenous fluid administration to elevate central venous pressure, or caval occlusion to reduce ventricular filling pressure. However in the following studies preload was not altered because of the difficulties in infusing fluid fast enough to significantly increase blood volume in horses and the need for surgical access to the vena cava.

Dobutamine, dopamine and dopexamine, have been advocated for the treatment of intra-operative hypotension in anaesthetised horses (Muir, 1992b; Donaldson, 1988; Trim, Moore and White, 1985). These studies enabled assessment of the primary effects of exogenous catecholamines in horses that had been premedicated with a long acting α_2 adrenoreceptor agonist before induction of anaesthesia. Currently in the UK long-acting α_2 adrenoreceptor agonists, romifidine and detomidine, are commonly employed with ketamine to induce general anaesthesia in horses (Johnston, Taylor, Holmes and Wood, 1995). The modulating effects of a residual background of α_2 adrenoreceptor agonist activity on the actions of exogenously administered catecholamines in horses is unknown. Previous studies used only small doses of the short acting agent xylazine before anaesthesia was induced using a barbiturate (Muir, 1992b; Swanson, Muir, Bednarski, Skarda and Hubbell, 1985). As romifidine and detomidine are known to have residual cardiovascular effects for up to 120 minutes after administration to conscious horses (Young, Long, Clutton, Molony and Darke, 1994), both drugs are likely to modulate the effects of agents administered during a subsequent general anaesthetic. Comparison of the results in the present studies with those of previous studies may help define the modulating influence of the α_2 adrenoreceptor agonist agents on exogenously administered catecholamines.

Despite widespread clinical use of dobutamine and dopamine in equine clinical anaesthetic practice no studies have been found which detail their haemodynamic effects during prolonged periods of infusion. A further aim of this study was to use the available echocardiographic and invasive techniques to evaluate the haemodynamic

effects of a single dose of these drugs when administered for 1 hour to horses anaesthetised with halothane after induction of anaesthesia with romifidine and ketamine. The longevity of their haemodynamic effects were assessed over a 30 minute period after the infusion was discontinued.

MATERIALS AND METHODS

Horses and preparation

Seven horses (1 - 6 and 8) were the subjects of this study. Horse 7 was excluded due to thrombosis of the raised carotid artery (see page 38). Each horse was anaesthetised and instrumented for transoesophageal echocardiography as described previously (see page 47). After a long axis view of the left ventricular outflow tract and aorta was obtained, high pulse repetition frequency (HPRF) Doppler echocardiographic measurements of aortic blood velocity were performed.

The heart was catheterised and calibrated strain gauge transducers were placed in the ascending aorta and left ventricle (see page 53). General anaesthesia was maintained with halothane at an end-expired concentration of 0.9% for 60 minutes before data were collected. Intermittent positive pressure ventilation was performed by a mechanical ventilator to maintain arterial $PaCO_2$ between 35 and 45 mmHg. Each horse was anaesthetised on three occasions and 1 month elapsed between anaesthetic episodes.

Data collection

Control data was collected after an end-tidal halothane concentration of 0.9% had been maintained for 60 minutes. Data were recorded during suspension of artificial ventilation. The ventilator was turned off immediately at the end of the inspiratory phase of it's cycle and the recording facilities were activated to coincide with the second 'p' wave of the base-apex electrocardiogram after ventilation stopped. Twenty seconds

of pressure data from each strain gauge transducer was collected and stored on the hard disk of the Macintosh computer. This was then analysed later using the analysis programme described previously (see page 56). The average mean, systolic and diastolic pressures for the aortic transducer and the average left ventricular systolic pressure and heart rate were computed by the programme. The left ventricular end-diastolic pressure was measured using electronic calipers (see page 57). The left ventricular pressure waveform was differentiated to obtain maximum rate of rise of left ventricular pressure.

All Doppler derived data were obtained from video taped images of the Doppler echocardiographic studies recorded simultaneously with the blood pressure data. The measurements were made planimetrically by a single observer using electronic calipers. Measurements from the aortic blood flow spectra comprised; velocity time integral (VTI), maximum acceleration (dv/dt_{max}), maximum velocity (V_{max}), left ventricular ejection time (ET) and pre-ejection period (PEP).

Data from the velocity spectra of five consecutive cardiac cycles, coinciding with the start of blood pressure data acquisition, were averaged for each data point. Cardiac output was calculated using the equation:

$$\text{Cardiac output} = \text{VTI} \times \text{aortic cross sectional area} \times \text{heart rate}$$

Aortic cross sectional area was calculated using the equation:

$$\text{Aortic cross sectional area} = 3.14 \times (\text{radius})^2$$

Aortic diameter was measured from a 2-D standard transoesophageal image, of the sino-tubular junction using the centre wall to centre wall method (Figure 24). To derive the radius, three measurements were taken during systole from three consecutive cardiac cycles and an average figure calculated. The 2-D images were recorded onto video tape immediately before each data collection period.

Experimental protocol

Dobutamine hydrochloride (Dobutrex[46]), dopamine hydrochloride (Inotropin[47]) and dopexamine hydrochloride (Dopacard[48]) were adminstered to each horse during one anaesthetic episode in a randomised sequence. Five hundred milligrams of each drug were dissolved in 1L of 0.9% saline solution. The 500 $\mu g.ml^{-1}$ solution was freshly prepared before each study. Use of a standard concentration ensured that each individual horse received the same volume of fluid regardless of the drug being administered. After control data had been collected 4 $\mu g.kg^{-1}.min^{-1}$ of the catecholamine was infused for sixty minutes. The infusion was delivered by an infusion pump through a 13 gauge teflon catheter placed in the jugular vein. The accuracy of the infusion pump had been confirmed by timing delivery of known volumes of fluid, after it had been programmed to deliver fluid at a rate similar to that used in the study (240 $mls.hr^{-1}$). The intravenous infusion was continued for 60 minutes. Doppler echocardiographic and blood pressure data were collected 10, 20, 40 and 60 minutes after the infusion started and 10, 20 and 30 minutes after the end of each infusion.

When administration of any drug produced disturbances to cardiac rhythm that were considered a risk to the horse, the infusion was discontinued and the anaesthetic episode terminated. No data from such discontinued studies were included in statistical analyses. Any discontinued studies were repeated in the same horse using the same inotrope, one month after the remaining studies for that animal had been completed.

After the final data had been recorded the cardiac catheters and transoesophageal echocardiography probe were removed from the horse. Haemostasis was achieved by

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[46] Dobutrex, 250mg in 20 ml solution, Eli Lilley and Company Limited , Kingsclere Road, Basingstoke, Hampshire, UK.

[47] Inotropin , 200mg in 5ml solution, Dupont Pharmaceuticals Limited, Avenue One, Letchworth Garden City, Hertfordshire, UK.

[48] Dopacard Powder, Fisons Pharmaceutical Division, Bakewell Road, Loughborough, Leicestershire, UK.

manual pressure on the raised carotid artery, and a firm bandage was applied to the area before winching the horse into a paddded recovery area. After the endotracheal tube was removed supplemental oxygen was supplied at 15 $L.min^{-1}$ to each horse through a flexible narrow bore nasopharyngeal tube. Recovery to a standing posture was observed continuously for each horse.

Statistical analysis

Haemodynamic variables for each recording time point in the study were compared both with the value obtained during the control period and the preceeding value in the series using a paired Wilcoxon test. A probability of < 0.05 was considered to be significant.

RESULTS

Table 11 shows the median percentage change from control values after 60 minutes of drug administration for all measured haemodynamic variables. Dobutamine caused the highest percentage change from control values for all measured blood pressures, infusion of dopamine produced the least effect on these variables and the effects of dopexamine administration were intermediate. Dobutamine also caused the greatest fall in the systolic time intervals PEP and ET. The greatest percentage increase in cardiac output occurred after infusion of dopexamine. Dobutamine caused the lowest overall increase in both cardiac output and in the related Doppler variable VTI. All three drugs significantly increased heart rate during the 60 minute intravenous infusion, but after 60 minutes the heart rate was significantly elevated above control values for dobutamine and dopexamine only. Of the three drugs only dobutamine caused significant increases in aortic and left ventricular systolic pressures.

Maximum aortic acceleration (dv/dt_{max}) was as sensitive as maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$) in reflecting the changes in cardiac performance associated with administration of dobutamine and dopexamine. Dopamine infusion

caused a slightly greater effect on dv/dt_{max} than $LVdp/dt_{max}$ (Table 11). Maximum aortic velocity (V_{max}) also increased during inotrope infusion and followed similar trends with individual drug administration as did dv/dt_{max} and $LVdp/dt_{max}$. The percentage change in V_{max} was smaller than for the other two variables, so although it responded to alterations in left ventricular performance, it appears to be less sensitive than dv/dt_{max} and $LVdp/dt_{max}$.

Two studies were terminated early as a result of supraventricular tachycardia. In both cases dysrhythmia occurred during infusion of dobutamine. Horse 8 developed numerous ventricular ectopic beats followed by a supraventricular tachycardia after 20 minutes of infusion. Immediately before the supraventricular tachycardia developed the systolic arterial blood pressure exceeded 240 mmHg and $LVdp/dt_{max}$ was 2047 $mmHg.s^{-1}$. The same study with dobutamine was repeated uneventfully eight weeks later, and the data included in the analysis. Horse 6 developed junctional tachycardia 6 minutes after beginning the dobutamine infusion (Figure 27 and Figure 28). The same rhythm developed when the infusion was administered on a second occasion. Data from horse 6 is therefore missing from the analysis of all dobutamine data. In both animals heart rate had returned to normal sinus rhythm within 10 minutes of stopping dobutamine administration.

Table 11: Median percentage change from control values of measured variables, following 60 minute infusions of 4 $\mu gkg^{-1}min^{-1}$ of dobutamine, dopexamine and dopamine in seven Thoroughbred horses anaesthetised with halothane at 0.9% end tidal concentration (Values in parenthesis indicate maximum and minimum changes)

	DOBUTAMINE	DOPEXAMINE	DOPAMINE
Heart rate	21 (0 - 31)[a]	32 (0 - 69)[a]	6 (-7 - 17)
Maximum rate of LV pressure rise (LVdp/dtmax)	361 (263 - 503)[a]	138 (75 - 365)[a]	11 (-14 -27)
Systolic LV pressure (LVP sys)	75 (49 - 114)[a]	16 (-6 - 23)	3 (-7 - 10)
End diastolic LV pressure (LVP end-dias)	46 (25 - 69)[a]	-22 (-58 - 15)	6 (0 - 32)
Maximum aortic velocity (V max)	60 (27 - 65)[a]	28 (4 - 65)[a]	15 (-16 - 26)
Maximum aortic acceleration (dv/dt max)	368 (286 - 407)[a]	147 (70 - 295)[a]	64 (-3 - 96)[a]
Pre-ejection period (PEP)	-63 (-68 - -46)[a]	-48 (57 - -24)[a]	-25 (-38 - 23)[a]
Ejection time (ET)	-18 (-43 - 2)[a]	17 (2 - 32)[a]	18 (-13- 26)[a]
Velocity time integral (VTI)	14 (-2 - 28)[a]	66 (24 - 100)[a]	43 (-30 - 53)
Cardiac output (CO)	31 (21 - 53)[a]	114 (48 - 136)[a]	49 (-33 - 74)[a]
Systolic aortic pressure (AoP sys)	77 (44 - 108)[a]	13 (-20 - 26)	4 (-15 - 10)
Mean aortic pressure (AoP mean)	66 (51 - 138)[a]	16 (-21 - 25)	3 (-18 - 18)
Diastolic aortic pressure (AoP dias)	62 (47 - 120)[a]	6 (-25 - 20)	-2 (-24 - 28)

[a] indicates a significant difference from control values.
$p < 0.05$ by a paired Wilcoxon test.

Table 13: Median values (interquartile range in parenthesis) of measured haemodynamic variables. These data were obtained during a 30 minute period after discontinuation of an hour long infusion of 4 $\mu g.kg^{-1}.min^{-1}$ **dobutamine** The control values were obtained after 60 minutes of 0.9% end-tidal halothane anaesthesia. The numerics indicate time after stopping infusion.

	Control	10	20	30
Heart rate (**b.p.m**)	29 (27 - 30)	32 (31 - 36) [a]	31 (28 - 34) [ab]	31 (28 - 34) [a]
LV dp/dt max (**mmHg.s^{-1}**)	254 (218 - 265)	618 (546 - 744) [ab]	353 (318 - 394) [ab]	289 (278 - 296) [ab]
LVP sys (**mmHg**)	74 (72 - 81)	104 (100 - 110) [ab]	88 (84 - 90) [ab]	79 (75 - 82) [ab]
LVP end-dias (**mmHg**)	20 (16 - 28)	28 (23 - 28) [ab]	24 (21 - 27) [b]	23 (20 - 25) [b]
V max (**m.s^{-1}**)	0.87 (0.87 - 0.89)	1.00 (0.95 - 1.03) [ab]	0.83 (0.79 - 0.89) [b]	0.81 (0.79 - 0.88) [ab]
dv/dt max (**m.s^{-2}**)	5.34 (4.35 - 5.53)	11.62 (11.0 - 14.3) [ab]	6.72 (5.78 - 7.69) [ab]	5.66 (4.97 - 6.00) [b]
PEP (s)	0.24 (0.21-0.25)	0.15 (0.13 - 0.15) [ab]	0.18 (0.17 - 0.20) [ab]	0.21 (0.19 - 0.24) [b]
ET (**s**)	0.48 (0.47 - 0.51)	0.50 (0.48 - 0.52) [b]	0.59 (0.56 - 0.60) [ab]	0.59 (0.57 - 0.60) [ab]
VTI (**cm**)	25.23 (22.8 - 27.1)	29.9 (27.2 - 32.7) [a]	30.8 (29. 7 - 34.0) [a]	29.6 (28.7 - 34.4) [a]
CO (**L.min^{-1}**)	25.8 (24.5 - 31.3)	37.1 (34.8 - 38.7) [a]	38.0 (30.2 - 43.7) [a]	38.3 (27.8 - 40.3) [a]
AoP sys (**mmHg**)	78 (77 - 85)	108 (106 - 116) [ab]	93 (90 - 93) [ab]	83 (80 - 88) [ab]
AoP mean (**mmHg**)	69 (62 - 69)	93 (90 - 102) [ab]	79 (76 - 81) [ab]	71 (67 - 76) [ab]
AoP dias (**mmHg**)	57 (49 - 59)	75 (72 - 83) [ab]	64 (60 - 68) [ab]	57 (53 - 62) [b]

[a] indicates a significant difference from control values.
[b] indicates a significant difference from the preceeding value.
$p < 0.05$ by a paired Wilcoxon test.

Table 15: Median values (interquartile range in parenthesis) of measured haemodynamic variables. These data were obtained during a 30 minute period after discontinuation of an hour long infusion of 4 $\mu g.kg^{-1}.min^{-1}$ **dopexamine** The control values were obtained after 60 minutes of 0.9% end-tidal halothane anaesthesia. The numerics indicate time after stopping infusion.

	Control	10	20	30
Heart rate (**b.p.m**)	29 (26 -34)	30 (27 - 34) [ab]	30 (28 - 32)	28 (26 - 32)
LV dp/dt max (**mmHg.s^{-1}**)	215 (165 - 314)	363 (324 - 482) [ab]	283 (240 - 362) [ab]	252 (224 - 310) [ab]
LVP sys (**mmHg**)	80 (69 - 85)	84 (78 - 101)	83 (75 - 99)	81 (79 - 83)
LVP end-dias (**mmHg**)	23 (20 - 26)	20 (19 - 23) [b]	22 (20 - 25)	21 (20 - 24)
V max (**m.s^{-1}**)	0.90 (0.83 - 0.92)	1.00 (0.84 - 1.05) [ab]	0.90 (0.77 - 0.93) [ab]	0.83 (0.72 - 0.91) [ab]
dv/dt max (**m.s^{-2}**)	5.43 (4.17 - 7.31)	7.70 (5.92 - 8.36) [ab]	6.08 (5.48 - 7.44) [ab]	4.92 (4.43 - 6.52) [b]
PEP (s)	0.21 (0.19 - 0.25)	0.14 (0.12 - 0.16) [ab]	0.18 (0.17 - 0.20) [b]	0.23 (0.21 - 0.23) [b]
ET (s)	0.51 (0.47 - 0.54)	0.67 (0.64 - 0.71) [ab]	0.68 (0.66 - 0.71) [ab]	0.67 (0.64 - 0.70) [a]
VTI (**cm**)	25.4 (21.3 - 28.1)	36.7 (34.6 - 40.0) [a]	33.7 (31.5 - 36.0) [ab]	29.4 (28.5 - 33.5) [ab]
CO (**L.min^{-1}**)	28.1 (24.2 - 33.2)	44.6 (37.9 - 47.9) [ab]	37.7 (34.8 - 41.8) [ab]	33.2 (30.8 - 37.4) [ab]
AoP sys (**mmHg**)	79 (65 - 88)	80 (70 - 85)	81 (67 - 82)	79 (70 - 84)
AoP mean (**mmHg**)	67 (52 - 79)	66 (58 - 71)	68 (56 - 69)	67 (61 - 71)
AoP dias (**mmHg**)	53 (44 - 67)	51 (46 - 56)	54 (45 - 55)	53 (51 - 56)

[a] indicates a significant difference from control values.
[b] indicates a significant difference from the preceding value.
$p < 0.05$ by a paired Wilcoxon test.

Table 17: Median values (interquartile range in parenthesis) of measured haemodynamic variables. These data were obtained during a 30 minute period after discontinuation of an hour long infusion of 4 $\mu g.kg^{-1}.min^{-1}$ **dopamine** The control values were obtained after 60 minutes of 0.9% end-tidal halothane anaesthesia. The numerics indicate time after stopping infusion.

	Control	10	20	30
Heart rate (**b.p.m**)	30 (29 - 33)	29 (28 - 32) [b]	29 (27 - 32) [b]	29 (27 - 31)
LV dp/dt max (**mmHg.s^{-1}**)	256 (193 - 322)	276(230 - 331)	269 (230 - 328)	255 [b] (200 - 275)
LVP sys (**mmHg**)	78 (63 - 87)	85 (72 - 95) [ab]	82 (70 - 94) [ab]	81 (66 - 91)
LVP end-dias (**mmHg**)	19 (18 - 26)	25 (18 - 26)	24 (17 - 25) [b]	24 (17 - 25)
V max (**m.s^{-1}**)	0.81 (0.74 - 0.85)	0.77 (0.72 - 0.79) [b]	0.76 (0.73 - 0.81)	0.77 (0.66 - 0.81)
dv/dt max (**m.s^{-2}**)	4.62 (4.06 - 5.37)	4.98 (4.82 - 6.79)	4.98 (4.31 - 5.33)	4.35 (3.90 - 5.19)
PEP (s)	0.24 (0.21 - 0.27)	0.21 (0.20 - 0.23) [b]	0.23 (0.22 - 0.24) [b]	0.23 (0.23 - 0.26)
ET (s)	0.51 (0.46 - 0.53)	0.56 (0.52 - 0.61) [ab]	0.56 (0.52 - 0.60) [a]	0.57 (0.51 - 0.60) [a]
VTI (**cm**)	24.0 (21.7 - 28.3)	26.7 (22.5 - 28.5) [b]	25.5 (21.0 - 26.9)	24.4 (20.3 - 29.1)
CO (**L.min^{-1}**)	29.5 (24.6 - 31.0)	31.0 (27.3 - 35.1) [b]	29.5 (22.9 - 32.6)	29.1 (26.1 - 30.4)
AoP sys (**mmHg**)	80 (61 - 93)	79 (69 - 96) [ab]	83 (68 - 97)	82 (67 - 89) [b]
AoP mean (**mmHg**)	71 (52 - 82)	71 (58 - 81) [b]	74 (58 - 80) [b]	73 (60 - 61)
AoP dias (**mmHg**)	57 (42 - 68)	59 (46 - 65) [b]	61 (47 - 63)	58 (49 - 71)

[a] indicates a significant difference from control values.
[b] indicates a significant difference from the preceeding value.
$p < 0.05$ by a paired Wilcoxon test.

HAEMODYNAMIC EFFECTS OF INDIVIDUAL INFUSIONS

Dobutamine

The haemodynamic effects of dobutamine are recorded in Table 12 and Appendix Chapter 5: Dobutamine, Graphs 1 - 13 (Pages 258 - 265). Heart rate was significantly less at 10 minutes after the infusion commenced than dring the control period, and only became significantly greater than control values after 60 minutes of infusion. Dobutamine infusion significantly increased $LVdp/dt_{max}$, V_{max}, and dv/dt_{max} at 10, 20, 40 and 60 minutes. There was a marked cumulative effect of the infusion on $LVdp/dt_{max}$ and dv/dt_{max}, demonstrated by Graphs 2 and 6 (Pages 259 and 261). Left ventricular and aortic blood pressures were increased during infusion of dobutamine. From Graphs 11 - 13 (Page 264 - 265) the effect of the infusion on all the measured blood pressures had begun to reach a plateau after 20 minutes of infusion. Dobutamine also increased left ventricular end-diastolic pressure. The infusion caused progressive shortening of the pre-ejection period and ejection time. Cardiac output and velocity time integral were not significantly increased above control values until 40 minutes of infusion (Graphs 9 and 10, Page 262).

The downstroke of the aortic velocity spectra developed a notch within 20 minutes of commencing dobutamine infusion in all horses (Figure 29). The notch persisted throughout the infusion, but had disappeared 10 minutes after it was discontinued. Marked spectral dispersion in the early downstroke of the velocity spectra of Horses 2, 4, 5 was also noted associated with administration of the catecholamine (Figure 30).

After discontinuing the infusion there was a progressive return of haemodynamic variables towards normal (Table 13), although heart rate, $LVdp/dt_{max}$, V_{max}, VTI, cardiac output, left ventricular systolic pressure and systolic and mean aortic

pressure all remained elevated above control values 30 minutes later. Ejection time had returned to control values 10 minutes after the infusion had been turned off, but then it continued to increase beyond the control value. Ejection time was still significantly longer than its control value at the time the final data was collected (Graph 8, Page 262).

Dopexamine

The haemodynamic effects of dopexamine are recorded in Table 14 and Appendix Chapter 5: Dopexamine, Graphs 1 - 13 (Pages 266 - 273). Heart rate was higher than control values after 10 minutes of infusion, and was maintained at this elevated level throughout the remainder of drug administration (Graph 1, Page 267). Dopexamine caused progressive increases in $LVdp/dt_{max}$, dv/dt_{max}, and cardiac output similar to dobutamine (Table 14). VTI also showed a cumulative effect during the infusion period, which reached statistical significance between the 20 and 40 minute values (Graph 9, Page 271). Infusion of dopexamine caused no significant changes in systolic, mean and diastolic aortic blood pressure (Graphs 11 - 13, Pages 272 - 273). Left ventricular end-diastolic pressure also remained unchanged (Graph 4, Page 268). Dopexamine had little effect on left ventricular systolic pressure although it was significantly elevated above control values at 20 minutes (Graph 3, Page 268). In common with dobutamine, dopexamine reduced pre-ejection period (Graph 7, Page 270), but in direct contrast, dopexamine significantly increased left ventricular ejection time (Graph 8, Page 270). Ejection time increased progressively throughout the infusion and continued to increase for ten minutes after the infusion was discontinued. Ejection time was still significantly greater than control values 30 minutes after the infusion was discontinued. The remaining haemodynamic variables showed a gradual return towards pre-infusion values during the 30 minute period after drug administration stopped (Table 15), although $LVdp/dt_{max}$, V_{max}, VTI, and cardiac output still remained higher than control values when the final data was collected.

A notch in the downstroke of the aortic velocity spectra of Horses 1, 4, and 6 was observed from twenty minutes of infusion, but spectral dispersion in the early deceleration period was not a feature associated with dopexamine infusion (Figure 31).

Dopamine

The haemodynamic effects of dopamine are recorded in Table 16 and Appendix Chapter 5: Dopamine, Graphs 1 - 13 (Pages 274 - 281). There was a small increase in heart rate which occurred within 10 minutes of drug administration and was maintained throughout the remaining infusion (Graph 1, Page 275). Infusion of dopamine had minimal effects on $LVdp/dt_{max}$, although there was a small but statistically significant fall 10 minutes after the infusion began (Graph 2, Page 275). There was a small but significant cumulative increases in dv/dt_{max} up to 40 minutes of the 60 minute infusion (Graph 6, Page 277). Systolic, diastolic and mean aortic blood pressure was lower than control values for the first 20 minutes of infusion (Table 5). Systolic and diastolic aortic pressures returned to control values by 40 minutes (Graph 11 and 13, Pages 280 and 281) and mean pressure had returned at 60 minutes (Graph 12, Page 280). After the infusion was discontinued there was a tendency for mean, systolic and diastolic aortic blood pressures of some animals to increase, although this increase was only statistically significant after 10 minutes (Table 17). Left ventricular systolic pressure showed a similar tendency to decrease for the first 20 minutes after dopamine infusion commenced, but it exceeded control levels at 60 minutes. This increase continued for 20 minutes after dopamine was discontinued (Graph 3, Page 276). Infusion of dopamine caused no change in left ventricular end diastolic pressure. Cardiac output and VTI were significantly increased during dopamine infusion (Graph 9 and 10, Page 279). Infusion of dopamine caused small but significant decreases in PEP and small but significant increases in ET (Graph 7 and 8, Page 278).

Dopamine infusion caused minimal changes to the aortic velocity spectra in all horses. The spectra widened but did not change shape and spectral dispersion was not observed (Figure 32).

Prolonged infusion of dopamine in Horse 1 altered CO, VTI, ET and PEP in a different manner to all other horses in the group. These variables followed similar trends as in the other horses at the 10 and 20 minute data collection points, however at 40 minutes CO, and VTI were half their preceding value, PEP had increased to 0.34 s, whilst ET had fallen to 0.34 s. These effects continued after the infusion was discontinued after 60 minutes. Cardiac output fell to it's lowest level 10 minutes after stopping the infusion and was still 12 L below it's control value after 30 minutes.

SIDE-EFFECTS

Dobutamine

Supraventricular and junctional tachycardia were observed in two horses at an infusion rate of 4 $\mu g.kg^{-1}.min^{-1}$. The dysrhythmia occurred on a two separate occasions in one animal, but the drug was administered uneventfully on a second occasion in the other horse.

Dopexamine

During administration of dopexamine profuse sweating occurred in every horse. The sweating began within 10 minutes of the start of the infusion and by twenty minutes sweat was pooling between the thighs and forming discrete drops in five out of seven horses (Figure 33). The volume of fluid lost in sweating could not be quantified, but in the worst affected cases the theatre floor became saturated despite attempts to catch fluid accumulating on the padded bed. Copious urination was noted in horses 1, 2, 3 and 4 during anaesthesia. In six horses, recovery from anaesthesia was associated with excitement and violent shivering. These responses were not seen during recovery after

dopamine or dobutamine administration. Colic occurred in 2 horses after dopexamine: Horse 2 was found in colic, 3 hours after an excitable recovery. The horse had been returned to her stable one hour after standing, but was found flank watching and rolling two hours later. Auscultation revealed an absence of intestinal borborygmi and a heart rate of 45 beats per minute. Rectal examination was normal. The mare was treated with 4.4 $mg.kg^{-1}$ phenylbutazone[49] by slow intravenous injection. She responded quickly and no further signs of colic were observed. Horse 8 showed signs of colic in the recovery box, immediately after regaining consciousness he became excited, began rolling and showed bouts of violent colic for the next 2 hours. Intestinal sounds were absent, and heart rate was less than 50 bpm. Phenylbutazone was administered after rectal examination had revealed no abnormalities. The horse appeared dull over the following 12 hours, but no further signs of severe abdominal discomfort were observed.

Dopamine

In most horses the arterial blood pressure fell during the early part of dopamine infusion despite increases in CO. This may be of concern if the drug is being employed to overcome hypotension in anaesthetised horses. One horse showed a reduction in CO and VTI after 40 minutes of dopamine infusion at 4 $\mu g.kg^{-1}.min^{-1}$.

[49] Equipalazone Injection, Arnolds Veterinary Products, Cartmel drive, Harlescott, Shrewsbury, UK.

DISCUSSION

THE SENSITIVITY OF MAXIMUM ACCELERATION, MAXIMUM VELOCITY AND MAXIMUM RATE OF RISE OF LEFT VENTRICULAR PRESSURE TO INOTROPIC INTERVENTION

Maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$) is used almost exclusively for measurement of myocardial contractility in horses and was selected in the following studies as the invasive standard of contractility measurement for comparison with the Doppler phase indices of left ventricular function.

This study shows that the indices of ventricular function derived from transoesophageal echocardiography are as sensitive to changes in left ventricular performance in anaesthetised horses as $LVdp/dt_{max}$, the index derived from direct measurement. Specifically dv/dt_{max} was as sensitive as $LVdp/dt_{max}$ in detecting changes in inotropy when percentage change from control values was used to gauge sensitivity. Maximum aortic velocity also changed in response to catecholamine administration but the magnitude of the changes were less than for dv/dt_{max}, reflecting reduced sensitivity to the drugs administered in this study.

Influence of ventricular loading conditions

Maximum rate of rise of left ventricular pressure occurs in the isovolumic period of systole before the aortic valve has opened. Theoretically $LVdp/dt_{max}$ is independent of afterload, but is influenced directly by preload (Milnor, 1990c), since increased venous return increases end-diastolic fiber length and promotes more forceful contraction by the Frank Starling mechanism. Maximum aortic acceleration and V_{max} occur after the aortic valve has opened i.e. they are cardiac ejection phase indices, and as a result are both afterload and preload dependent. Because of this it is widely held that ejection phase indices are unable to differentiate changes in contractility from changes in ventricular load (Bedotto, Eichhorn and Grayburn, 1989). In the present

studies contractility and afterload were manipulated by drugs expected to have different effects on inotropy and ventricular loading conditions. From the percentage changes which occurred in dv/dt_{max} and $LVdp/dt_{max}$ it appears that the two indices are equally sensitive to changes in cardiac performance, despite $LVdp/dt_{max}$ occurring in the isovolumic period and dv/dt_{max} occurring during ejection.

Afterload

Maximum rate of rise of left ventricular pressure has been demonstrated to be afterload dependent (Mason, 1969; Wallace, Skinner and Mitchell, 1963), despite being obtained during the isovolumic period. This is contrary to the theoretical considerations of Van den Bos, Elzinger, Westerhof and Noble (1973). This effect may explain the significant fall in $LVdp/dt_{max}$ after 10 minutes of dopamine infusion and the lack of significant increases in $LVdp/dt_{max}$ above its control level for the rest of the dopamine infusion in the present studies. The fall in $LVdp/dt_{max}$ at 10 minutes implies that either dopamine is acting as a negative inotrope, which is unlikely, or that the effect on $LVdp/dt_{max}$ has been attenuated by a simultaneous alteration in left ventricular loading conditions. Throughout most of the dopamine infusion left ventricular end-diastolic pressure was increased implying that left ventricular preload had been augmented, an effect that that might be expected to increase $LVdp/dt_{max}$. Dopamine infusion caused aortic blood pressure to fall in the anaesthetised horses in this study, despite significant increases in cardiac output, suggesting that afterload was reduced by drug administration. A similar effect has been demonstrated in humans by Borow and colleagues (1992) who showed that $LVdp/dt_{max}$ showed markedly disparate responses to dopamine infusion in human patients with dilated cardiomyopathy. These workers demonstrated that when aortic diastolic pressure fell after dopamine, the aortic valve opened before true $LVdp/dt_{max}$ was attained. As a result left ventricular pressure potential was not fully developed, and the maximum rate of pressure rise was underestimated.

In the present studies dv/dt_{max} showed a slightly greater percentage change in response to dopamine infusion than $LVdp/dt_{max}$ which might imply less dependence of the latter on ventricular afterload. However afterload reduction has been demonstrated to increase dv/dt_{max} and V_{max} (Wallmeyer, Wann, Sagar, Czakanski, Kalbfleish and Klopfenstein, 1988; Bedotto, Eichhorn and Grayburn, 1989), an effect promoting changes opposite to those on $LVdp/dt_{max}$. Because dopexamine also reduces systemic vascular resistance the increases in $LVdp/dt_{max}$ that occurred during infusion of the drug may have been attenuated, whilst the changes in the ejection phase indices may have been augmented by afterload reduction.

Preload

Both ejection phase and isovolumic indices of ventricular performance are affected by end diastolic fiber length. In these studies it was decided not to alter preload directly due to practical problems. However any changes in preload caused by the drug treatments in the studies would be expected to affect all indices similarly. Since the indices were measured simultaneously it is therefore valid to make direct comparisons of their inotropic sensitivity. Changes in preload are also diffficult to quantify, as preload cannot be measured directly. However left ventricular end-diastolic pressure is frequently used as an index of left ventricular preload (Milnor, 1990c), since most evidence suggests that left ventricular compliance is not altered by inotropic stimuli or halothane (Prys-Roberts, Gersh, Baker and Reuben, 1972).

In the present studies 40 minutes after commencing dopexamine infusion there were significant decreases in left ventricular end-diastolic pressure which would have attenuated any increases in dv/dt_{max}, $LVdp/dt_{max}$ and V_{max}. During dobutamine infusion left ventricular end-diastolic pressure was significantly increased, inferring that the increases in $LVdp/dt_{max}$, dv/dt_{max} and V_{max} seen with this drug were augmented by the effect of increased preload and do not reflect changes in inotropy alone.

Load dependence: Conclusions

There have been several studies attempting to assess the load dependence of $LVdp/dt_{max}$, dv/dt_{max} and V_{max} (Harrison, Clifton, Berk and DeMaria, 1989; Gardin, 1989; Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986; Quinones, Gaasch and Alexander, 1976; Mahler, Ross, O'Rourke and Covell, 1975; Mason, Braunwald, Covell, Sonnenblick and Ross, 1971). The results are conflicting, some workers claiming load independence for their respective index, only to have the opposite finding proven by other workers using a different preparation. The present studies show that the indices, dv/dt_{max} and V_{max}, derived from transoesophageal echocardiography, are no more load dependent than $LVdp/dt_{max}$, the conventional index used in horses. Similar conclusions that the Doppler indices, dv/dt_{max} and V_{max}, are 'as sensitive as invasive indices to changes in contractility' have been made by other workers in both humans and dogs (Gardin, 1989; Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986).

Heart rate dependence

In addition to dependence upon preload and afterload the indices of ventricular performance, $LVdp/dt_{max}$, dv/dt_{max} and V_{max} are also influenced by heart rate (Wallmeyer, Wann, Sagar, Kalbfleisch and Kloppfenstein, 1986; Bedotto, Eichhorn and Grayburn, 1989; Mason, 1969). In the present studies heart rate was increased by both dopexamine and dopamine, and this may have augmented the increases in the haemodynamic variables that occurred during the studies. Dobutamine caused heart rate to fall after ten minutes of infusion which may also have influenced these variables at this time.

VELOCITY TIME INTEGRAL AND CARDIAC OUTPUT

Estimates of cardiac output made from transoesophageal echocardiographic studies agreed well with those obtained by thermodilution (Chapter 4). The present

studies show that VTI and CO increased in response to dopexamine and dopamine and to a lesser extent with dobutamine. The afterload dependence of these indices is clearly illustrated in the present studies. Velocity time integral and CO were most increased by dopexamine and dopamine, drugs with known afterload reducing properties. Velocity time interval was not significantly increased by dobutamine infusion, despite the drug causing the greatest increases in contractility, indicated by the largest increases in $LVdp/dt_{max}$, dv/dt_{max} and V_{max}. Cardiac evaluation should include measurement of cardiac output (Braunwald, 1971), but the limitations of equating increased cardiac output directly to increased contractility are clearly demonstrated by these studies.

PRE-EJECTION PERIOD (PEP) AND EJECTION TIME (ET)

The three drugs studied had disparate effects on PEP and ET. All three drugs decreased PEP, although the magnitude of the decrease was greatest for dobutamine. Pre-ejection period comprises the electromechanical delay and the isovolumic contraction period. Inotropic intervention should shorten the PEP by increasing the rate of intraventricular pressure development. This can be modified by decreases in diastolic aortic pressure, which leads to further reductions in PEP, by reducing the time available for isovolumic contraction. Since dobutamine increased aortic diastolic pressure the marked shortening of PEP associated with this drug is more likely to reflect an increased rate of rise of intraventricular pressure (Talley, Meyer and McNay, 1971). Increased inotropy generally results in a reduction in ET because of increased velocity and extent of fibre shortening (Lewis, Rittgers, Forester and Boudoulas, 1977). Predictably dobutamine caused ET to fall significantly, but it increased with both dopamine and dopexamine infusions. These unexpected increases in ET are likely to result from the marked increases in stroke volume which has been demonstrated to accompany administration of both agents (Weissler, Peeler and Roahll, 1961). Ejection time continued to increase for at least 20 minutes after dopexamine infusion was

discontinued. This finding is difficult to explain from current knowledge of its actions. Thirty minutes after the infusion was discontinued VTI was still elevated above the control value, but was significantly less than the value after 60 minutes of infusion, yet ET was significantly higher 30 minutes after the infusion had stopped than it had been at any time during infusion. As a result the prolonged ET cannot be attributed to increased stroke volume alone. The arterial blood pressure and left ventricular end-diastolic pressures were unchanged, so no other evidence for alterations in afterload and/or preload which might explain altered ejection dynamics was found.

It has been suggested that changes in systemic vascular resistance or mean arterial blood pressure do not provide an adequate measure of afterload during dopamine and dobutamine infusion in dogs (Borow, Lang, Neumann, Janzen and Altman, 1986). If this also applies in horses, changes in afterload and hydraulic load of the left ventricle cannot be discounted and may account for the altered ejection dynamics 30 minutes after dopexamine was discontinued. This sustained effect was also observed after dopamine and dobutamine infusions when ET was also greater than the control value 30 minutes after stopping both infusions. Again considerations of the preload and afterload as assessed by left ventricular end-diastolic pressure and mean aortic pressure fail to explain the increase in ET.

The altered dynamics may have resulted from changes in vascular inpedance caused by an inbalance in the duration of receptor activities of the three drugs. All three drugs have both peripheral vascular and cardiac effects and if the duration of the drugs' inotropic actions are shorter than their vascular effects, this may explain the current findings. In intact animals the autonomic nervous system modulates cardiac contractility and heart rate in response to inotropic and vasodilator agents (Vatner, Rutherford and Ochs, 1979). It is also possible that after prolonged infusion of catecholamines there remains an altered balance of autonomic tone causing the observed changes in the pattern of left ventricular ejection.

INTEGRATED APPROACH TO THE MEASUREMENT OF VENTRICULAR CONTRACTILITY

Binks and Jewell (1972) were of the opinion that no index will ever truly provide a satisfactory measure of contractility in the intact animal. The present studies support this suggestion. A better approach appears to be to judge contractility from several indices of pressure, flow and cardiac dimensions, not from a single number (Milnor, 1990c). Because of the large array of indices that are readily available from transoesophageal Doppler echocardiography the technique has great potential for evaluating the complex haemodynamic disturbances of the anaesthetised horse and for monitoring its responses to therapy.

HAEMODYNAMIC EFFECTS OF INDIVIDUAL DRUGS

Cumulative effects of dopexamine and dobutamine

There is evidence from the present studies that continuous administration of 4 $\mu g.kg^{-1}.min^{-1}$ dopexamine and dobutamine failed to illicit a maximum effect on a number of haemodynamic variables within the 60 minute infusion period. Maximum rate of rise of left ventricular pressure, CO, VTI and dv/dt_{max} all increased throughout the infusion period. Dopexamine also caused progressive increases in left ventricular ET, which continued after the infusion was discontinued.

Pharmacological studies in dogs have shown that the plasma half life of dobutamine is 2 minutes and steady plasma levels of the catecholamine can be achieved after 10 minutes of continuous infusion (Murphy, Williams and Kau, 1976). In human medicine it is accepted that the half life of the catecholamines is less than five minutes and their peak effects are achieved rapidly (Opie, 1995). Because of the rapid clearance of the drugs their cardiovascular effects are short-lived, waning within 10 - 15 minutes of stopping infusion (Leier and Binkley, 1991). This pharmacological data has been directly transposed into veterinary medicine and it is generally accepted that the same

situation occurs in horses (Muir, 1991). Most studies of the haemodynamic effects of dobutamine or dopexamine in anaesthetised horses have utilised serially increasing infusion rates (Muir, 1992b; Swanson, Muir, Bednarski, Skarda and Hubbell, 1985; Wertz, Dunlop, Wagner, Heath and Chapman, 1991). In these studies a maximum of 15 minutes elapsed before data were collected and the infusion rate was again increased. In the present studies the effect of the two drugs on heart rate and left ventricular and aortic blood pressure had reached a plateau after 20 minutes. Stabilisation of blood pressure after drug administration has been used to define the peak effect of intropic agents or a "steady state" in many studies (Hinchcliffe, Mc Keever and Muir, 1991; Bedotto, Eichhorn and Grayburn, 1989; Harrison, Clifton, Berk and DeMaria, 1989). This assumption may explain why the cumulative effects of these drugs on other haemodynamic variables in anaesthetised horses have not been reported previously.

The present studies show that the haemodynamic effects of dobutamine and dopexamine persist longer than has been described in other species. This finding is corroborated by the data of Muir (1992b) which indicated that $LVdp/dt_{max}$ and CO had not returned to baseline values 60 minutes after discontinuing a infusion of 20 $\mu g.kg^{-1}.min^{-1}$ of dopexamine. The studies of Trim, Moore and White (1985) also demonstrate the persistance of haemodynamic effects following dopamine infusion. These authors allowed 30 minutes to elapse between incremental infusions in anaesthetised horses to allow the cardiac output to return to baseline values. However examination of their data reveals that cardiac output remained significantly elevated 30 minutes after 2.5 and 5.0 $\mu g.kg^{-1}.min^{-1}$ dopamine infusions and systemic vascular resistance was still significantly below control values at this time.

The differences in pharmacokinetics of these drugs in anaesthetised horses, conscious humans and dogs may be attributable to effects of general anaesthesia which alters tissue and plasma clearance of the drugs or delays their removal from the receptors. Haemodynamic variables failed to return to control levels 45 minutes after

infusion of dobutamine was discontinued in anaesthetised dogs (Orchard, Chakrabarti and Sykes, 1982). The authors attributed their findings to an action of dobutamine, or a product of it's action that persisted for longer than 45 minutes, or they postulated that improvement in haemodynamic variables had occurred unrelated to dobutamine infusion resulting from a time related change in their experimental preparation. As the half life of dobutamine was 2 minutes in conscious dogs (Murphy, Williams and Kau, 1976), they attributed their findings to time-related changes in their animal model. A similar effect cannot be ruled out in the present studies since it has been shown that the cardiac output of horses anaesthetised by a constant halothane concentration increases from a low level immediately after induction of anaesthesia to a plateau after around 2 hours (Steffey, Kelly and Woliner, 1987; Steffey, Woliner and Dunlop, 1990). However the residual increase in ejection time after dopexamine and dobutamine infusions did not occur in the same horses after dopamine infusion, indicating that this effect is likely to result from drug administration. Similarly there were no significant differences between the other measured haemodynamic variables 30 minutes after dopamine infusion and their pre-infusion control values. Since this study was performed in the same group of animals after an identical anaesthetic protocol, it suggests that the residual effects after dopexamine and dobutamine can be directly or indirectly attributed to the drugs administered.

These studies indicate that inotropic and vasodilator agents do not necessarily attain their peak effect after 10 - 15 minutes in anaesthetised horses, and that their effects have not completely resolved within 30 minutes of discontinuing drug administration.

SPECIFIC HAEMODYNAMIC EFFECTS OF DOBUTAMINE

In the present study, a sixty minute infusion of 4 $\mu g.kg^{-1}.min^{-1}$ of dobutamine significantly increased arterial blood pressure, dv/dt_{max}, $LVdp/dt_{max}$ and V_{max}. The effect

of dobutamine on cardiac output was much smaller than either dopamine or dopexamine administered to the same horses. These findings are in general agreement with other studies carried out in horses (Swanson, Muir, Bednarski, Skarda and Hubbell, 1985). However the effect of dobutamine on arterial blood pressure in horses differs from that in humans and dogs, in which it has little pressor effect (Vainionpaa, Nuutinen, Mokka and Tuononen, 1983; Vatner, McRitchie and Braunwald, 1974). Swanson, Muir, Bednarski, Skarda and Hubbel (1985) found that their estimate of total peripheral resistance was unchanged by dobutamine when the drug was given to anaesthetised horses. In the present studies the increases in cardiac output and heart rate were small despite the large increases in arterial blood pressure that occurred. These data suggest that dobutamine did produce peripheral vascular effects, since in the absence of increases in heart rate and stroke volume, increases in arterial blood pressure must be mediated by an increase in systemic vascular resistance. A similar effect was described by Hinchcliffe, McKeever and Muir (1991) when low doses of dobutamine administered to conscious horses increased cardiac work, by increasing arterial blood pressure without increasing cardiac output.

Human studies have shown that the increase in cardiac output that occurs with dobutamine is associated with an increased stroke volume (Ihlen, Amlie, Dale, Forfang, Nitter-Haige, Simonsen and Myhre, 1984). This contrasts findings in the present study when dobutamine infusion failed to significantly alter VTI until 40 minutes after the infusion commenced. Quantitatively the changes in VTI were much smaller than occurred with dopexamine and dopamine, indicating that increased stroke volume was a less prominent mechanism of dobutamine's activity in horses. A smaller increase in VTI with dobutamine is explicable because the large increase in V_{max} was offset by significant decreases in left ventricular ET.

The different haemodynamic effects of dobutamine in anaesthetised horses compared to dogs and humans may be explained by differences in the structure of

peripheral vascular adrenoreceptors in horses. It is possible that these differences might upset the normal balance of the vascular actions of the two stereoisomers which constitute the racemic mixture of dobutamine. If the affinity of dobutamine for equine α adrenoreceptors was predominant the mutual antagonism between the (-) enantiomer and the (+) enantiomer in the vasculature could be disturbed, resulting in net vasoconstriction. It is well known that the relative sensitivity to α_2 adrenoreceptors agonists varies markedly between different species. Recently radioligand binding studies have identified different α_2 adrenoreceptor subtypes in a variety of species, this is likely to contribute to inter-species divergence in pharmacodynamic responses to α_2 adrenoreceptor ligands (Daunt, Link, Chruscinski and Kobilka, 1994). Species heterogenicity has also been demonstrated in α_1 adrenoreceptors (Berkowitz and Schwinn, 1994), and it is therefore conceivable a similar effect could account for the observed difference in pressor response with dobutamine in horses, dogs and humans.

In the present study infusion of dobutamine was associated with significant increases in left ventricular end-diastolic pressure. Assuming that ventricular compliance was normal it can be inferred that dobutamine increased left ventricular preload. Some support for this is available from studies in calves in which dobutamine caused venoconstriction and decreased venous capacitance (Binkley, Murray, Watson, Myerowitz and Leier, 1991). Similar venoconstriction mediated by an α adrenoreceptor mechanism was also demonstrated in dogs (Fuch, Rutlen and Powell, 1976). Increases in preload may have significantly contributed to the increases in $LVdp/dt_{max}$, dv/dt_{max}, and V_{max} which occurred with dobutamine infusion (Sonnenblick, 1962a), therefore the changes in these variables cannot be ascribed to increased contractility alone.

During dobutamine infusion the down-stroke of aortic velocity spectra became notched and spectral dispersion was evident during the deceleration component in a number of animals. Spectral dispersion indicates that non-laminar flow is occurring

within the vessel. Non laminar flow has been observed previously in the central core of aortic blood flow after isoprenaline infusion in dogs (Falsetti, Caroll, Swope and Chen, 1977). These workers also noted that the turbulence existed throughout the deceleration component of the aortic blood flow. Deceleration is a more disorganised process than acceleration, so that deceleration instability with associated spectral broadening is characteristic of flows in great arteries (Weyman, 1994c). Since dobutamine increases both inotropy and lusitropy and increases V_{max}, deceleration must increase. This may explain the increased spectral broadening which occurred during dobutamine administration, and to a lesser extent during administration of dopexamine.

The notching on the down-stroke of the aortic velocity envelope has not been reported previously in horses. Additional momentum must have been imparted to the blood, or opposition to blood flow must have suddenly decreased, for velocity during the deceleration phase to suddenly increase. It is possible that there is recruitment of cardiac contractile elements at this time, or a sudden increase in developed tension. This explanation seems unlikely since most studies suggest that there is almost synchronous activation of the left ventricular contractile mass and that left ventricular ejection is "more like striking a piston with a mallet than like squeezing blood out of a chamber" (Rushmer, 1964). An alternative explanation lies in a change in ventricular-vascular coupling induced by dobutamine infusion. Dobutamine infusion has been shown to have beneficial effects on ventricular-vascular coupling in human patients with congestive heart failure (Binkley, VanFossen, Nunziata, Unverferth and Leier, 1990). In these patients increased stroke volume was accompanied by complimentary changes in the aortic impedance spectrum which optimally matched it to the increased contractile state of the ventricle, maximising the efficiency of power transfer to the circulation. The characteristics of hydraulic impedance are greatly influenced by body shape and this phenomenon has been used to explain the different aortic pressure wave profiles observed in different species (Nichols and O'Rourke, 1990a). Differences in

early wave reflectance caused by peripheral vasodilation or changes in ventricular ejection time can induce a mismatch between the early minimal value of impedance modulus and the maximal values of flow harmonics, a relationship which is necessary to optimise cardiovascular efficiency (Nichols and O'Rourke, 1990a). Sharp reductions in ejection time occur with dobutamine infusion which may be accompanied by alterations in vascular resistance in horses. It is possible that the sudden increase in flow velocity during the deceleration period corresponds to a sudden reduction in impedance modulus at a later stage in ventricular ejection.

Similar notching of pulmonary arterial flow velocity waveforms have been observed in human patients with pulmonary hypertension (Martin-Duran, Larman, Trugena, Vasquez De Prada, Ruano, Torres, Figuero, Pajaron and Nistal, 1986). Similar findings were also obtained when pulmonary hypertension was induced in dogs (Matsuda, Sugishita, Yamaguchi, Tamura and Ita, 1981). These authors suggested that the flow pattern was altered by changes in stroke volume and peripheral wave reflection resulting from right ventricular pressure overload, altered ejection dynamics and increased right ventricular outflow impedance. This may be a similar mechanism to that responsible for the notching of the aortic velocity waveforms observed in the present studies

Arrhythmogenicity of dobutamine

Tachydysrhythmia occurred in two horses during dobutamine infusion. This is in contrast to previous reports of the use of dobutamine in anaesthetised horses. Swanson, Muir, Bednarski, Skarda and Hubbel (1985) noted that heart rate fell after infusions of 2.5 and 5 $\mu g.kg^{-1}.min^{-1}$ but had returned to baseline after a 10 $\mu g.kg^{-1}.min^{-1}$ infusion in a study examining serial increasing infusions of dobutamine. Donaldson (1988) reported a 28% incidence of dysrhythmia after 1.7 $\mu g.kg^{-1}.min^{-1}$ was administered to horses anaesthetised for elective surgery. These dysrhythmias were exclusively associated with reduction in heart rate. In the present study after 20

minutes of an infusion of 4 $\mu g.kg^{-1}.min^{-1}$ there was a significant decrease in heart rate, similar to the findings of Swanson, Muir, Bednarski, Skarda and Hubbel (1985) however drug administration was not continued beyond 6 minutes in horse 6 as supraventricular tachycardia developed in this animal at this time on two separate occasions. Horse 7 developed supraventricular tachycardia after 20 minutes during dobutamine infusion, but this data was not included in the results as the infusion was administered uneventfully on another occasion.

The appearance of tachydysrhythmia in two horses in the present study may be attributable to the α_2 adrenoreceptor agonist, romifidine, administered as a premedicant agent. It has been documented that a related drug, xylazine, decreases the dose of adrenaline necessary to produce tachydysrhythmias in dogs (Muir, Werner and Hamlin, 1975). However the chemical structure of romifidine differs from that of xylazine by the presence an imidazole ring (Gasthuys, Parmentier, Goossens and DeMoor, 1990). Studies have demonstrated that a related drug, dexmedetomidine, had antiarrhythmic properties in halothane anaesthetised dogs. (Hayashi, Sumikawa, Maze, Yamatodani, Kamibayashi, Kuro and Yoshiya, 1991). The antiarrhythmic properties of this drug have been attributed to the presence of an imidazole ring in the parent compound (Hayashi and Maze, 1994). Specific studies investigating the arrhythmogenicity of the α_2 adrenoreceptor agonists have not been reported in horses and it is possible that the situation with romifidine is complex.

The threshold for arrhythmogenesis with dobutamine infusion is known to decrease in response to vagotomy in horses (Light, Hellyer and Swanson, 1992) and dogs (Bednarski and Muir, 1983), which infers that the parasympathetic nervous system modulates responses to dobutamine infusion. Modulation of parasympathetic tone by the long acting α_2 adrenoreceptor agonist is an alternative explanation for the increased arrhythmogenicity seen with dobutamine infusion in the present study. Romifidine has a potent vagal stimulatory effect in conscious horses (Young, Long,

Clutton, Molony and Darke, 1994), but the modulating effect of the drug on parasympathetic activity in anaesthetised horses is currently unknown. The present studies suggest that romifidine, administered as a premedicant drug, may alter the cardiovascular responses to infused catecholamines in certain individuals.

Dobutamine showed less arrythmogenic potential in dogs than did isoprenaline, noradrenaline or dopamine (Tuttle and Mills, 1975; Holloway and Frederickson, 1974). Failure of dobutamine to significantly increase arterial blood pressure in dogs and humans is believed to contribute to its low arrhythmogenic potential (Holloway and Frederickson, 1974). Increases in arterial blood pressure result in greater developed tension in the contracting myocardium which is known to increase purkinje cell automaticity (Muir, 1977; Moore, Morse and Price, 1964). In horses infusion of dobutamine elevates arterial blood pressure (Light, Hellyer and Swanson, 1992; Muir, 1992b; Donaldson, 1988; Swanson, Muir, Bednarski, Skarda and Hubbell, 1985). Interestingly in the present study, in the two horses which developed tachycardia with dobutamine infusion, the arterial blood pressure increased to much higher values than in the other animals immediately before the arrhythmia commenced. Romifidine is known to cause peripheral vasoconstriction and resultant increases in arterial blood pressure in conscious horses (Young, Long, Clutton, Molony and Darke, 1994), it is possible that residual activity of romifidine at peripheral α adrenoreceptors may have been responsible for a greater effect of dobutamine on arterial blood pressure resulting in the appearance of arrhythmia in 2 of these animals at much lower infusion rates than has been observed previously.

SPECIFIC HAEMODYNAMIC EFFECTS OF DOPEXAMINE

Infusion of 4 $\mu g.kg^{-1}.min^{-1}$ dopexamine increased cardiac output and stroke volume without affecting arterial blood pressure. The drug also increased $LVdp/dt_{max}$, V_{max} and dv/dt_{max} suggesting that it increased cardiac contractility, findings that are

consistent with those of Muir (1992b). The cardiovascular effects of dopexamine in anaesthetised horses mirror that in humans (Baumann, Gutting, Pfaferott, Ningel and Klein, 1988; Jaski and Peters, 1988; Dawson, Thompson, Signy, Juul, Turnbull, Jenkins and Webb-Peploe, 1985) and the drug appears to have an ideal haemodynamic profile for the treatment of low cardiac output in horses. However the side effects noted in the present study may preclude its use in clinical equine anaesthesia.

Side-effects of dopexamine

Increased urine output is expected from a drug known to increase renal blood flow and promote natriuresis (Smith and O'Connor, 1988). The copious sweating seen in the present studies was not reported by Muir (1992b), neither has it been reported in other species. Dopamine and dobutamine did not produce a similar response in the horses in the present studies inferring that it is unlikely to arise from β_1, DA_1 or α adrenoreceptor stimulation. Dopexamine is an agonist at β_2 receptors (Biro, Douglas, Keon and Taichman, 1988; Brown, Dixon, Farmer, Hall, Humphries, Ince, O'Connor, Simpson and Smith, 1985) and direct stimulation of β_2 receptor subtypes may be responsible for the profuse sweating noted in these studies. Intravenous administration of the β_2 adrenoreceptor agonist drug, clenbuterol, to anaesthetised horses also caused profuse sweating (Bartram, Young, Diamond, Gregg and Jones, 1993), providing additional evidence that a β_2 adrenergic mechanism might be involved. That sweating was not observed in the studies by Muir (1992b) may be explained as follows: The protocol used differed from the present study in the drugs used to induce anaesthesia. The dose of α_2 adrenergic agonist agent administered in the present studies as a premedicant agent was high, to allow induction of anaesthesia with ketamine. The long duration of action of romifidine would ensure it's continued presence during the inotrope infusion. Romifidine, in common with other α_2 adrenergic agonist drugs, is known to cause sweating after intravenous administration in conscious horses (Hall and Clarke, 1992). In the study by Muir (1992b) a low dose of the shorter acting α_2

adrenergic agonist drug, xylazine, was used to facilitate cardiac catheterisation, the effects of this drug are more likely to have waned by the time anaesthesia was induced. It is possible that the combined actions of romifidine and dopexamine were responsible for the profuse sweating seen in the present studies.

The excitement and shivering observed during recovery from anaesthesia in a high proportion of horses also appears to be unique to this species. One study in humans reported tremors and chest pain in 20% of conscious human patients during infusion of dopexamine (Dawson, Thompson, Signy, Juul, Turnbull, Jenkins and Webb-Peploe, 1985). Shivering may have occurred secondary to sweating; as the wet horse recovered in the colder environment of the recovery box, evaporation of surface moisture could reduce surface, then core temperature to a threshold that provoked shivering. Two of the horses that were noted to have had excitable recoveries showed signs of colic, which probably contributed to their poor quality recoveries. The 3 geldings urinated immediately after standing after dopexamine had been administered. Abdominal discomfort caused by a full bladder may have adversely influenced quality of recovery in these patients.

The most serious side-effect observed in these studies was colic seen in 2/7 animals, both horses responded to medical treatment over about 4 hours, but during the recovery period the likelihood of self trauma was high in horse 8. If either horse had undergone surgery for fracture repair, the colic that resulted could have compromised the surgical outcome. The mechanism of the gastrointestinal pain observed in these horses was uncertain and similar side-effects were not reported in the studies by Muir (1992b). Decreased intestinal motility, as evidenced by absence of intestinal borborygmi at clinical examination, could have resulted from a direct effect of dopexamine, or from a combination of dopexamine and the romifidine, a drug known to reduce intestinal motility (Hall and Clarke, 1992). Dehydration of gut contents caused by the profuse sweating that accompanied dopexamine infusion may also have

contributed to gastrointestinal dysfunction. Regardless of the aetiology, if the colic observed in these studies is typical, it represents a serious complication to administration of dopexamine and could preclude its clinical use.

SPECIFIC HAEMODYNAMIC EFFECTS OF DOPAMINE

Infusion of 4 $\mu g.kg^{-1}.min^{-1}$ of dopamine increased cardiac output and stroke volume in these anaesthetised horses whilst their arterial blood pressure tended to fall. Maximum rate of rise of left ventricular pressure, V_{max} and dv/dt_{max} were minimally affected by dopamine infusion implying that at the dose rate employed in these studies the drug was increasing cardiac output primarily through afterload reduction. This is in agreement with the studies of Goldberg (1974) who showed a similar haemodynamic effect when infusion rates of between 2 and 5 $\mu g.kg^{-1}.min^{-1}$ were employed in humans. The following studies are consistent with the conclusions of Swanson, Muir, Bednarski, Skarda and Hubbel (1985) namely that the haemodynamic effect of dopamine was similar in horses to other species.

INOTROPIC THERAPY FOR ANAESTHETISED HORSES

Of the three drugs under investigation dobutamine appeared to be most efficacious in increasing inotropy, but the least effective in increasing aortic blood flow. In equine anaesthesia support of mean arterial blood pressure has become an increasingly important goal (Hubbel, 1991), largely as a result of the work of two groups who showed that induced arterial hypotension in anaesthetised horses was associated with post-operative myopathy (Lindsay, Robinson, Brunson and Majors, 1989; Grandy, Steffey, Hodgson and Woliner, 1987). Retrospective clinical surveys have also linked occurrence of post-operative lameness to intra-operative hypotension (Richey, Hollans, McGrath, Dodman, Marshall, Court, Norman and Seeler, 1990; Klein, 1978). Pressures within Triceps brachii exceeding 60 mmHg have been

measured in the dependent fore-limbs of anaesthetised horses using wick catheters (Lindsay, McDonell and Bignell, 1980). This led to the hypothesis that postoperative myopathy was similar to the compartmental syndrome seen in man, when increasing pressure within a closed fascial compartment leads to a vicious circle of ischaemia, muscle damage and further increases in intracompartmental pressure (Mubarak and Hargens, 1983). It has been demonstrated experimentally that blood flow to muscle is decreased if internal pressure exceeds 50 mmHg, and flow reduces to 95% of normal when internal pressure exceeds 80 mmHg (Sheridan and Matsen, 1957). In other studies pressures greater than 30 mmHg have been shown to cause muscle damage (Rorabeck and MacNab, 1975). This data has been used to explain the muscle damage which can result from equine anaesthesia, and it has been suggested that a pressure difference of at least 30 mmHg must be maintained between mean arterial blood pressure and maximum intracompartmental pressure (Taylor, 1992). Advocates of this simplistic hypothesis have suggested that since intracompartmental pressures as high as 60 mmHg have been measured in anaesthetised horses in the laboratory (White and Suarez, 1986; Lindsay, McDonell and Bignell, 1980), to maintain a perfusion presure of 30 mmHg, mean arterial blood pressure must be maintained in excess of 90 mmHg (Taylor, 1992).

Despite the widespread and increasing use of dobutamine in clinical equine anaesthesia a reduction in the incidence of myopathy has not been reported. Young and Taylor (1993) failed to demonstrate a statistically significant decrease in the incidence of myopathy following the use of dobutamine, despite clearly demonstrating that the drug reduced the incidence of hypotension. They suggested that the cases of myopathy that occurred after the routine use of dobutamine were not as severe, as had been observed previously and attributed their aetiology to poor positioning. Unfortunately the cases in the Young and Taylor series were separated, not only by routine use of dobutamine, but also by a period of up to seven years. In this time advances in equine surgery have also

occurred, including increasing use of less invasive methods such as arthroscopy, refinement of techniques and surgical skills and more routine use of analgesia. It is likely that these factors also affect the outcome of equine anaesthesia, or the severity of any problems which do occur. Until prospective blind studies are conducted, a cause-effect relationship between low arterial blood pressure and postoperative lameness in clinical anaesthesia will be neither conclusively demonstrated nor disproved.

In some of the veterinary anaesthetic literature increased arterial blood pressure is often assumed to equate to increased cardiac output (Taylor, 1992; Klein, 1978). This assumption is not surprising since halothane anaesthesia has been shown to reduce cardiac output and blood pressure in horses, whilst not greatly affecting systemic vascular resistance (Steffey and Howland, 1978; Eberly, Gillespie, Tyler and Fowler, 1968). Dobutamine is known to increase cardiac index in humans and dogs, whilst having minimal effects on systemic vascular resistance, so when the drug is administered to anaesthetised horses it is logical to assume that when arterial blood pressure increases increased cardiac output is likely to be the cause. The present studies demonstrate that in anaesthetised horses arterial blood pressure may increase after dobutamine without accompanying increases in cardiac output. In fact in certain individuals, cardiac output fell, if a barorececeptor response to increased arterial blood pressure induced bradycardia or second degree heart block.

In the present studies dopexamine and dopamine increased cardiac output to a much greater extent than dobutamine. The fit Thoroughbred horses involved in these studies were anaesthetised for at least 3 hours during each procedure and their mean aortic blood pressures were often below the levels that would be considered the "safe" threshold. Interestingly it was also shown that the mean arterial pressure measured from the upper-most facial and great metatarsal arteries in horses in left lateral recumbency did not bear a constant relationship to mean aortic pressure (Clutton, Young and Long, 1994). In these studies mean pressures in the facial and metatarsal

areries were 13. 5 mmHg (standard deviation = 7.4 mmHg) and 17.8 mmHg (standard deviation = 6.5 mmHg) lower than mean aortic pressure respectively. In anaesthetised horses measurements of arterial blood pressure are generally made from these peripheral arteries, and their intraluminal pressures are then used as a basis for therapeutic decisions. In our studies mean pressures as low as 40 mmHg were regularly recorded from these arteries during dopamine and dopexamine infusions, yet all horses recovered after at least 3 hours of general anaesthesia with no evidence of muscle damage. Whilst low arterial blood pressure was associated with the development of myopathy in the studies of Lindsay, Robinson, Brunson and Majors (1989) and Grandy, Steffey, and Miller (1987), lameness was not detected in the present studies in fit healthy animals when facial artery pressures were reduced to similar levels for a similar period. Our animals were positioned on a padded surface with the lower thoracic limb pulled forward and the upper limbs supported perpendicular to the sternum, a position which has been shown to reduce intracompartmental pressures (White and Suarez, 1986). This may have reduced the tendency for muscle damage in the present study, although Grandy, Steffey, and Miller (1987), used the same positioning and obtained 100% incidence of obvious muscle dysfunction after a similar period of hypotension. It is possible that the duration of hypotension in the present study was insufficient to create the problems detected by the other workers. However with a 100% incidence of muscle damage detected by both groups it might be expected that one or more horses should have been at least mildly affected by lameness, in these studies. From the interquartile ranges of mean aortic pressure shown in Tables 14 to 17 individual horses had aortic blood pressures within the 55 - 66 mmHg range for at least 3.5 hours. As mean aortic pressures tend to exceed mean facial artery pressures, a higher proportion of the group probably fell into the hypotensive category of Lindsay, Robinson, Brunson and Majors (1989) and Grandy, Steffey, Hodgson and Woliner (1987).

In the studies of Lindsay, Robinson, Brunson and Majors (1989) and Grandy, Steffey, Hodgson and Woliner (1987) inspired halothane concentration was increased until mean facial artery pressure was in the range 55 and 65 mmHg. Halothane causes a dose dependent depression in cardiac output (Steffey and Howland, 1978), resulting in the low values of cardiac indices reported in the hypotensive period, 23.2 - 29.2 $ml.kg^{-1}.min^{-1}$ (Grandy, Steffey, Hodgson and Woliner, 1987) and 19.5 $ml.kg^{-1}.min^{-1}$ (Lindsay, Robinson, Brunson and Majors, 1989). In the present studies end-tidal halothane concentration did not exceed 0.9% and the cardiac index ranged from 53.9 - 78.9 $ml.kg^{-1}.min^{-1}$ (dopamine) and 52.0 - 99.8 $ml.kg^{-1}.min^{-1}$ (dopexamine). This questions the hypothesis of whether low mean arterial pressure was the single aetiological cause of the severe muscle damage produced in the early studies. The assumption that driving pressure is paramount in maintaining muscle perfusion has been widely accepted and has led to the increasing use of dobutamine in modern equine anaesthetic practice. It has been demonstrated in these studies that in the early stages of infusion in anaesthetised horses dobutamine may reduce cardiac output, despite mean arterial blood pressure increasing. In clinical usage, after arterial blood pressure has increased to an acceptable value, the drug is often discontinued. Lower doses of the drug, 0.5 - 2.0 $\mu g.kg^{-1}.min^{-1}$, are generally employed in the clinical situation and as a consequence of infusion bradydysrhythmias commonly result (Donaldson, 1988). It is unlikely, therefore, that used in this manner dobutamine would significantly increase cardiac output. If low blood pressure as a result of halothane overdose in the early foundation studies occurred secondary to low cardiac output, it is possible that low cardiac output contributed to the production of the devastating lamenesses reported by these workers. If this is the case, it may explain why routine use of dobutamine in clinical equine anaesthesia has not greatly improved its outcome. It is also possible that the haemodynamic effects produced in the anaesthetised horses in the laboratory were not representative of the clinical situation, as the dose of halothane administered greatly exceeded that normally used in general surgery. Clearly the mechanisms underlying

changes in muscle pressure and perfusion which result in muscle damage in anaesthetised horses are not yet fully understood. The established pressure-based theories of muscle perfusion, whilst attractive in their simplicity, are not adequate to explain the mechanisms of muscle dysfunction in this species. Attemps to ellucidate the relationship of driving pressure and blood flow to muscle represents an exciting area for future investigations.

FIGURES FOR CHAPTER 5

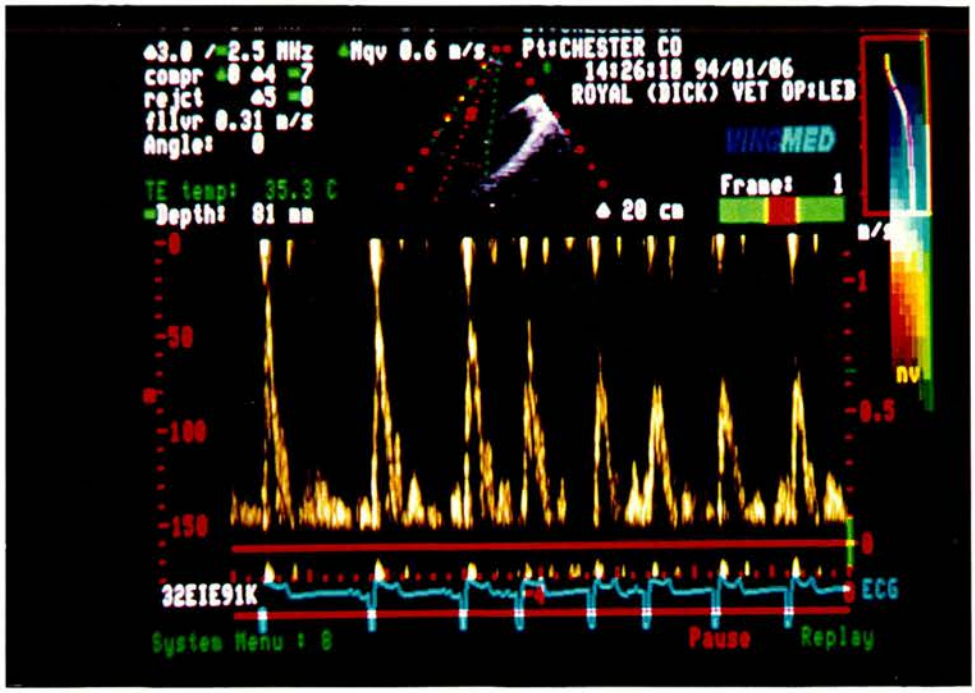

Figure 27: Aortic velocity spectra recorded from Horse 6 during infusion of 4 $\mu gkg^{-1}min^{-1}$ dobutamine.

Six minutes after commencing infusion of dobutamine the heart rate of Horse 6 accelerated into a junctional tachycardia (rate 150 bpm). The rhythm was short-lived and returned to normal sinus rhythm within 5 minutes of stopping dobutamine administration.

This slide shows the transition from normal sinus rhythm to junctional tachycardia. Note the reduction in amplitude and area under the velocity spectra (VTI) as the accelerated rhythm begins.

The study was repeated on a second occasion, and tachycardia reccurred approximately the same time after beginning the infusion.

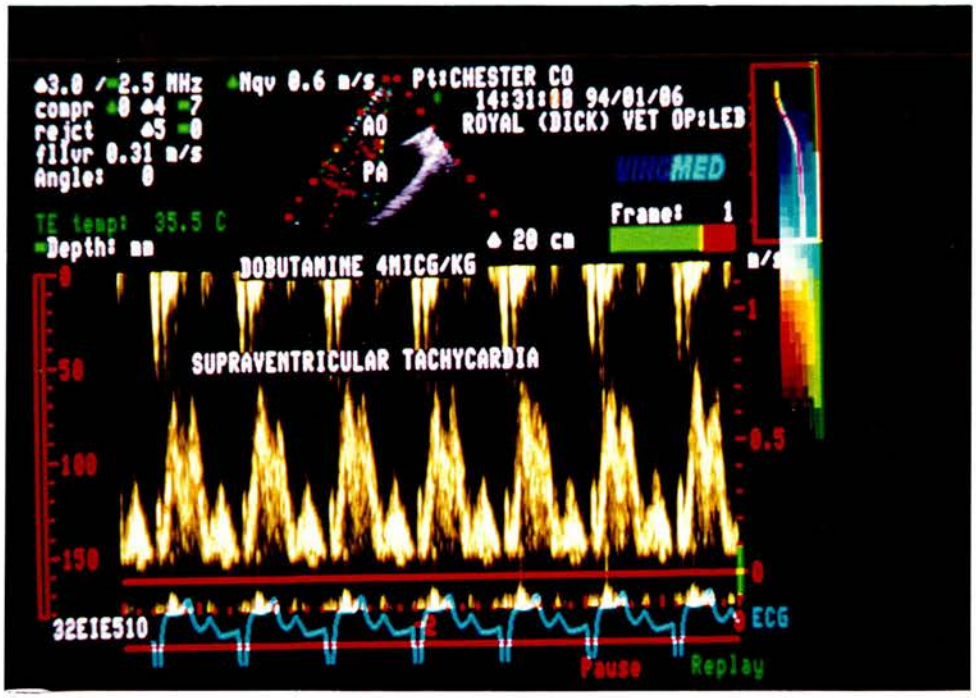

Figure 28: Aortic velocity spectra from Horse 6 during sustained junctional tachycardia.

The spectra are reduced in amplitude (< 0.8 ms^{-1}) and duration. Marked spectral dispersion is evident in the downstroke of the envelope.

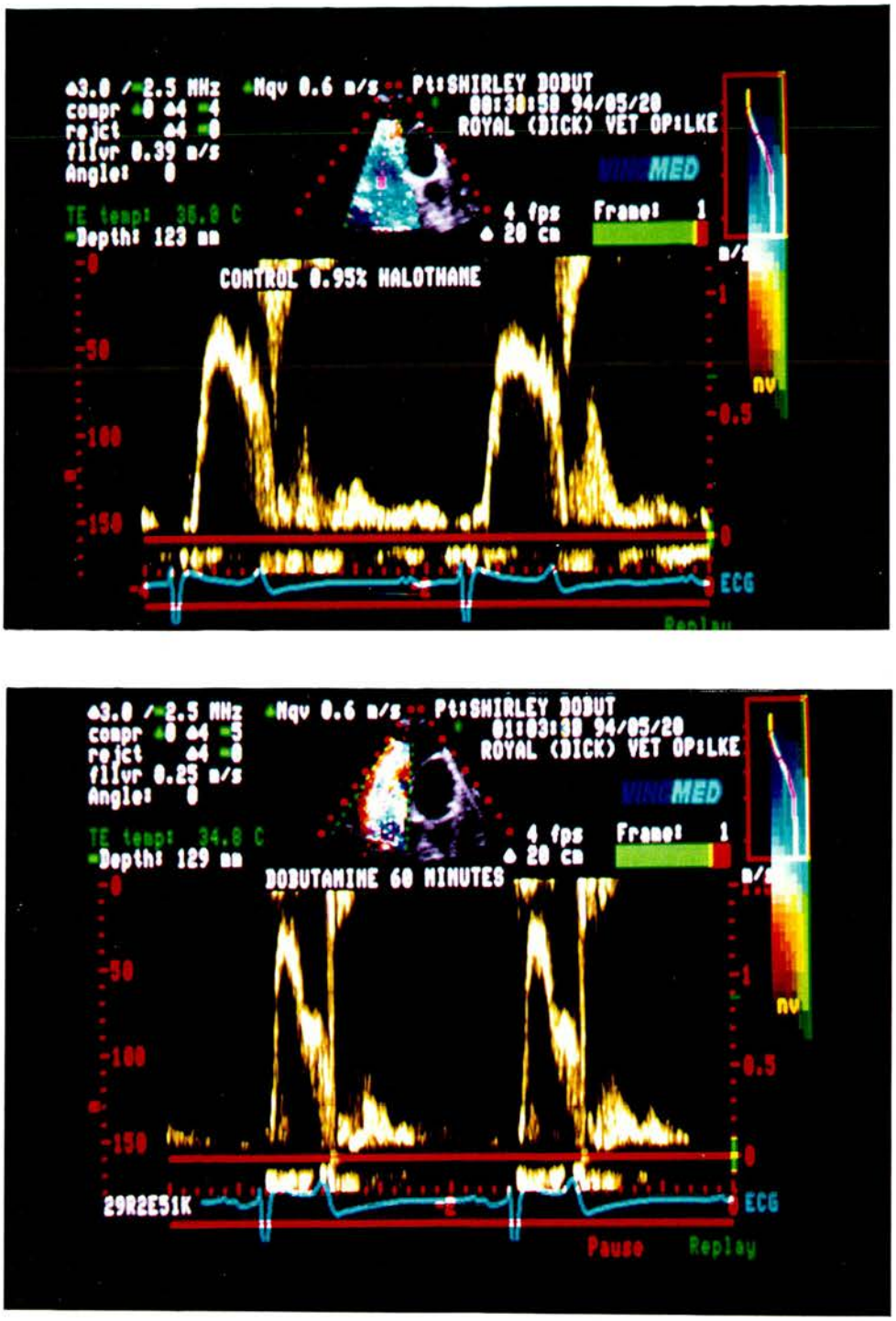

Figure 29: Aortic velocity spectra obtained from Horse 1 before (upper) and after (lower) 60 minutes of 4 $\mu gkg^{-1}min^{-1}$ dobutamine infusion

Notice the velocity scale has been increased from 1.0 to 1.5 ms^{-1}, indicating that maximum velocity (V_{max}) has increased. The upstroke of the spectra is steeper representing an increase in maximum acceleration (dv/dt_{max}) The downstroke of the spectra has become notched. Pre-ejection period (PEP) and ejection time (ET) have both reduced.

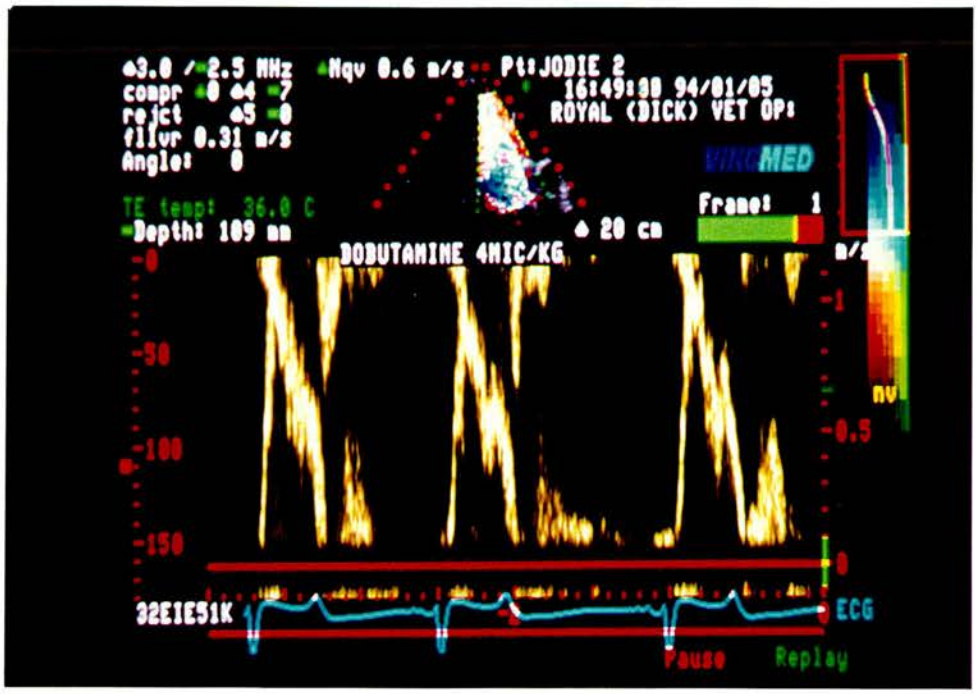

Figure 30: Spectral dispersion in the early downstroke of the aortic flow profiles of Horse 4 during infusion of 4 $\mu gkg^{-1}min^{-1}$ dobutamine

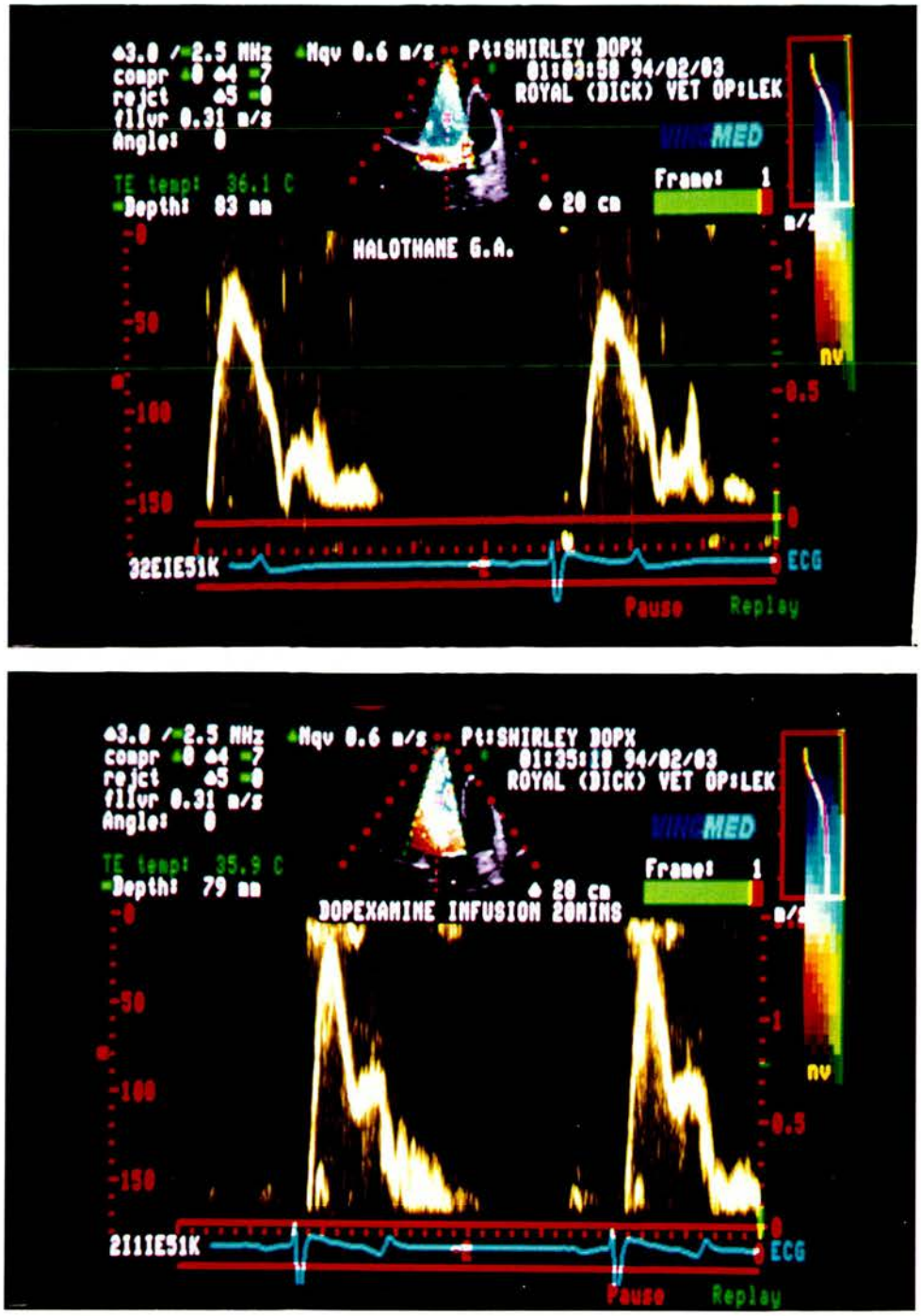

Figure 31: Aortic velocity spectra obtained from Horse 1 before (upper) and after (lower) 20 minutes of 4 $\mu gkg^{-1}min^{-1}$ dopexamine infusion

The velocity scale has been increased from 1.0 to 1.5 ms^{-1}, indicating that maximum velocity (V_{max}) has increased. The upstroke of the spectra is more steep representing an increase in maximum acceleration (dv/dt_{max}). The downstroke of the spectra became notched. Pre-ejection period (PEP) has reduced and ejection time has increased. Infusion of dopexamine was associated with large increases in cardiac output, evidenced by the increased area under the velocity envelope and slight increases in heart rate.

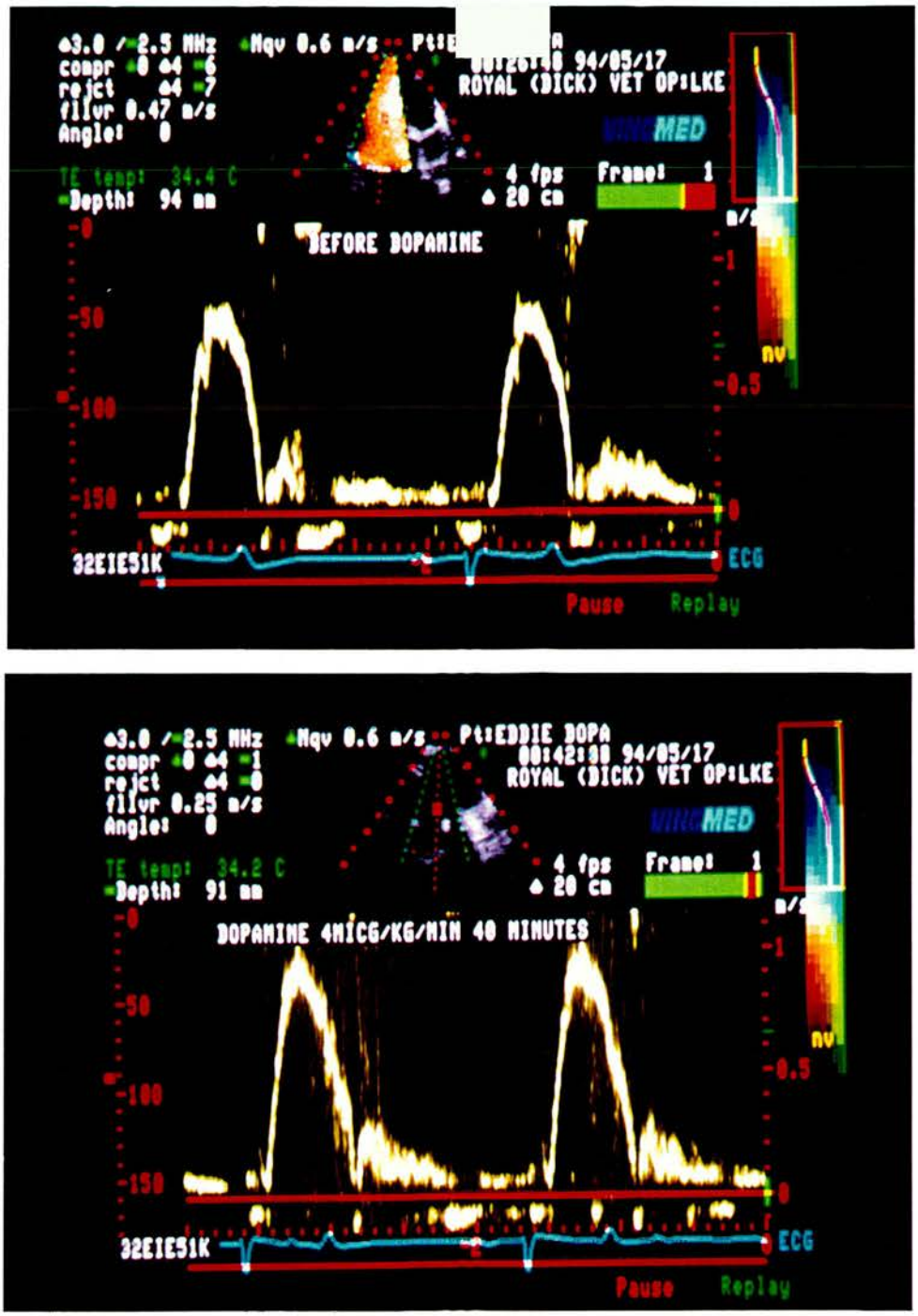

Figure 32: Aortic velocity spectra obtained from Horse 1 before (upper) and after (lower) 40 minutes of 4 $\mu gkg^{-1}min^{-1}$ dopamine infusion

Notice that there has been only a small increase in maximum velocity (V_{max}) and maximum acceleration (dv/dt_{max}). The overall shape of the spectra is unchanged. The area under the velocity profile (VTI) is larger because of a significantly increased ejection time (ET)

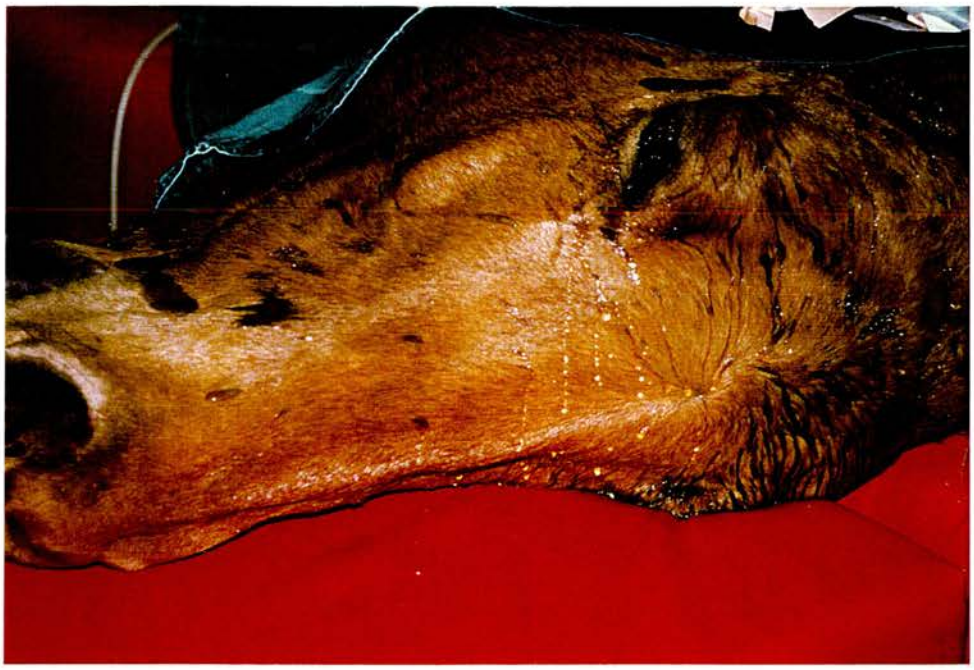

Figure 33: Horse 1 during infusion of 4 $\mu gkg^{-1}min^{-1}$ dopexamine.

Dopexamine was associated with pronounced sweating in all horses. This slide was taken 20 minutes after the start of infusion in Horse 1.

GENERAL DISCUSSION

Transoesophageal echocardiography has been demonstrated to be a valuable technique for assessment of left ventricular function in anaesthetised horses. The number of two dimensional (2-D) images obtainable from transoesophageal echocardiography in horses is limited compared to the large number of reference views available in humans. This probably results from the greater distance between the oesophagus and the heart, and the differences in thoracic anatomy between biped and quadruped species. However a long axis view of the left ventricular outflow tract and aorta was repeatably obtained by transoesophageal echocardiography in horses, and the alignment of the ultrasound beam with ascending aortic blood flow was ideal for Doppler echocardiography. Doppler echocardiographic studies of aortic blood flow velocity obtained from the oesophageal probe were suitable for measurement of indices of left ventricular performance.

In transoesophageal echocardiography the ultrasound transducer is fixed in the oesophagus and controlled from a site distant from the patient, it is thus ideally suited for use in the operating theatre. The technique is minimally invasive and appears to be well tolerated in healthy thoroughbred horses. Cardiac catheterisation is not required, removing the risks that have previously restricted haemodynamic monitoring to the laboratory. Transoesophageal echocardiography will allow haemodynamic monitoring to be performed in client-owned animals, so that the interactions between general anaesthesia and surgery can be evaluated in horses presented for both elective and emergency procedures.

Chapter 3 of this work showed that the repeatability of the indices of left ventricular performance derived from Doppler echocardiography were similar to those derived from cardiac catheterisation. Overall the repeatability of blood pressure and Doppler derived data were poor compared to those obtained previously for conscious

horses and humans. This suggests that general anaesthesia interferes with normal homeostatic control of cardiovascular performance in horses.

Transoesophageal echocardiography provides a non-invasive alternative to thermodilution method for measurement of cardiac output in anaesthetised horses. The technique affords a number of advantages over the traditional method, avoiding the need for cardiac catheterisation and allowing continuous prolonged monitoring to be performed. In these studies the limits of agreement and linear relationships between Doppler derived estimations of cardiac output and those derived from thermodilution exceeded those obtained when thermodilution was compared to transoesophageal echocardiography in humans and transthoracic echocardiography in conscious horses. The improved agreement probably reflects superior, and more repeatable, alignment of the ultrasound beam with aortic blood flow.

Chapter 5 of this work showed that the Doppler derived index of cardiac performance, maximum aortic acceleration (dv/dt_{max}), was as sensitive as the maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$) in detecting the changes in cardiac performance produced by administration of dobutamine, dopexamine and dopamine. Maximum aortic velocity (V_{max}) also changed with catecholamine infusion, but the magnitude of the changes were less than for $LVdp/dt_{max}$ and dv/dt_{max}, reflecting reduced sensitivity to the drugs administered. Despite being derived during ventricular ejection, dv/dt_{max} and V_{max} were no more load dependent than $LVdp/dt_{max}$, an index obtained during isovolumic systole. Velocity time interval (VTI) and the systolic time intervals (PEP and ET) also showed sensitivity to catecholamime infusion, supporting the suggestion that cardiac performance is better judged from as complete a set of data as possible, rather than from a single variable. Because transoesophageal echocardiography provides a number of indices of ventricular performance it has great potential for evaluating the complex haemodynamic disturbances of the anaesthetised horse.

Further information can be provided by 2-D echocardiography which permits measurement of chamber volumes and the non-invasive assessment of preload. Integration of 2-D and Doppler echocardiographic data should provide more complete assessment of cardiac performance and represents an exciting area for future investigations. Although the depth of intracardiac structures in horses currently limits the 2-D information available from transoesophageal echocardiography, advances in ultrasound technology and probe design may overcome this limitation.

Chapter 5 also called into question the hypothesis that low mean arterial blood pressure was associated with muscle dysfunction in anaesthetised horses. These studies showed that when cardiac index was high, post-anaesthetic lameness did not occur, despite prolonged periods of hypotension in horses anaesthetised with halothane. These findings suggest that fundamental mechanistic studies are now required to elucidate the relationship of pressure and flow in determining muscle perfusion. Ideally the intracompartmental pressure hypothesis should be tested by simultaneous measurement of muscle blood flow by techniques such as Laser Doppler flowmetry. The relationship between central and peripheral arterial pressures, cardiac output and muscle blood flow must be determined before rational preventative therapy for post-operative lameness and morbidity can be established. Because there is a higher incidence of morbidity and mortality associated with general anaesthesia in horses, improvements in our monitoring capabilities by the techniques provided by cardiac ultrasound must increase our understanding of the complex haemodynamic disturbances that occur in this species.

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APPENDICES

Appendix 1: Characteristics of Experimental Group

Horse	Stable Name	Age (yrs) at study start [a]	Sex	Weight (kg)	Abnormalities on cardiac auscultation/ECG
1	Shirley	6	Mare	495	Marked sinus block at rest
2	Vivienne	5	Mare	515	None
3	Hailey	4	Mare	519	None
4	Jodie	4	Mare	495	None
5	Eddie	4	Gelding	550	None
6	Chester	3	Gelding	600	None
7	Legs	3	Gelding	615	None
8	Khaloof	4	Gelding	560	Grade 2[b], late systolic tricuspid murmur[c]

[a] Age in years taken from 1st January according to Wetherby's regulations

[b] Grading of cardiac murmurs from (Long, 1993)

[c] Murmurs of tracuspid regurgitation are considered to have a point of maximal intensity on the right hemithorax (Long, 1993) Late systolic regurgitation of blood into the right atrium was also confirmed by colour Doppler echocardiography

APPENDIX FOR CHAPTER 3

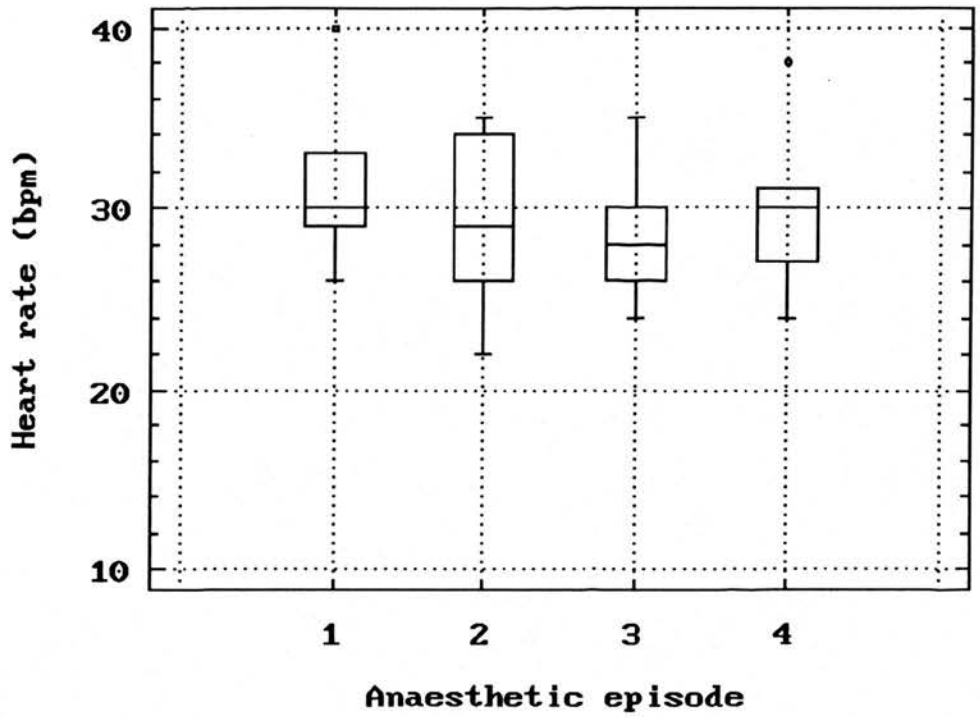
In all box and whisker plots the central horizontal lines in the boxes represent the median value.

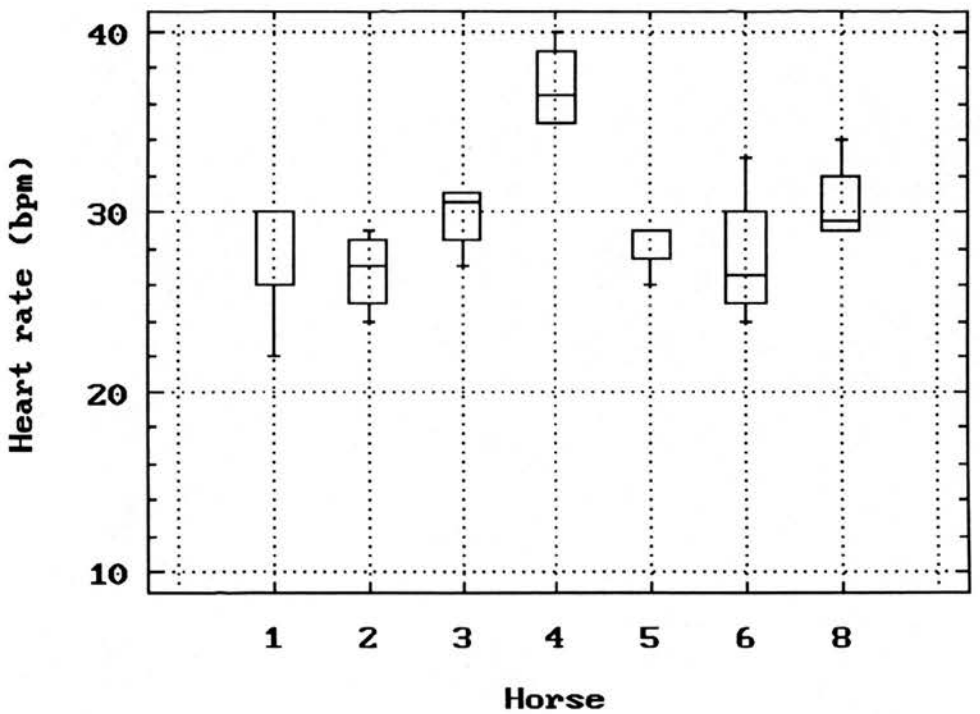
The upper and lower horizontal box boundaries are the upper and lower quartiles.

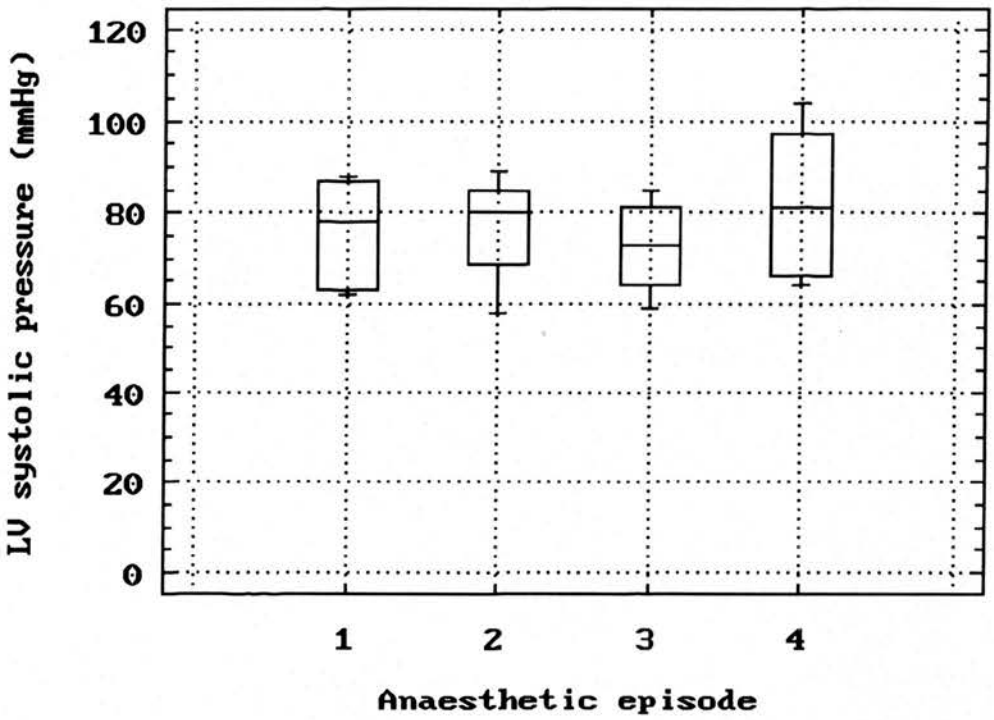
The vertical whiskers are drawn from the smallest, or largest data point, within 1.5 interquartile ranges from either quartile

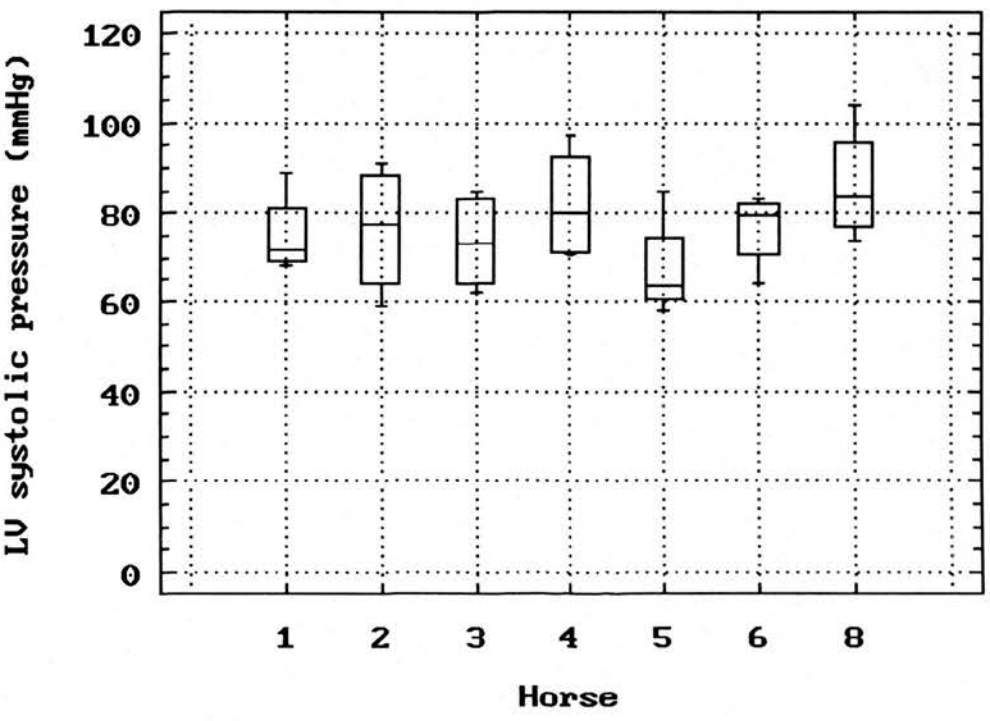
Outlying points are shown by a point.

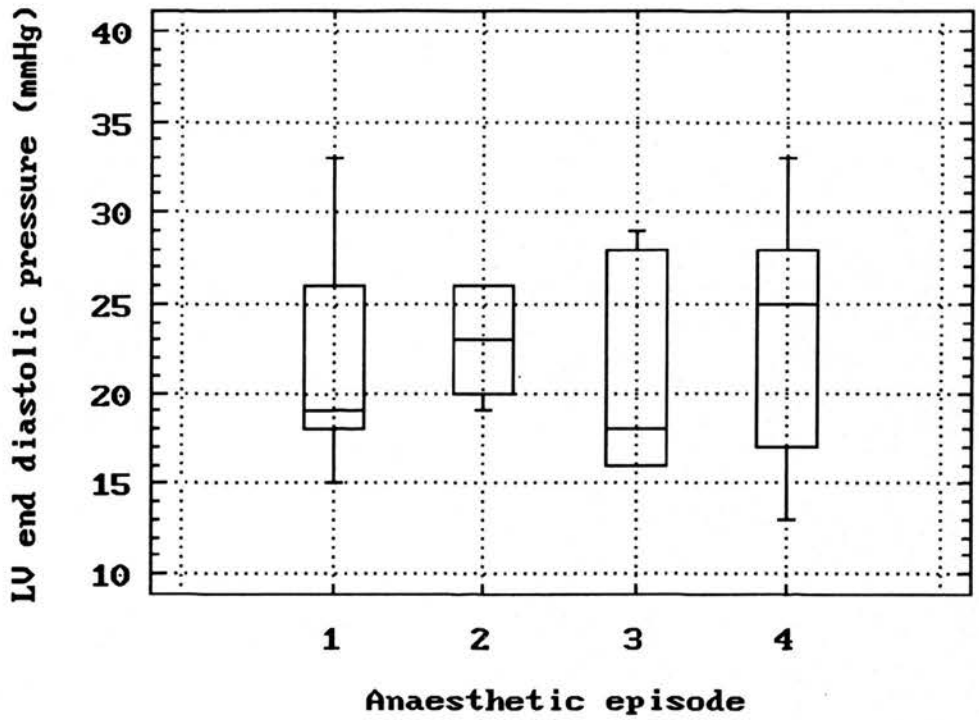
Special data points (e.g. crosses or elipses) are used to indicate far outlying data, more than three interquartile ranges from the upper, or lower, quartile

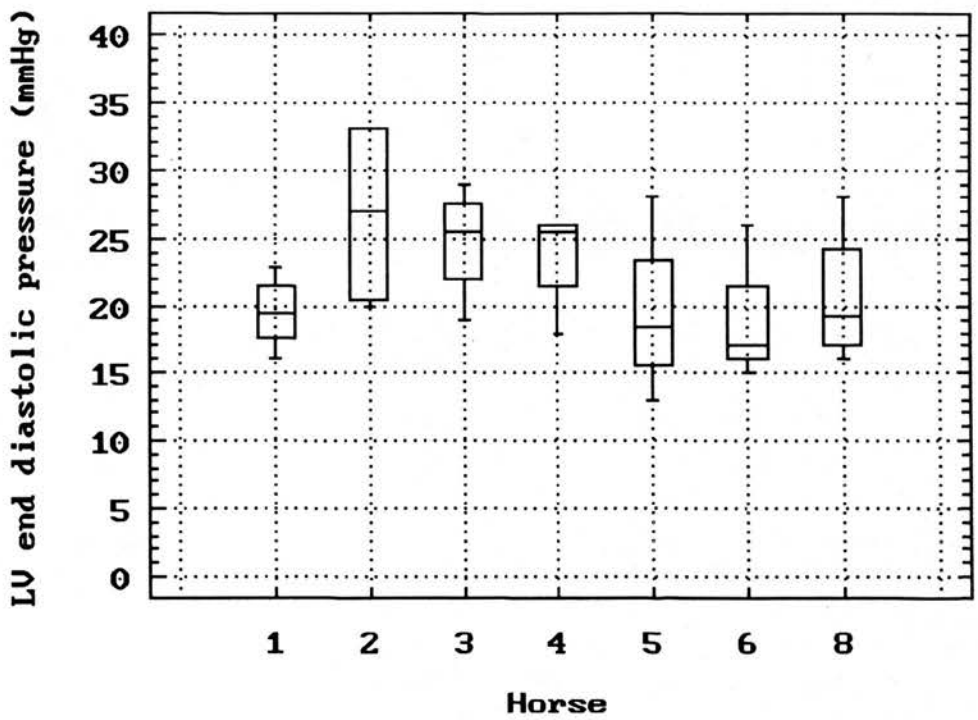

Heart rate (bpm)
40
30
20
10
1
2
3
4
Anaesthetic episode


Heart rate (bpm)
40
30
20
10
1
2
3
4
5
6
8
Horse


LV systolic pressure (mmHg)
120
100
80
60
40
20
0
1
2
3
4
Anaesthetic episode


LV systolic pressure (mmHg)
120
100
80
60
40
20
0
1
2
3
4
5
6
8
Horse


LV end diastolic pressure (mmHg)
40
35
30
25
20
15
10
1
2
3
4
Anaesthetic episode


LV end diastolic pressure (mmHg)
40
35
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25
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15
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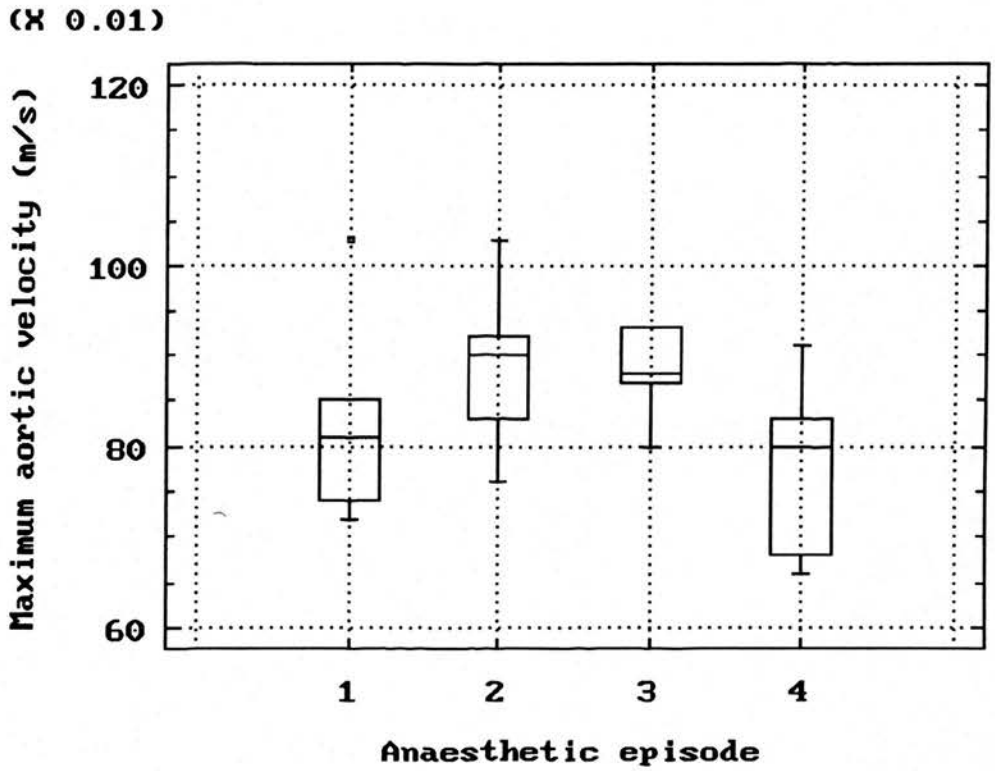
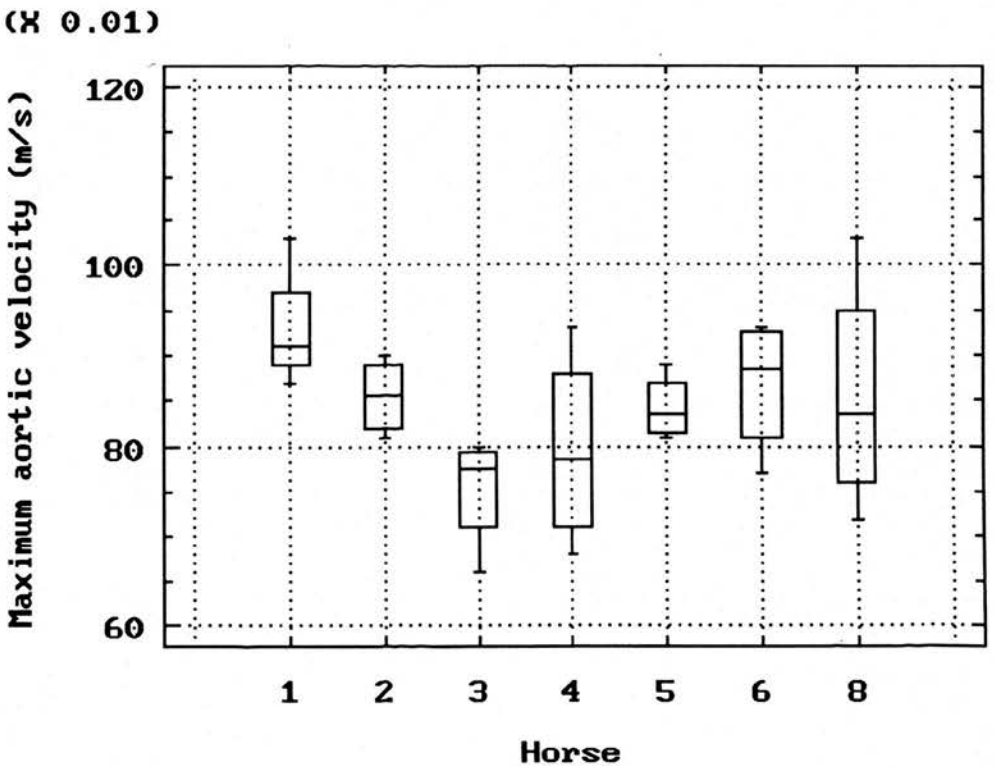
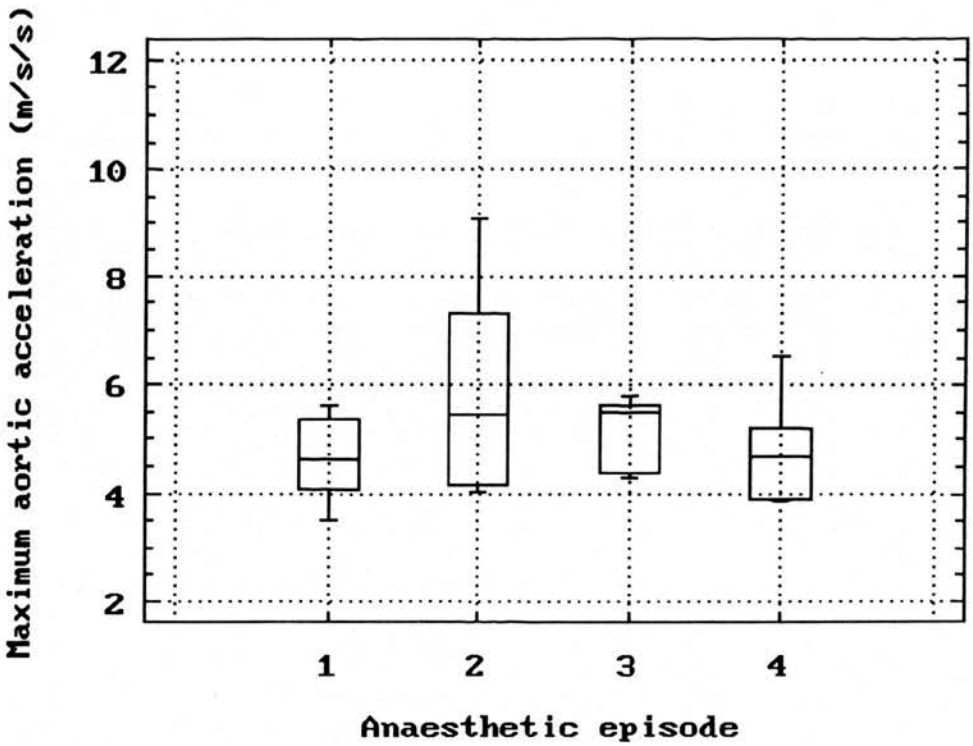
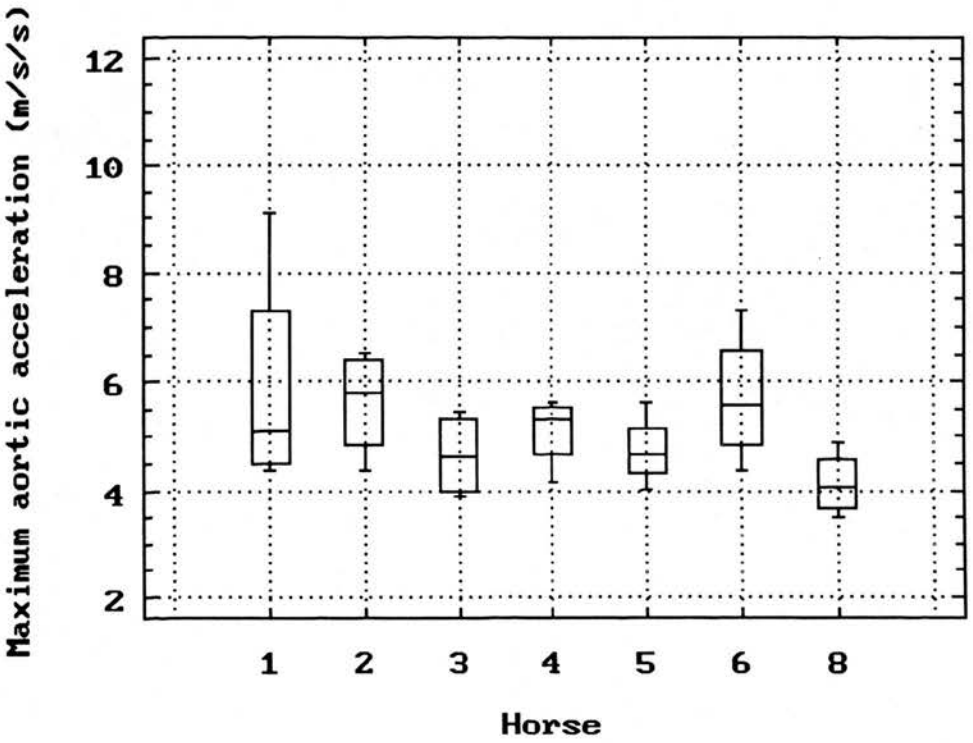
3
4
5
6
8
Horse


(X 0.01)
Maximum aortic velocity (m/s)
120
100
80
60
1
2
3
4
Anaesthetic episode


(X 0.01)
Maximum aortic velocity (m/s)
120
100
80
60
1
2
3
4
5
6
8
Horse


Maximum aortic acceleration (m/s/s)
12
10
8
6
4
2
1
2
3
4
Anaesthetic episode


Maximum aortic acceleration (m/s/s)
12
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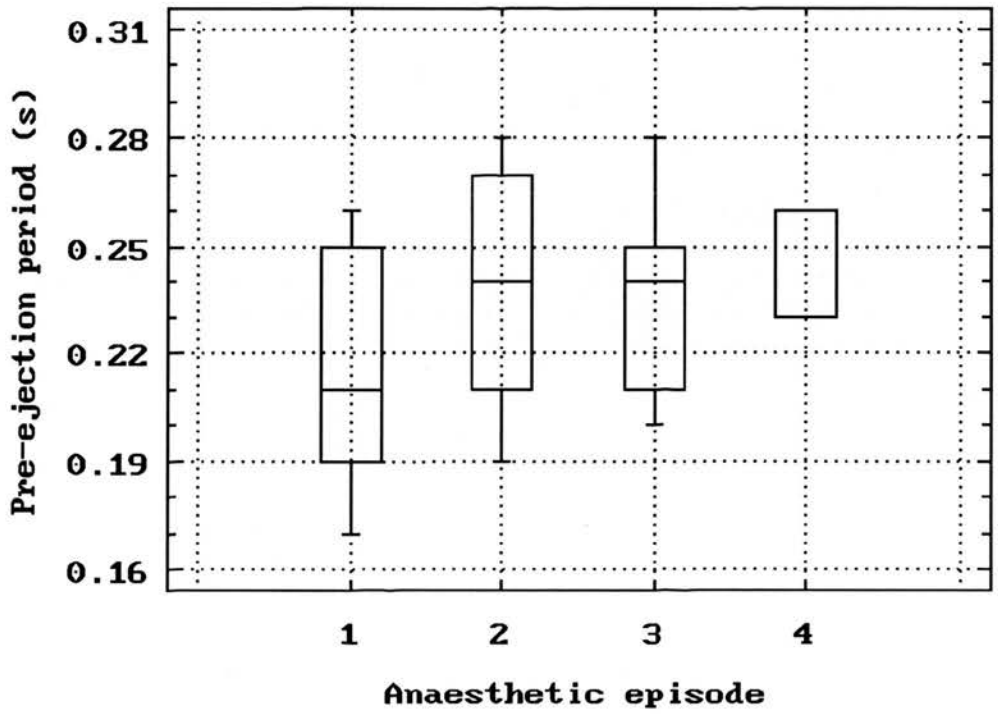
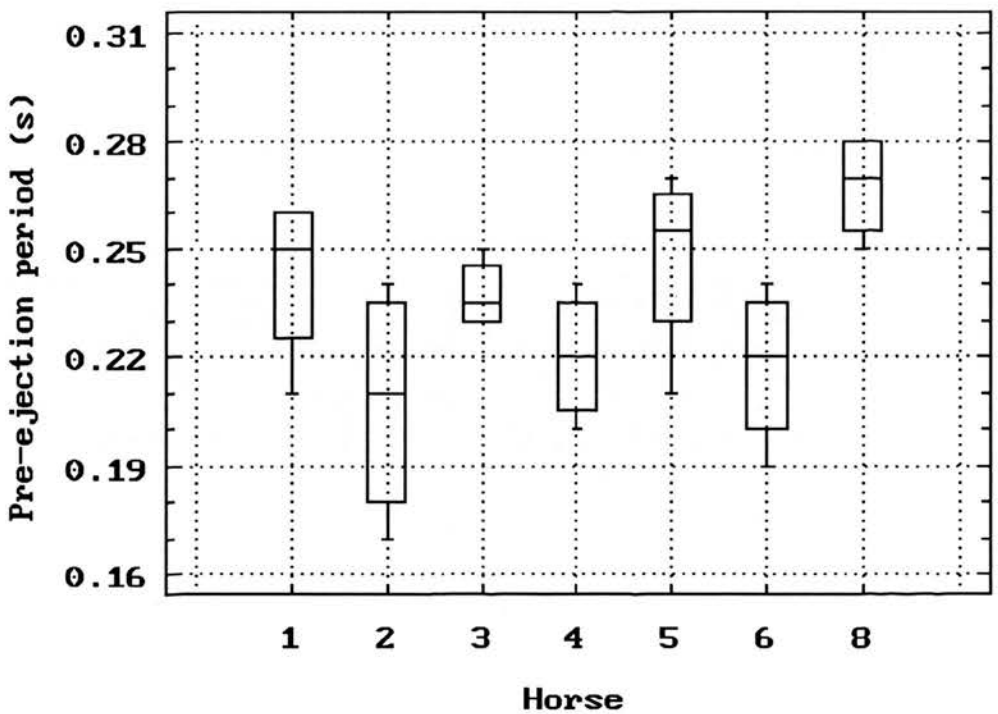
6
8
Horse


Pre-ejection period (s)
0.31
0.28
0.25
0.22
0.19
0.16
1
2
3
4
Anaesthetic episode


Pre-ejection period (s)
0.31
0.28
0.25
0.22
0.19
0.16
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2
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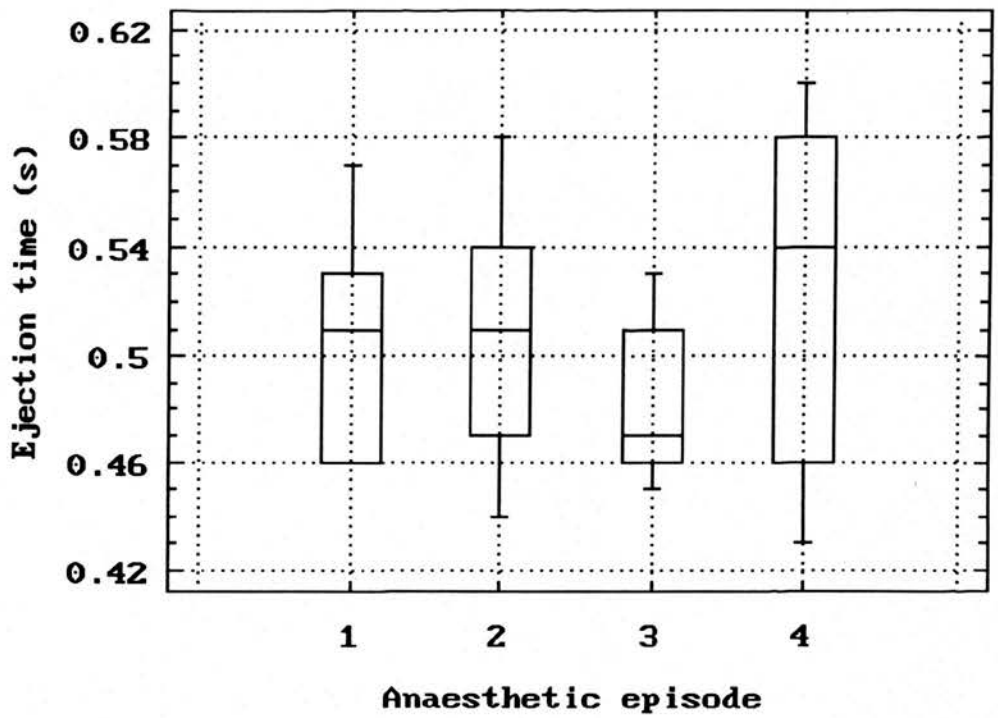
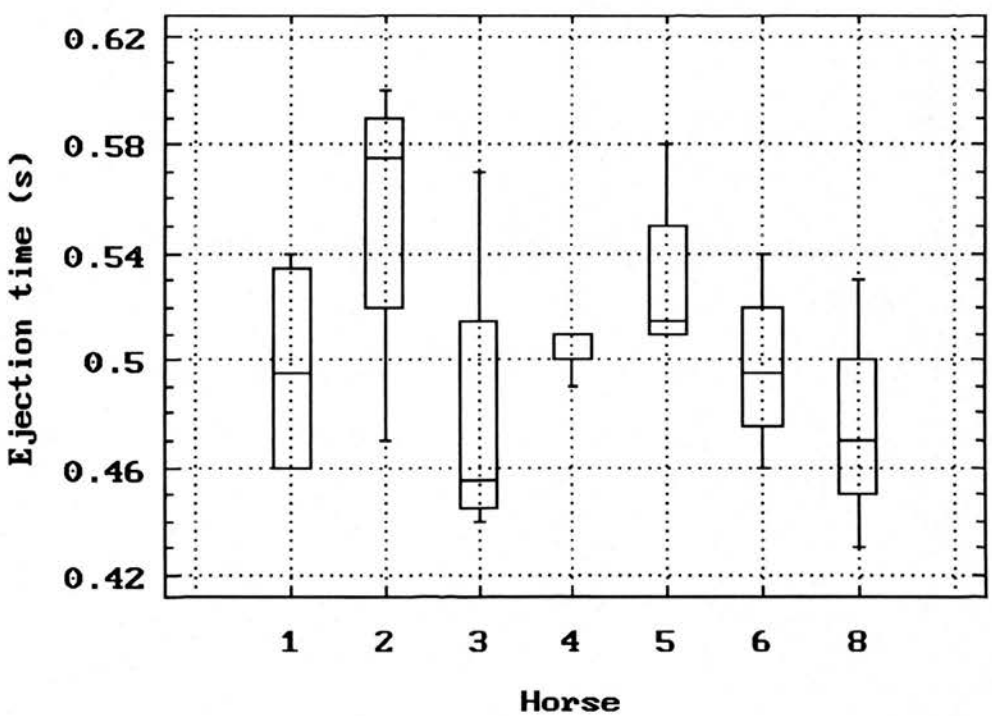
4
5
6
8
Horse


0.62
0.58
0.54
0.5
0.46
0.42
Ejection time (s)
1
2
3
4
Anaesthetic episode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0.42
Ejection time (s)
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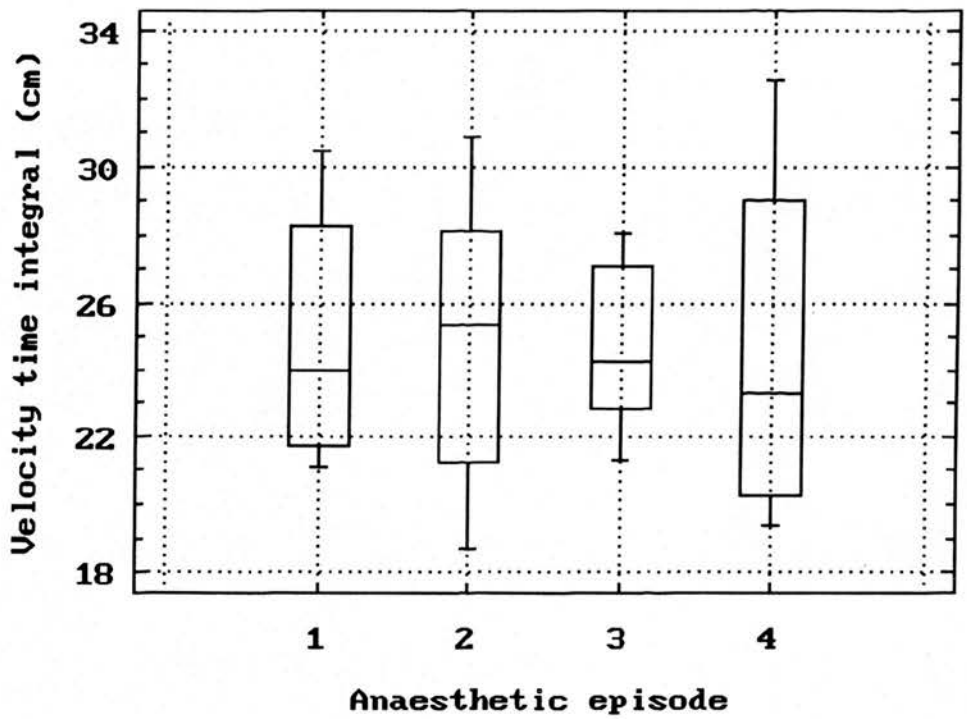
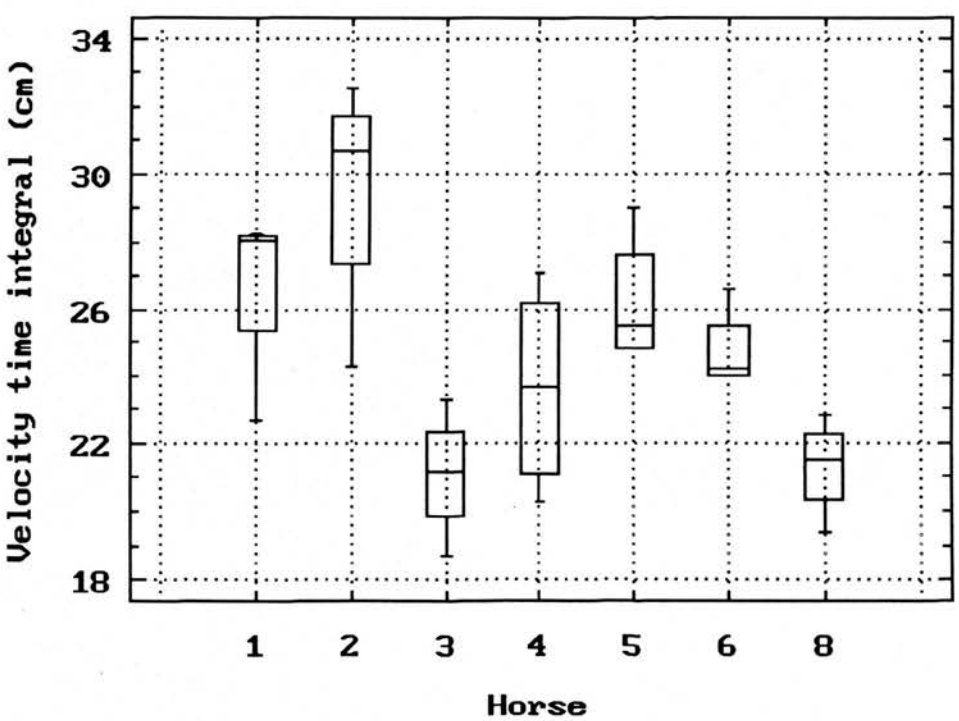
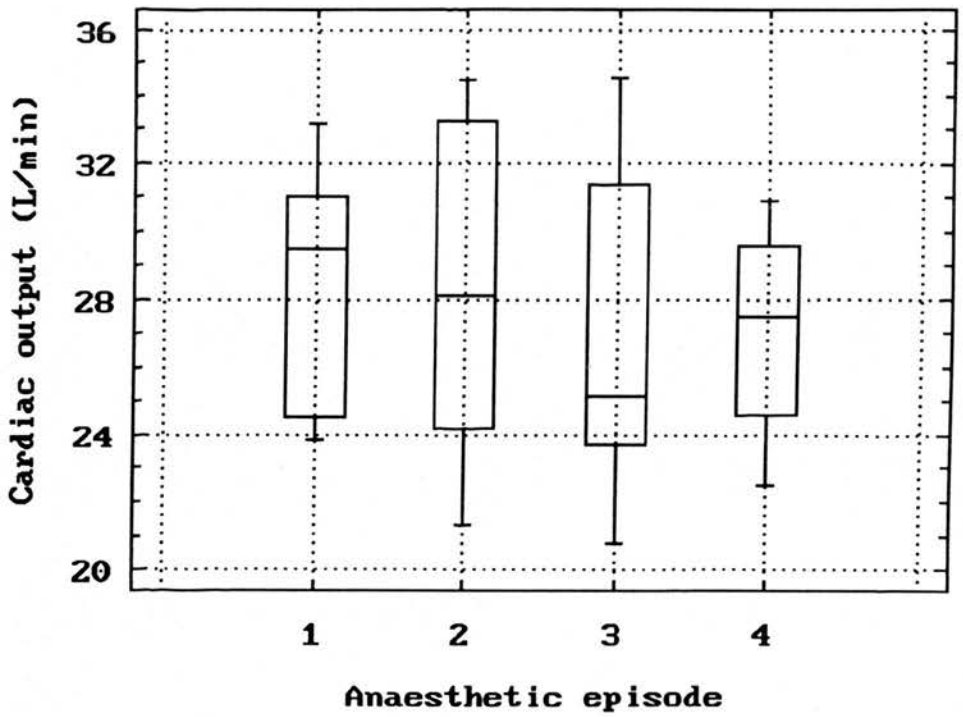
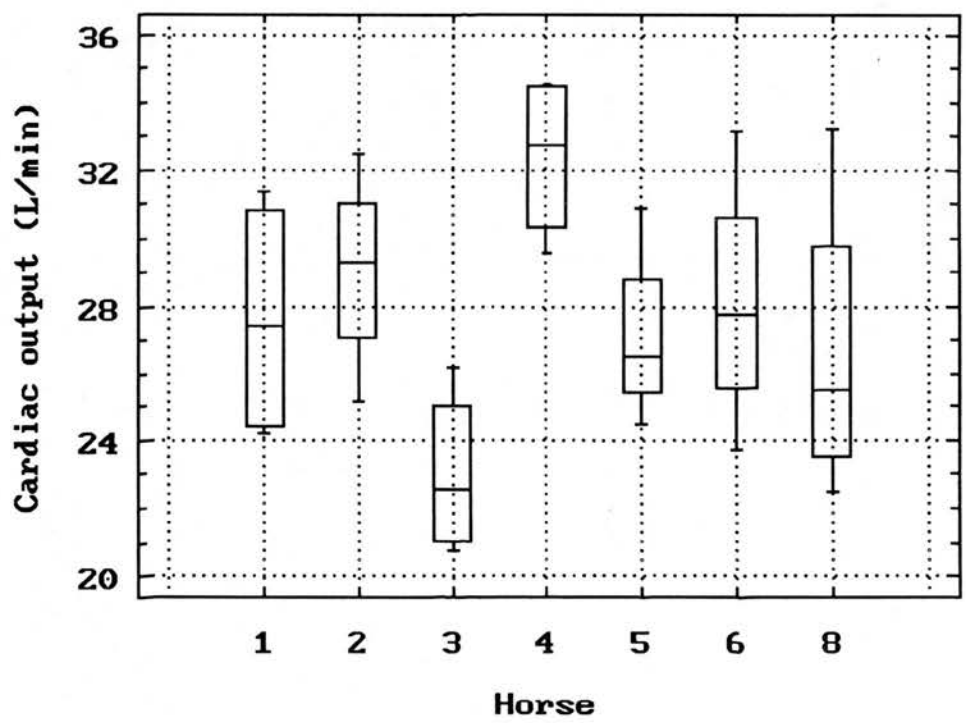
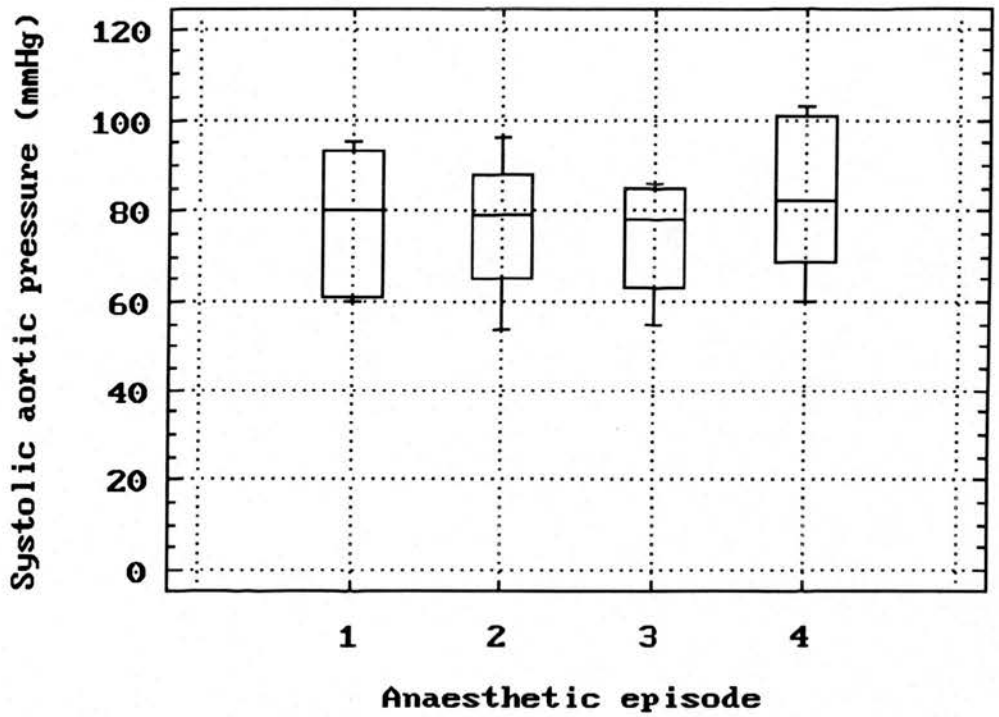
6
8
Horse

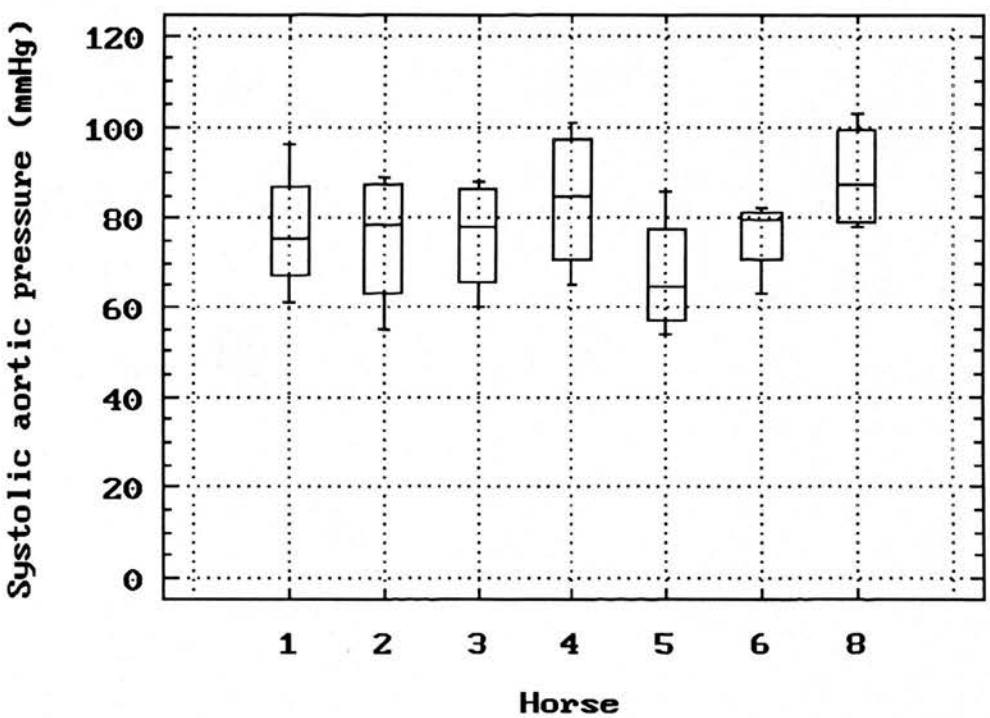

Velocity time integral (cm)
34
30
26
22
18
1
2
3
4
Anaesthetic episode

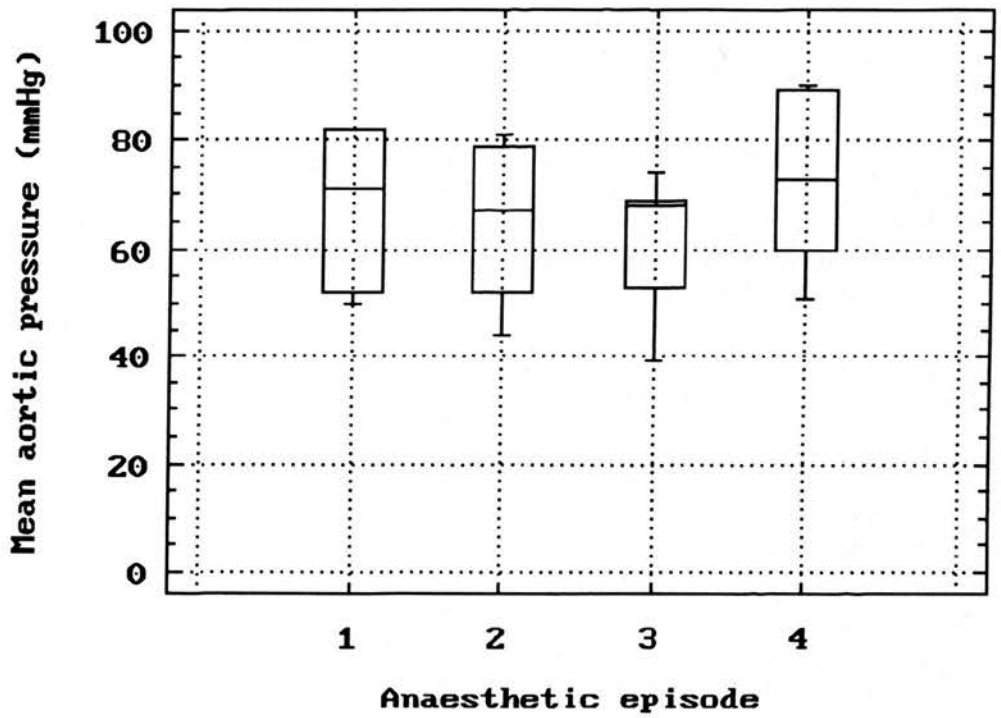

Velocity time integral (cm)
34
30
26
22
18
1
2
3
4
5
6
8
Horse

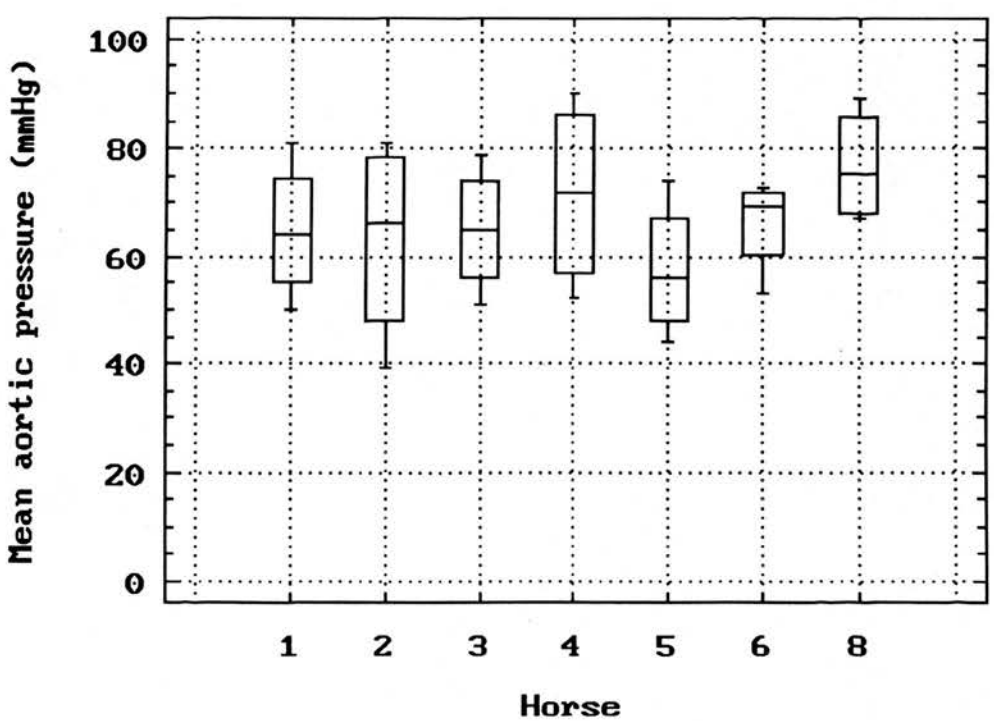

Cardiac output (L/min)
36
32
28
24
20
1
2
3
4
Anaesthetic episode

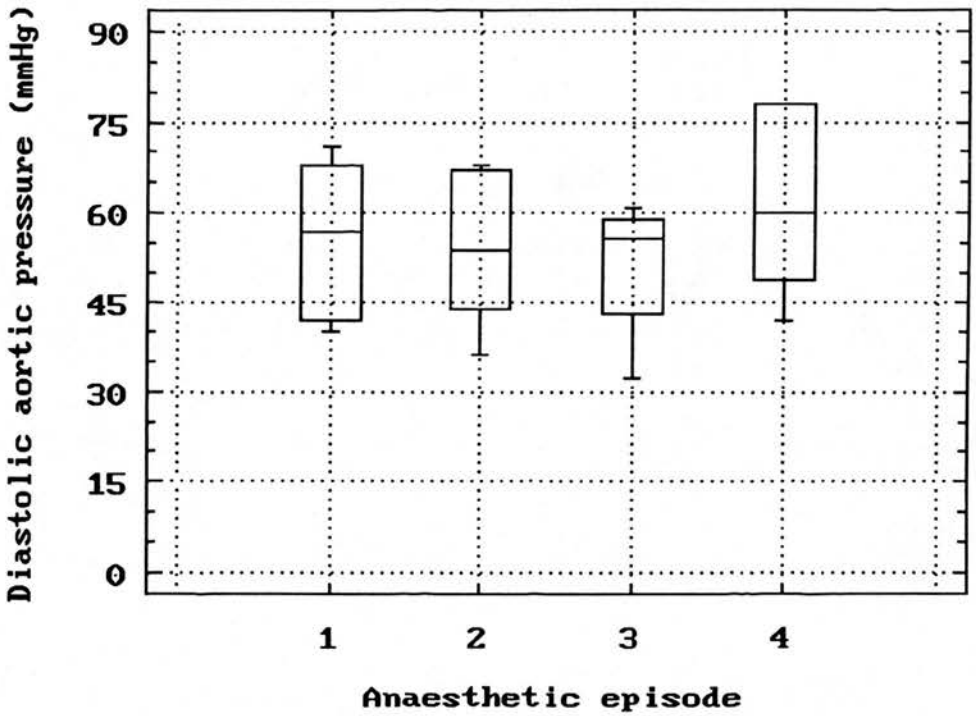

Cardiac output (L/min)
36
32
28
24
20
1
2
3
4
5
6
8
Horse

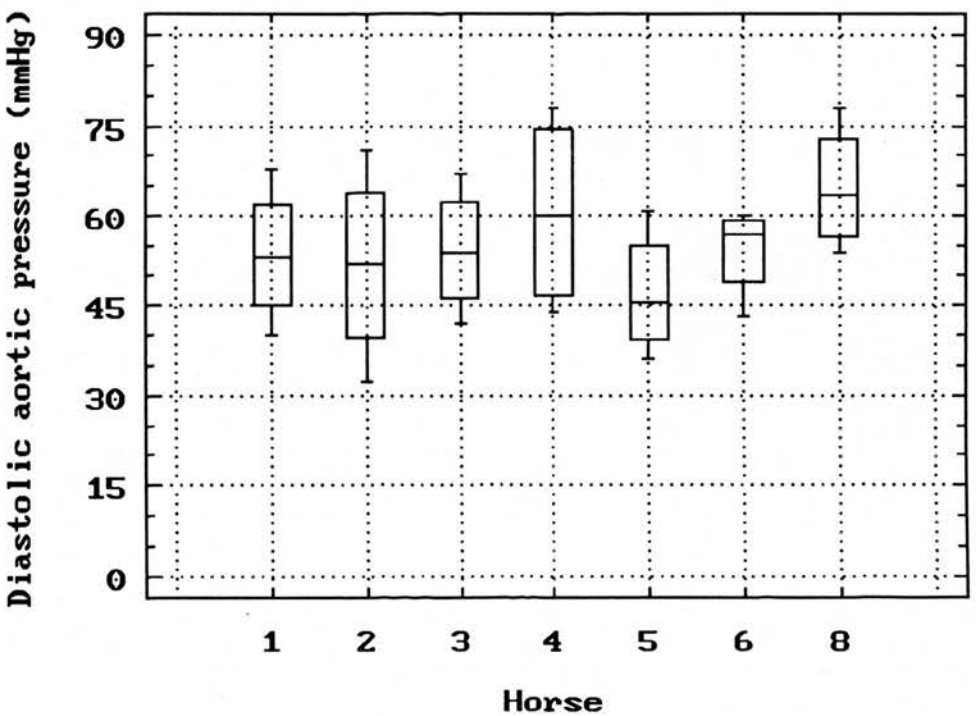

Systolic aortic pressure (mmHg)
120
100
80
60
40
20
0
1
2
3
4
Anaesthetic episode

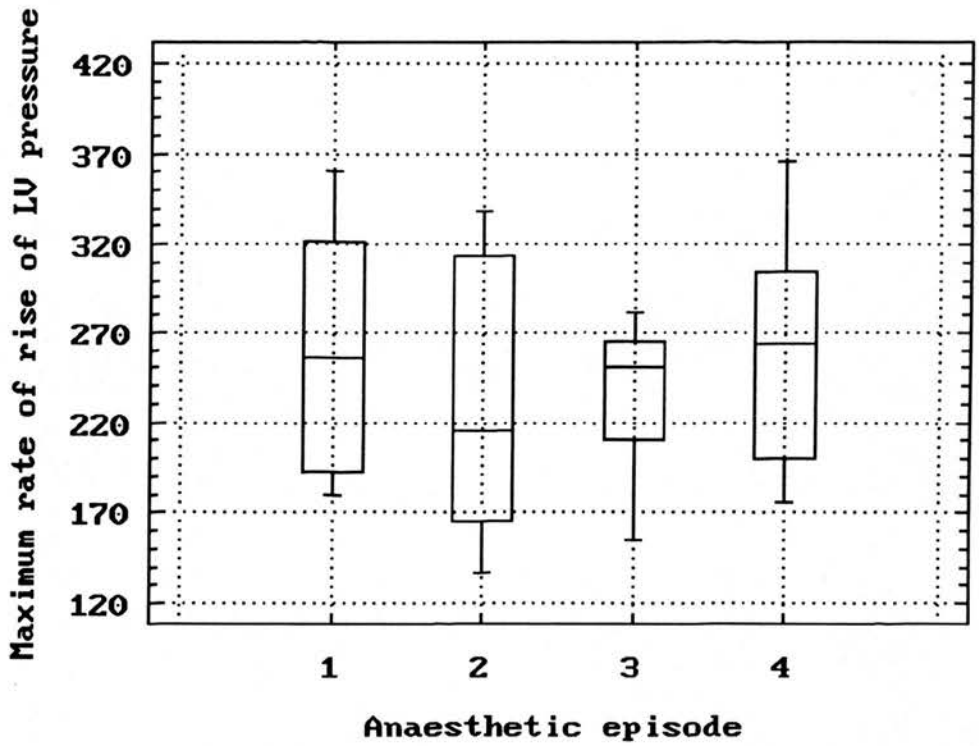

Systolic aortic pressure (mmHg)
120
100
80
60
40
20
0
1
2
3
4
5
6
8
Horse

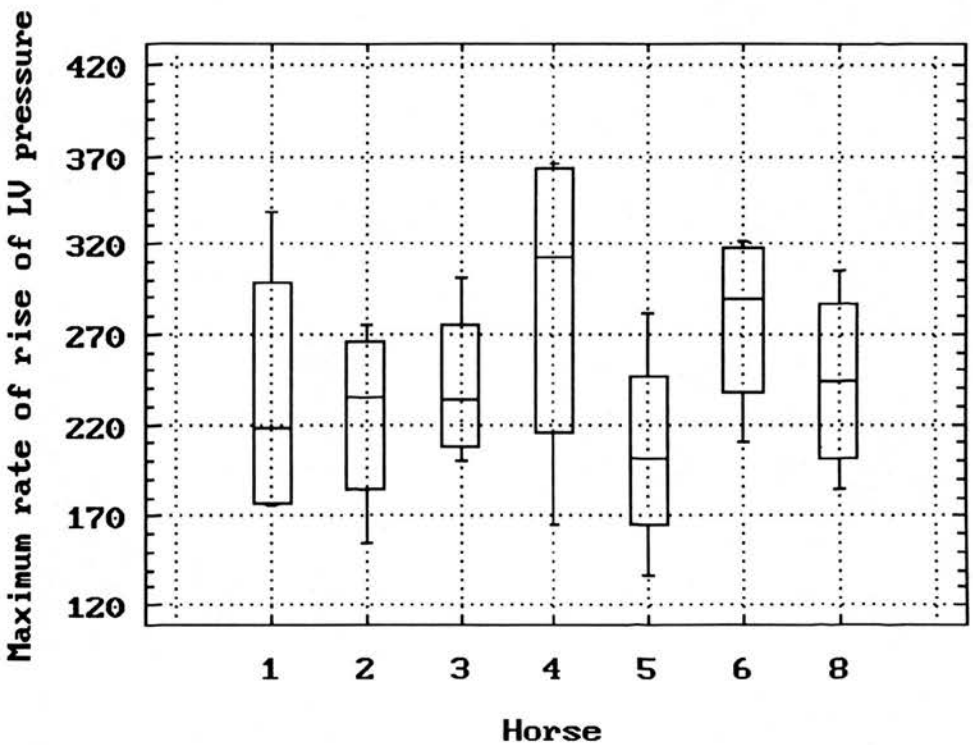

Mean aortic pressure (mmHg)
100
80
60
40
20
0
1
2
3
4
Anaesthetic episode


Mean aortic pressure (mmHg)
100
80
60
40
20
0
1
2
3
4
5
6
8
Horse

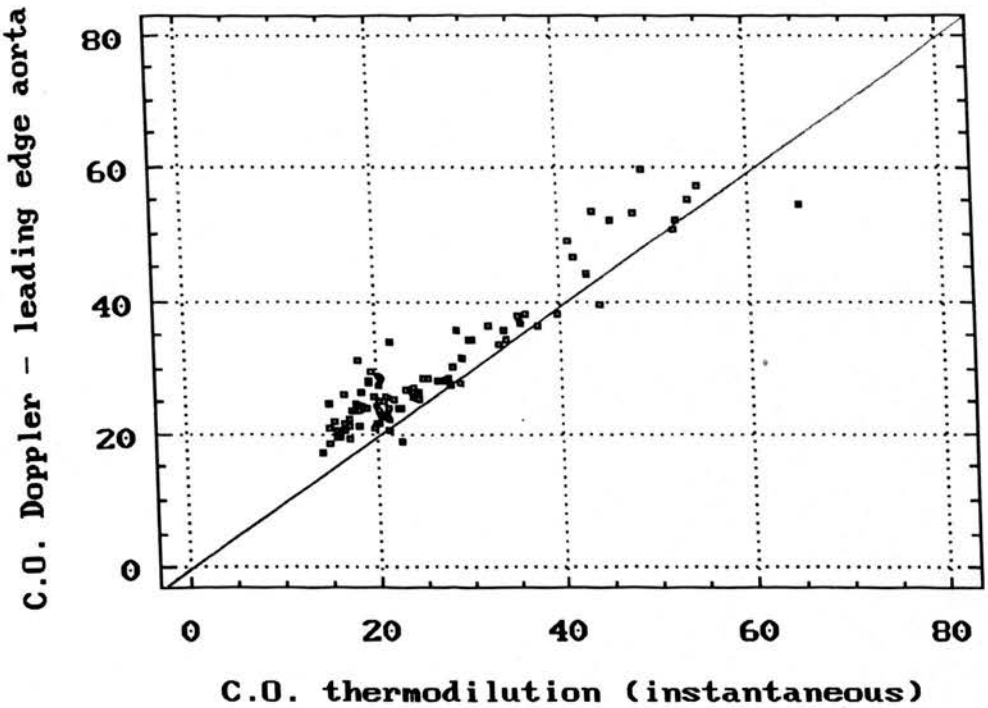

Diastolic aortic pressure (mmHg)
90
75
60
45
30
15
0
1
2
3
4
Anaesthetic episode

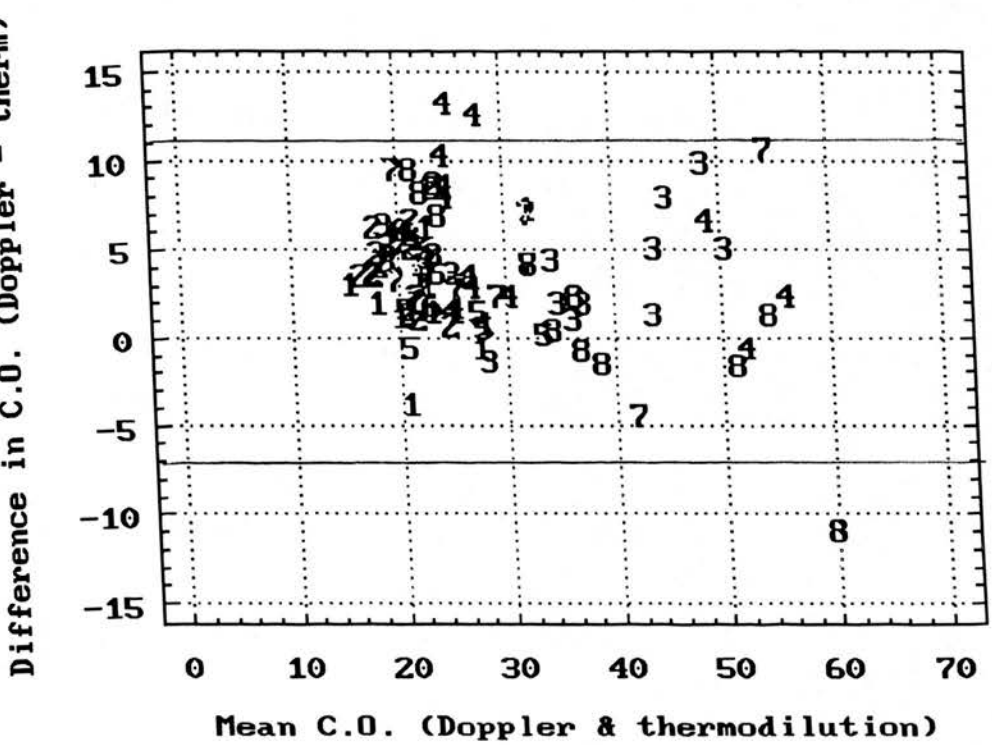

Diastolic aortic pressure (mmHg)
90
75
60
45
30
15
0
1
2
3
4
5
6
8
Horse

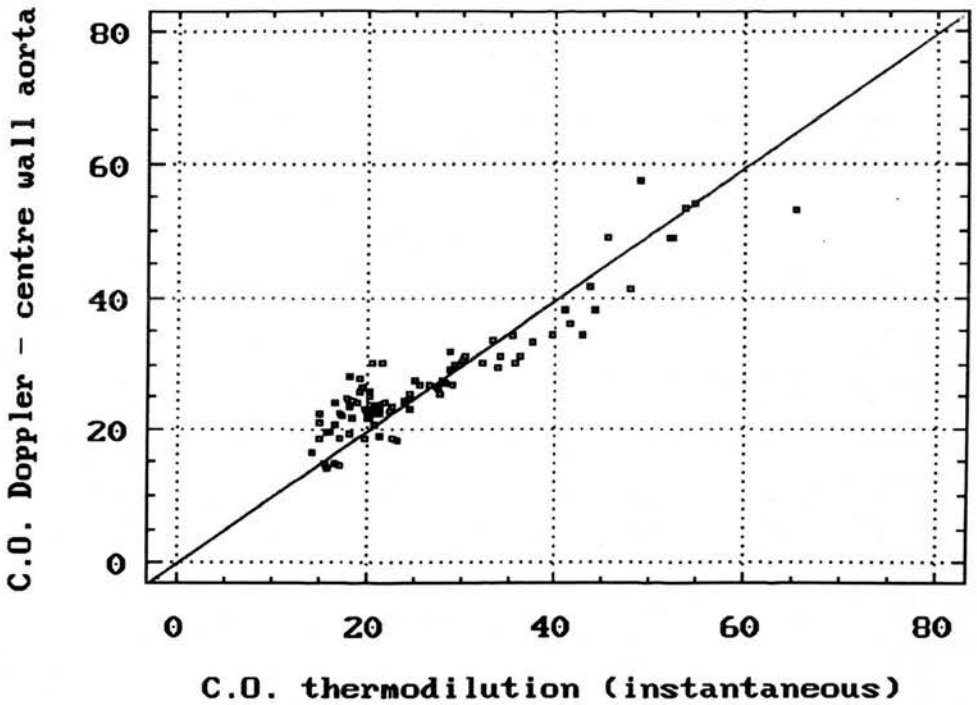

Maximum rate of rise of LV pressure
420
370
320
270
220
170
120
1
2
3
4
Anaesthetic episode

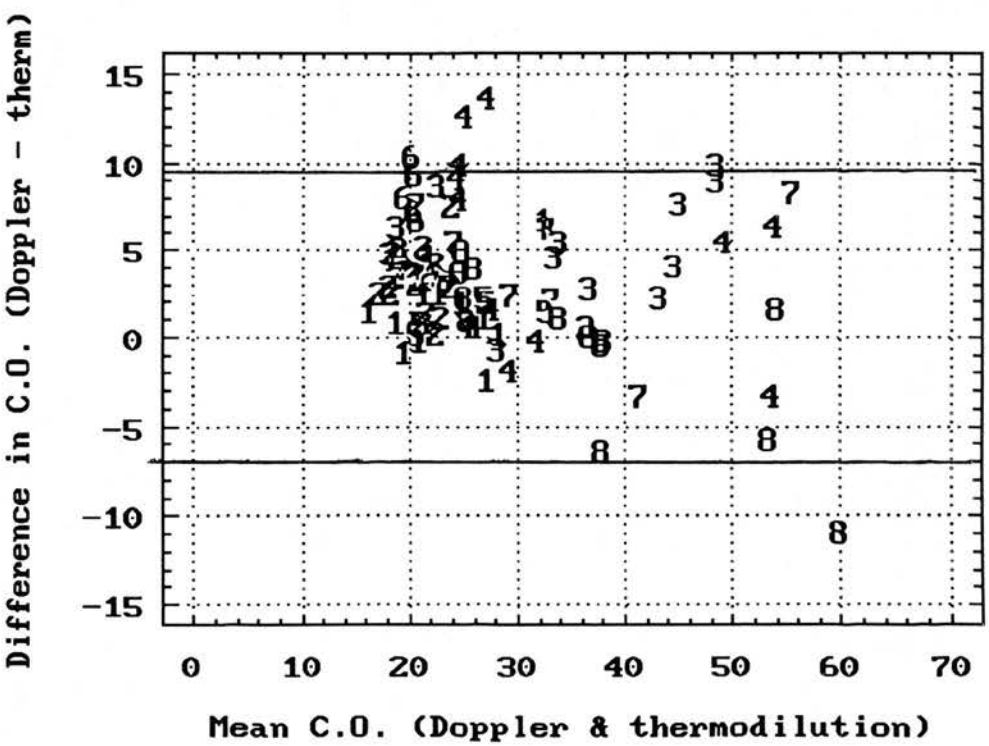

Maximum rate of rise of LV pressure
420
370
320
270
220
170
120
1
2
3
4
5
6
8
Horse

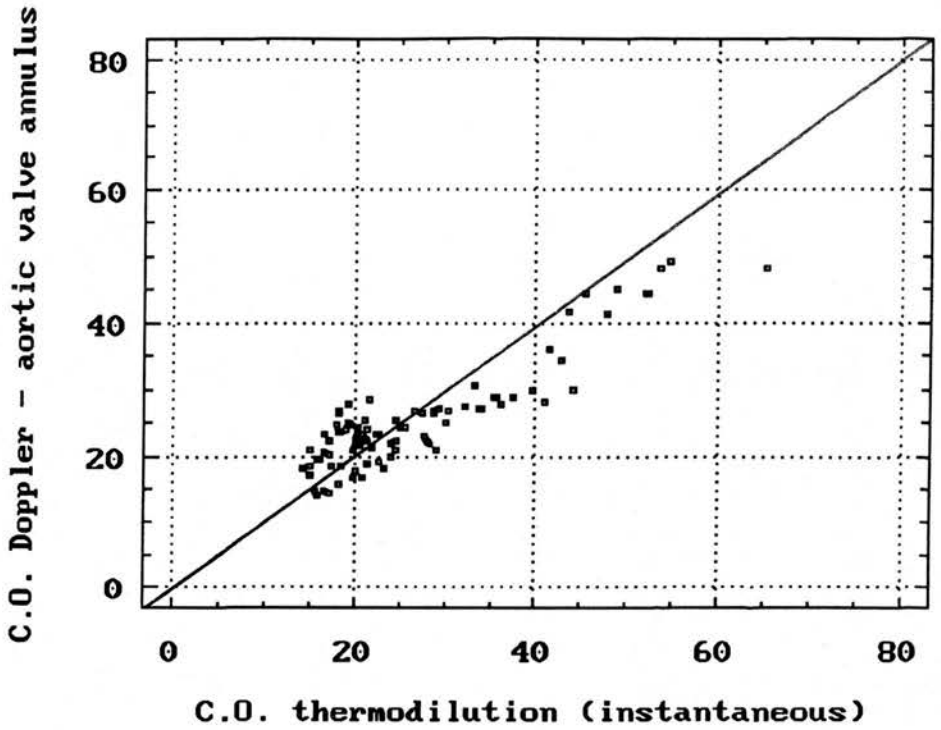
APPENDIX FOR CHAPTER 4

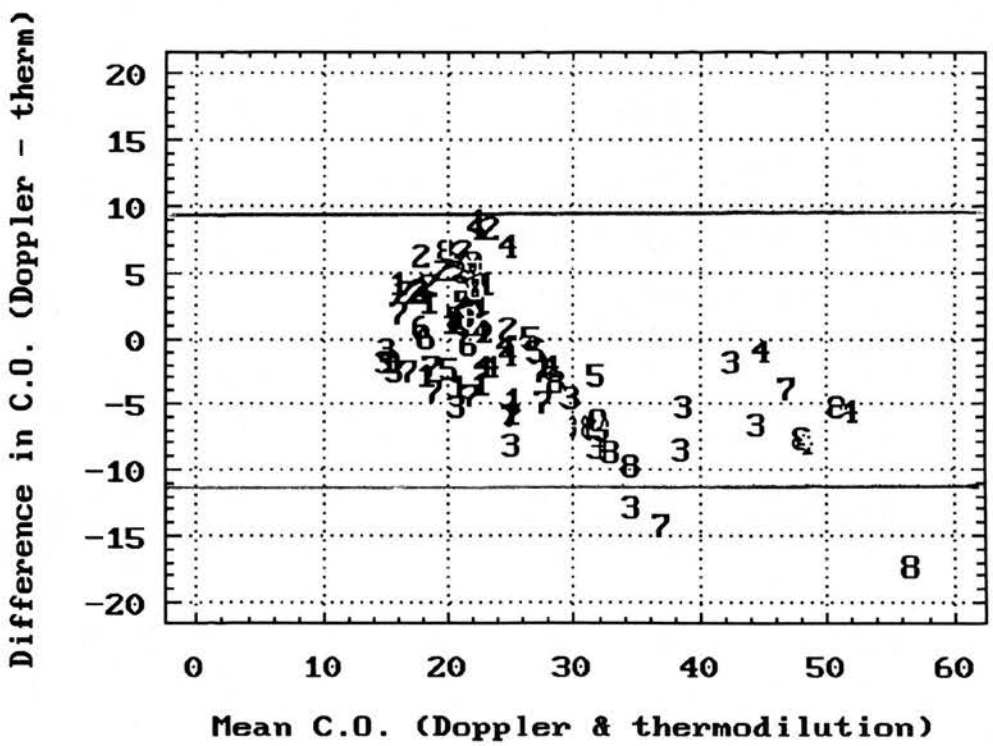

C.O. Doppler - leading edge aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (instantaneous)

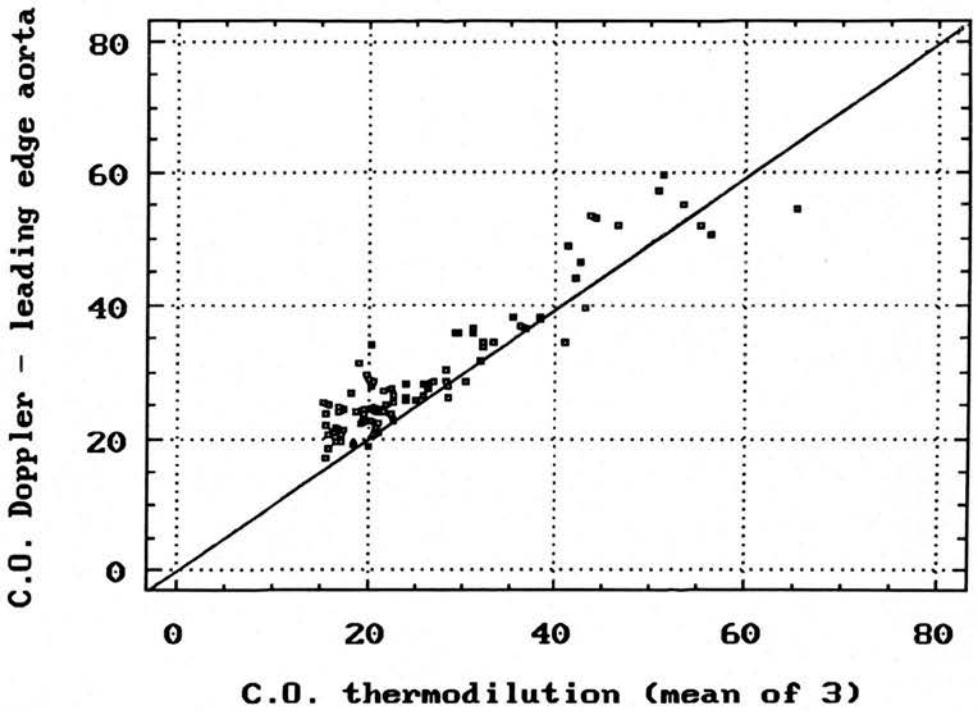

Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
0
10
20
30
40
50
60
70
Mean C.O. (Doppler & thermodilution)

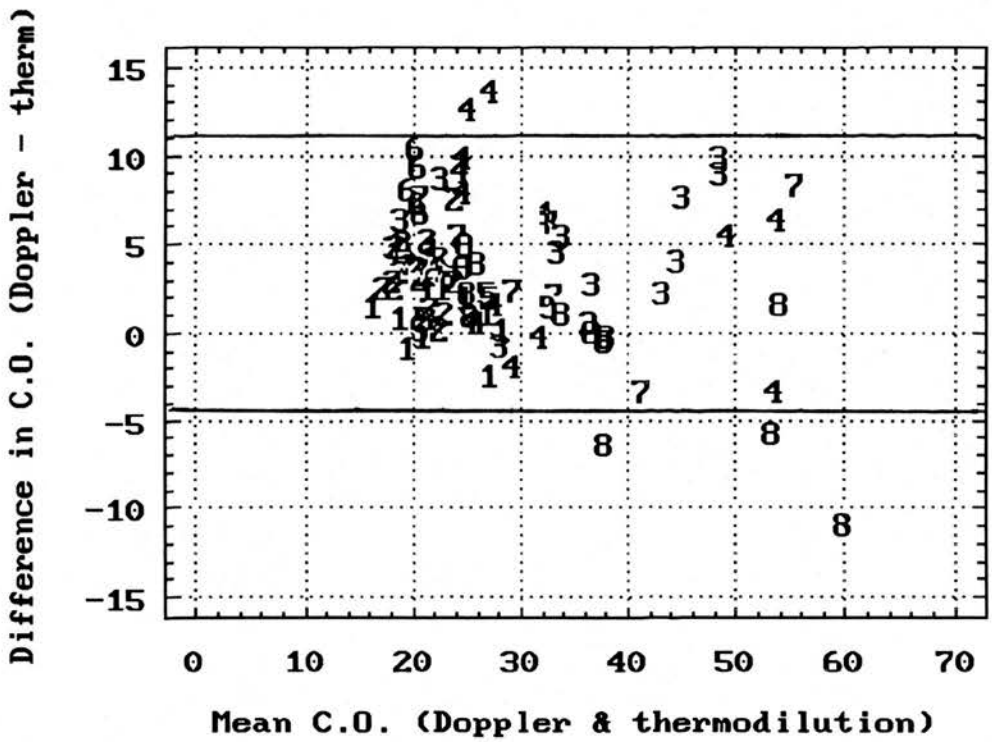

C.O. Doppler - centre wall aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (instantaneous)

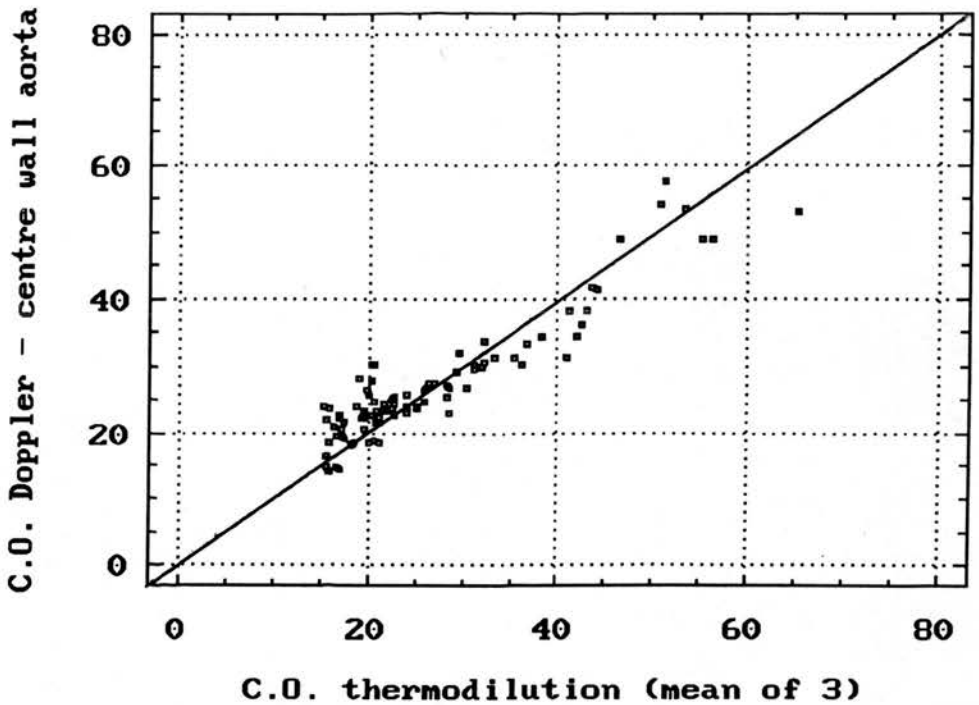

Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
0
10
20
30
40
50
60
70
Mean C.O. (Doppler & thermodilution)

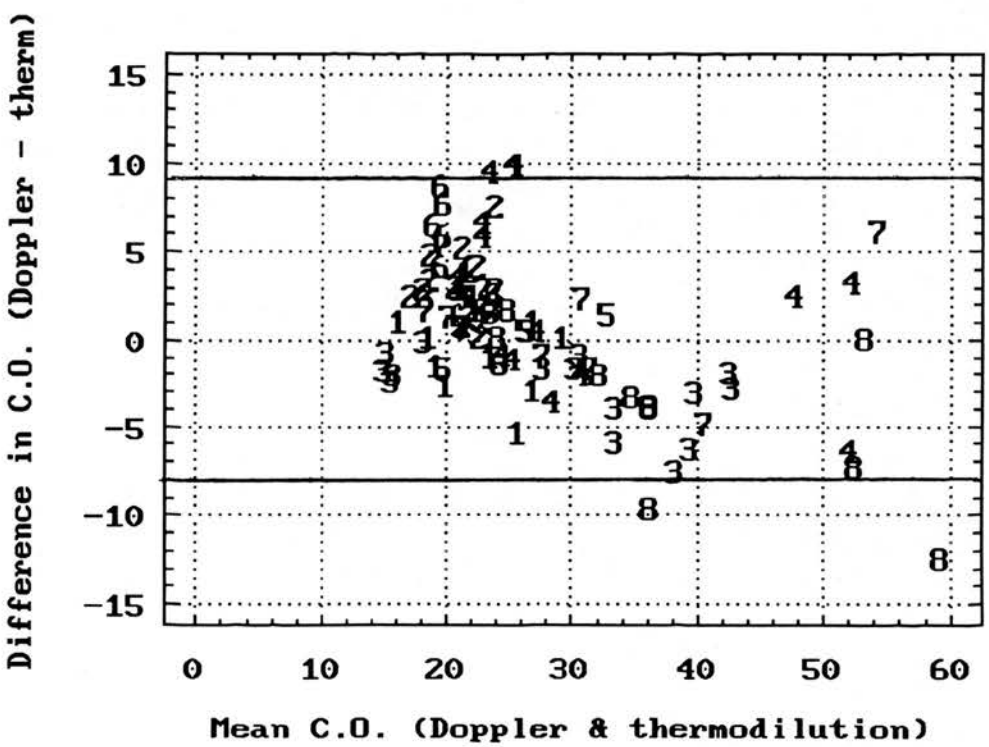

C.O. Doppler - aortic valve annulus
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (instantaneous)

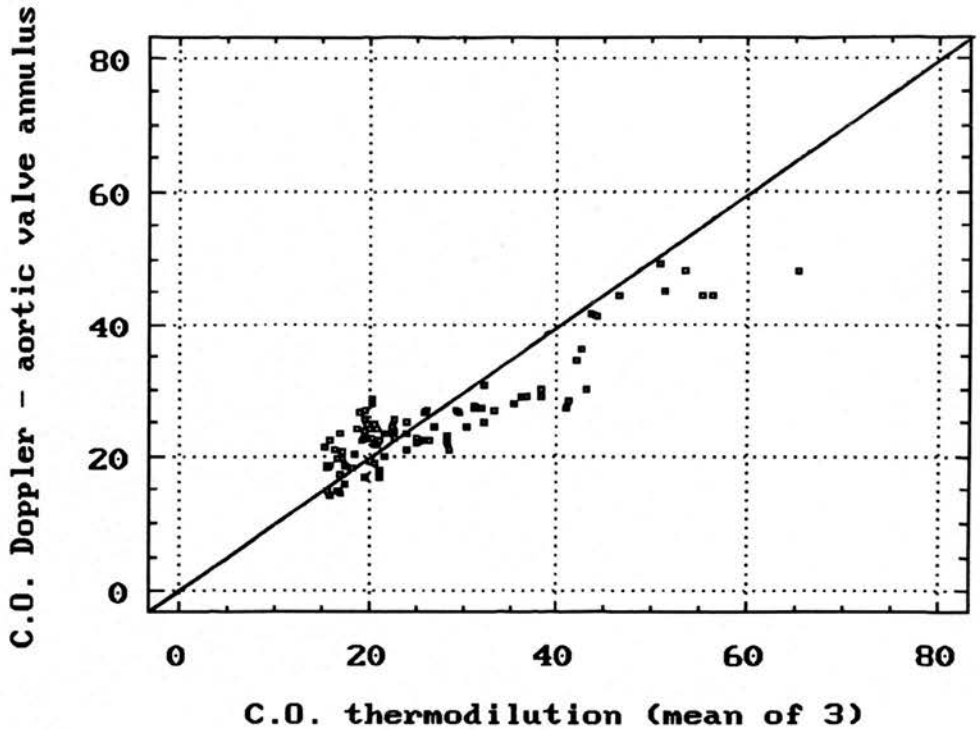

Difference in C.O. (Doppler - therm)
20
15
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
Mean C.O. (Doppler & thermodilution)

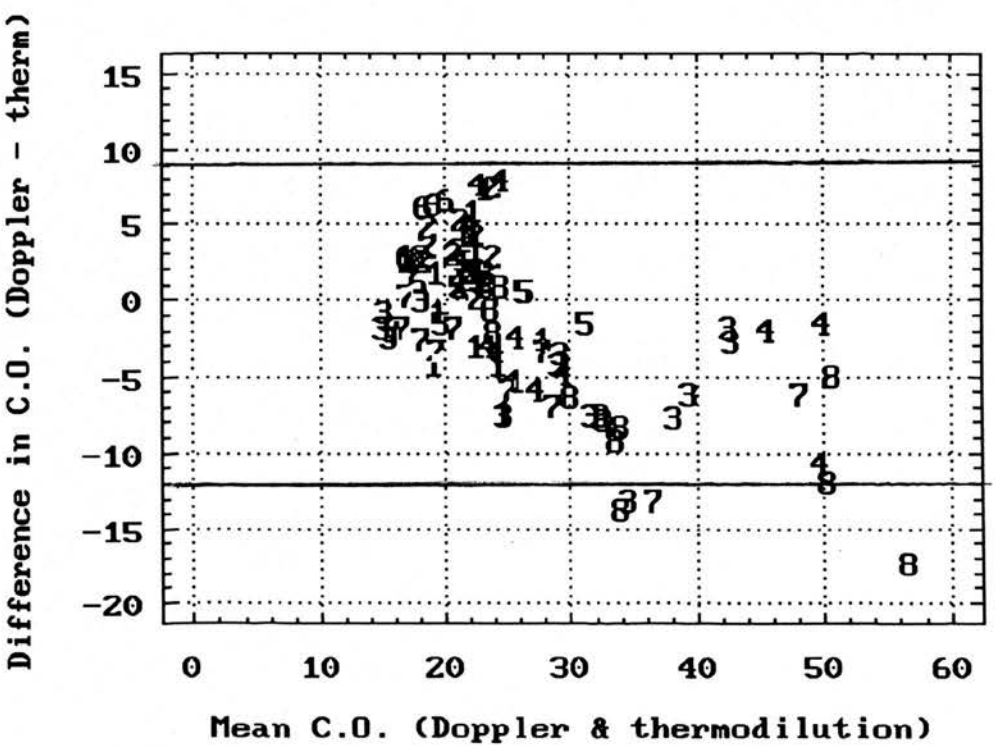

C.O. Doppler - leading edge aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)

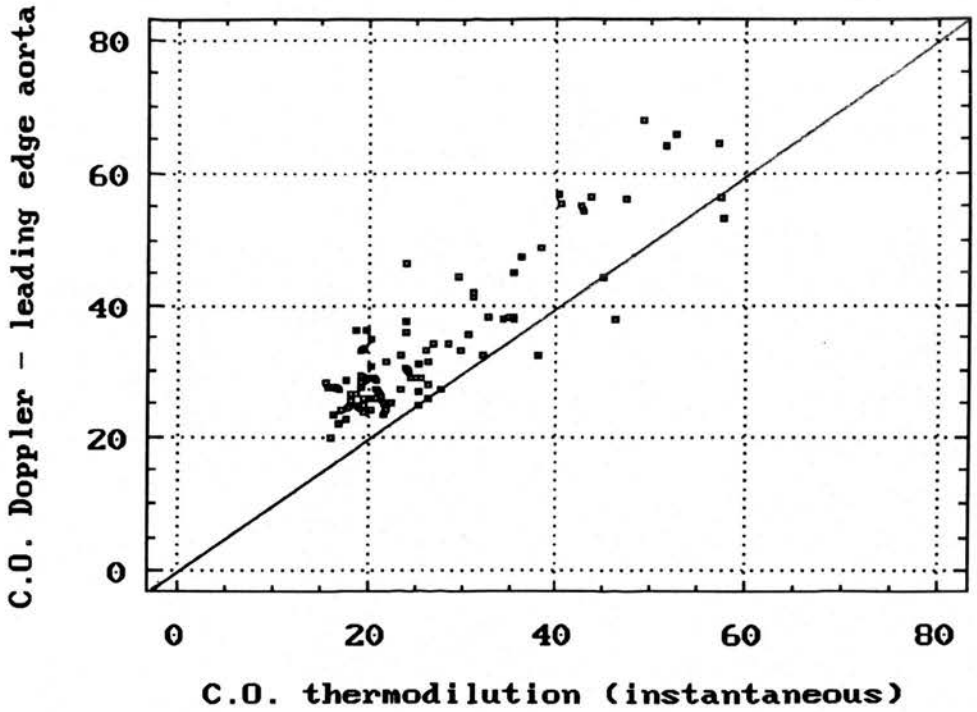

Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
0
10
20
30
40
50
60
70
Mean C.O. (Doppler & thermodilution)

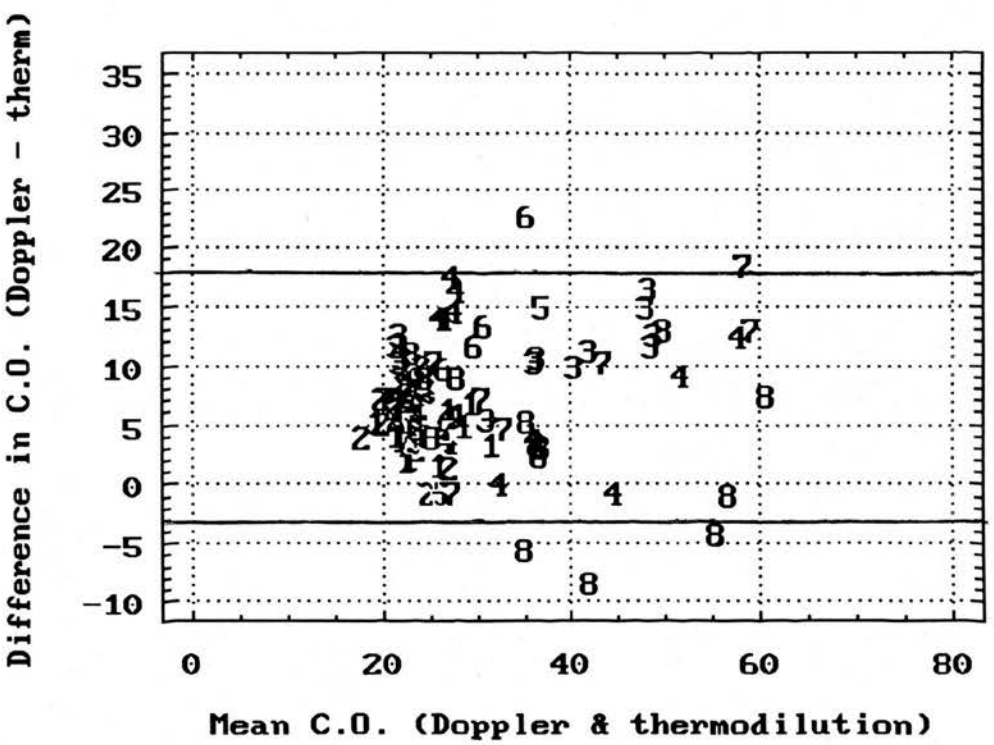

C.O. Doppler - centre wall aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)

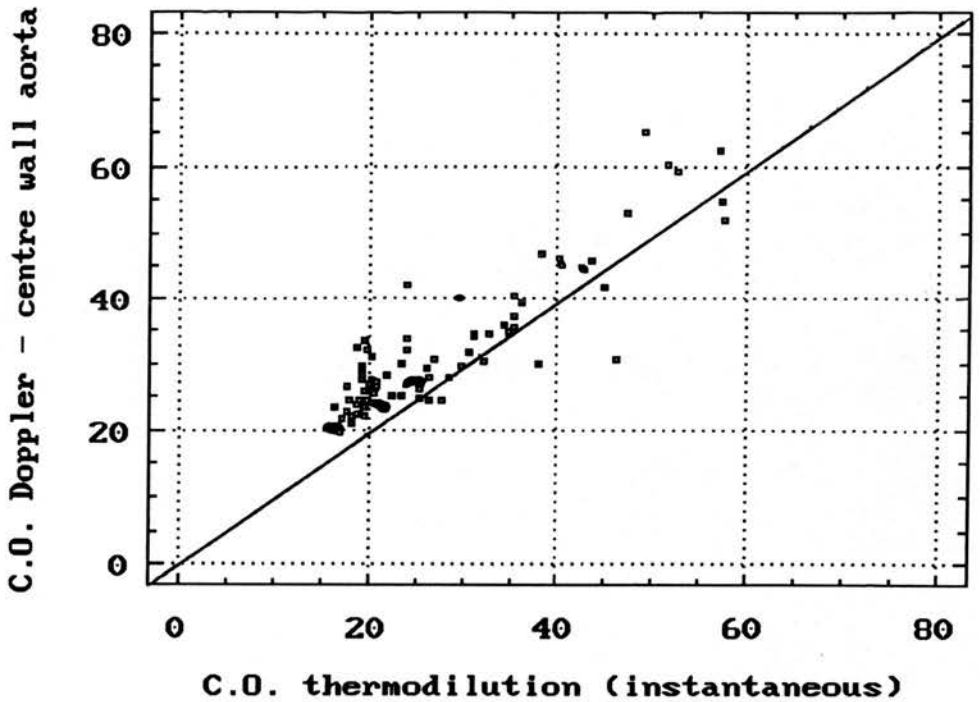

Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
0
10
20
30
40
50
60
Mean C.O. (Doppler & thermodilution)

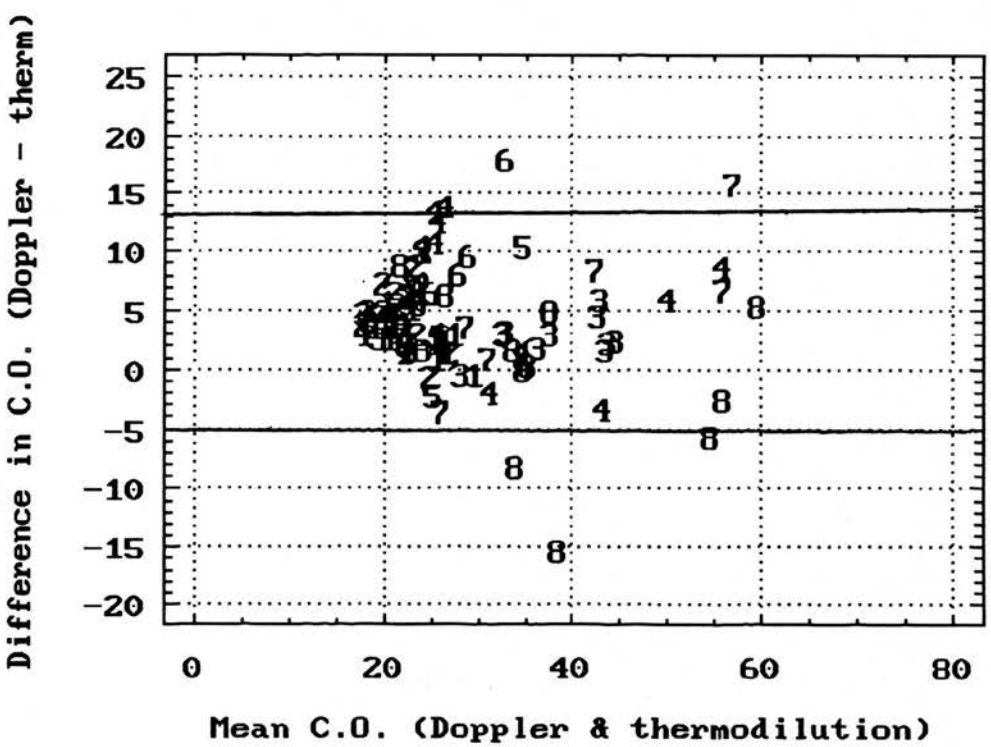

C.O. Doppler - aortic valve annulus
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)

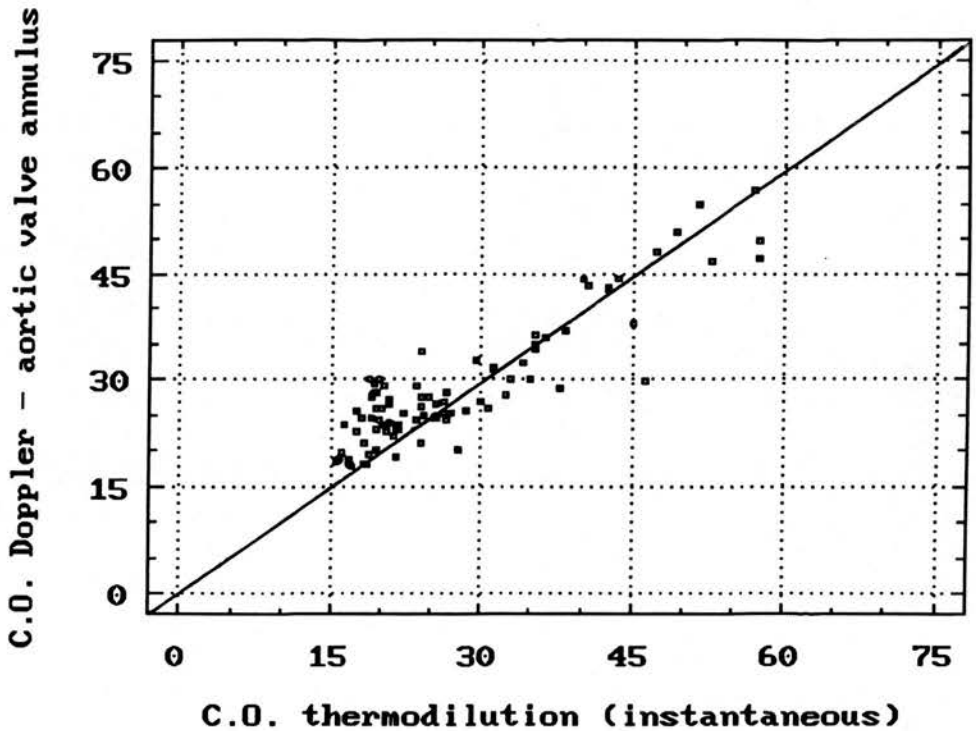

Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
Mean C.O. (Doppler & thermodilution)

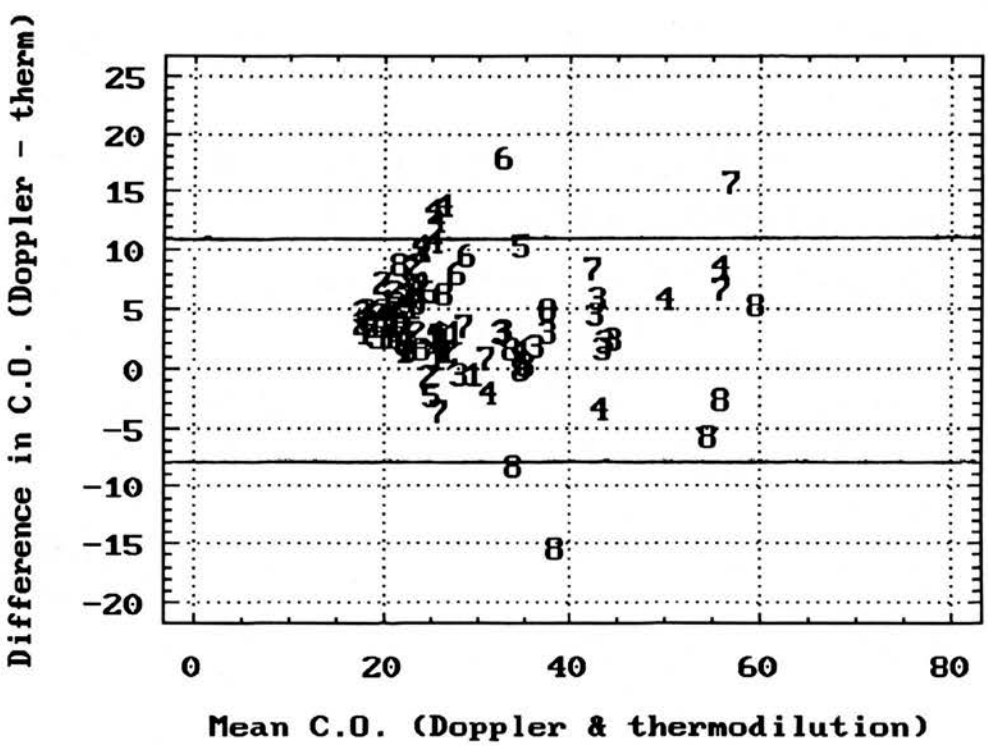

C.O. Doppler - leading edge aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (instantaneous)

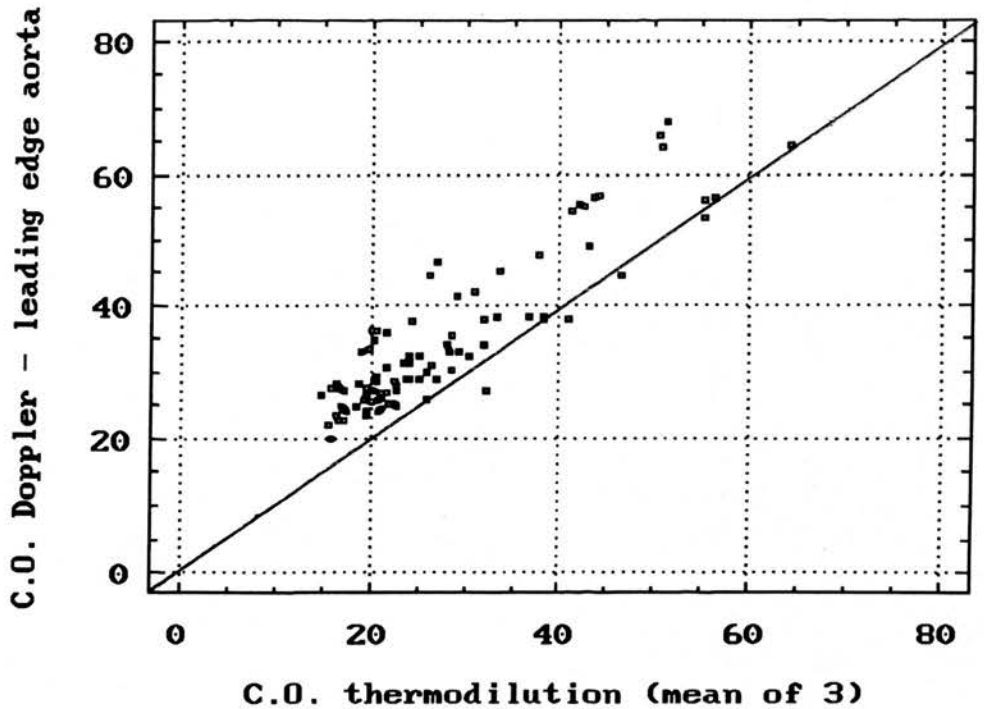

Difference in C.O. (Doppler - therm)
35
30
25
20
15
10
5
0
-5
-10
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)

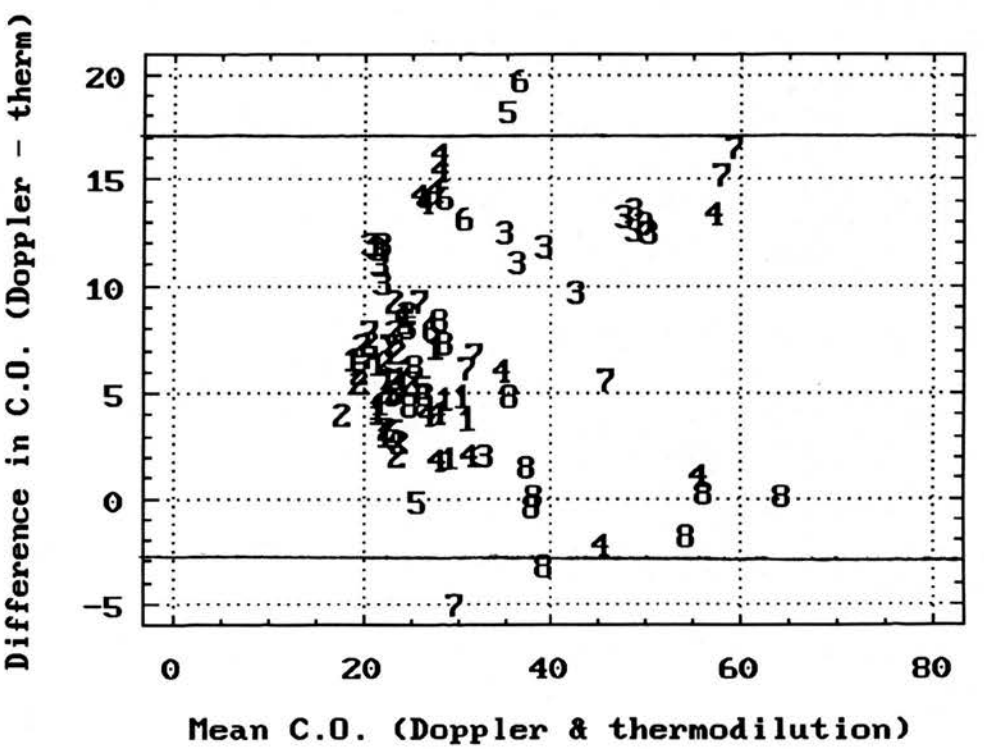

C.O. Doppler - centre wall aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (instantaneous)

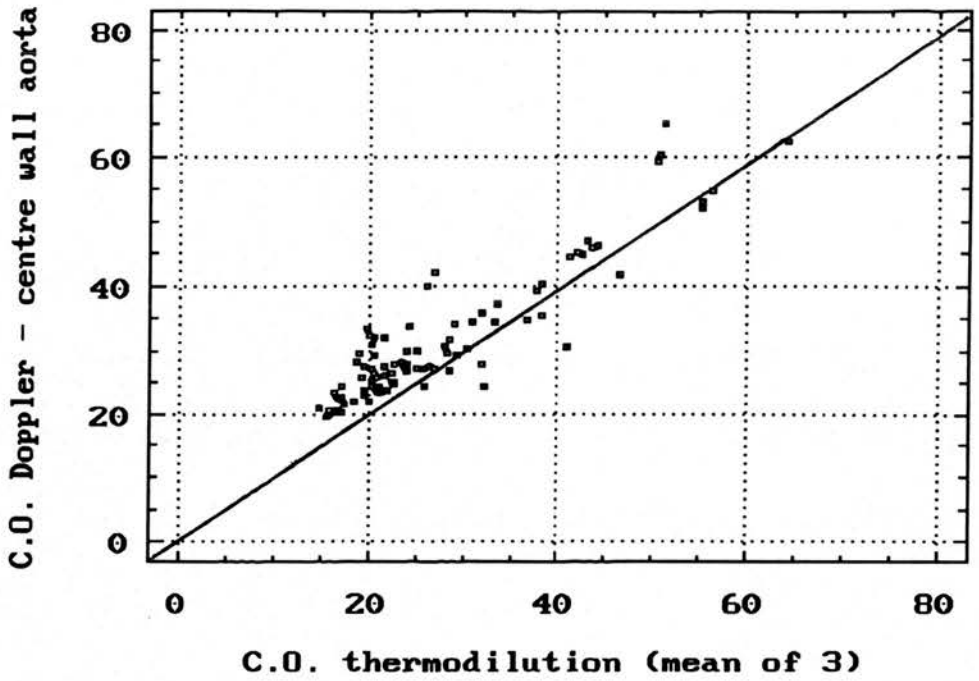

Difference in C.O. (Doppler - therm)
25
20
15
10
5
0
-5
-10
-15
-20
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)

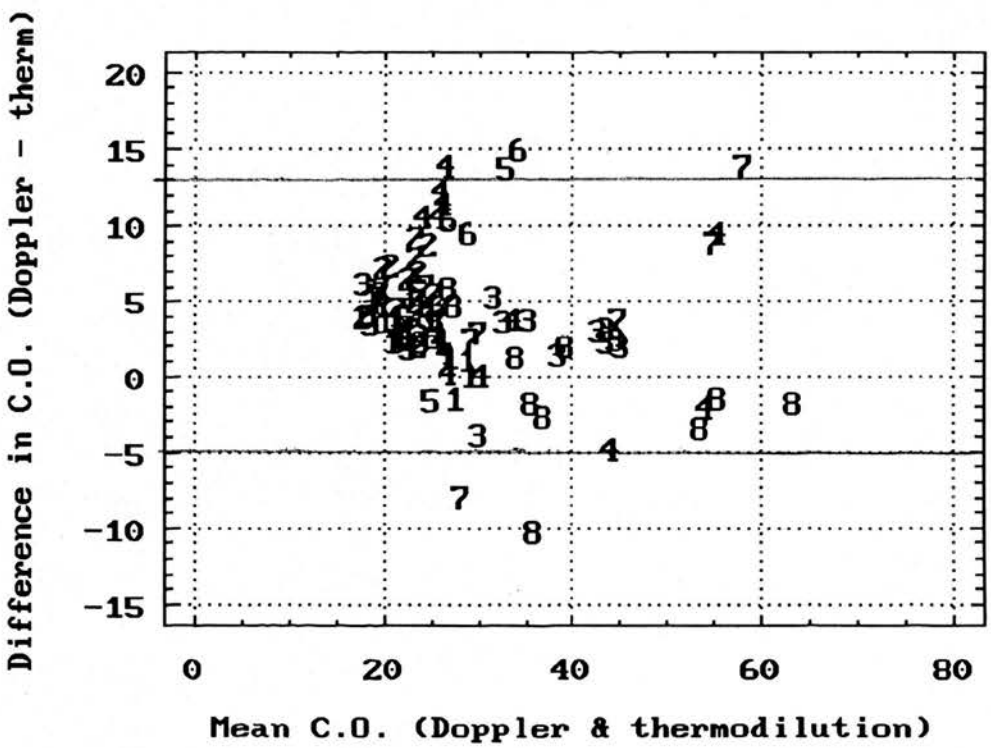

C.O. Doppler - aortic valve annulus
75
60
45
30
15
0
0
15
30
45
60
75
C.O. thermodilution (instantaneous)

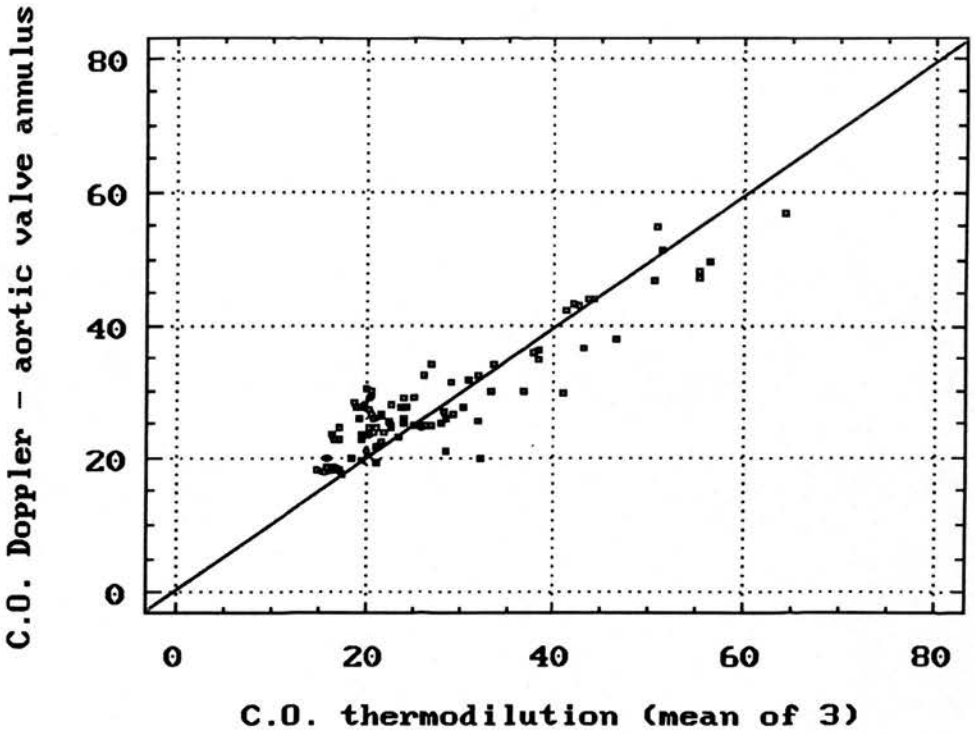

Difference in C.O. (Doppler - therm)
25
20
15
10
5
0
-5
-10
-15
-20
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)

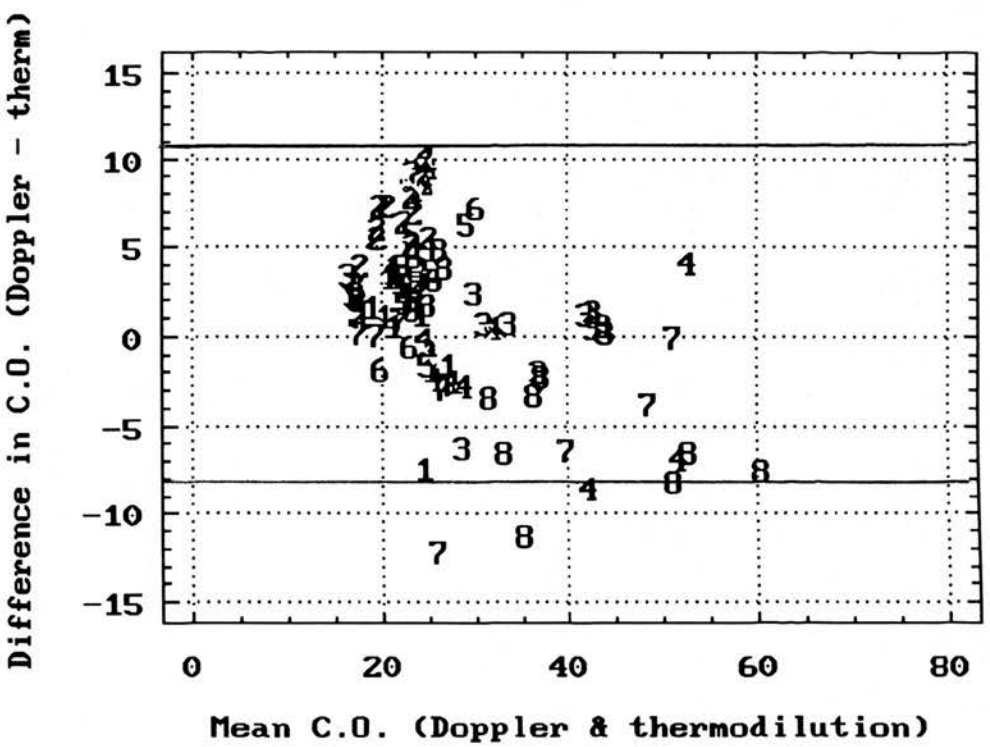

C.O. Doppler - leading edge aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)


Difference in C.O. (Doppler - therm)
20
15
10
5
0
-5
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)


C.O. Doppler - centre wall aorta
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)


Difference in C.O. (Doppler - therm)
20
15
10
5
0
-5
-10
-15
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)


C.O. Doppler - aortic valve annulus
80
60
40
20
0
0
20
40
60
80
C.O. thermodilution (mean of 3)


Difference in C.O. (Doppler - therm)
15
10
5
0
-5
-10
-15
0
20
40
60
80
Mean C.O. (Doppler & thermodilution)

APPENDICES FOR CHAPTER 5

CHAPTER 5 APPENDIX

DOBUTAMINE

In all box and whisker plots the central horizontal lines in the boxes represent the median value.

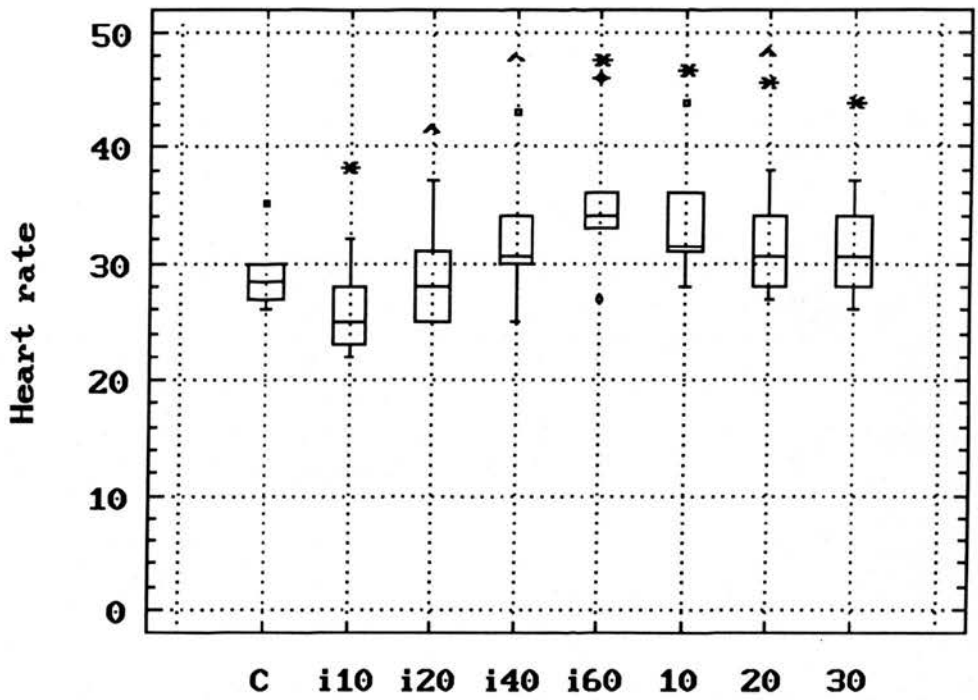
The upper and lower horizontal box boundaries are the upper and lower quartiles.

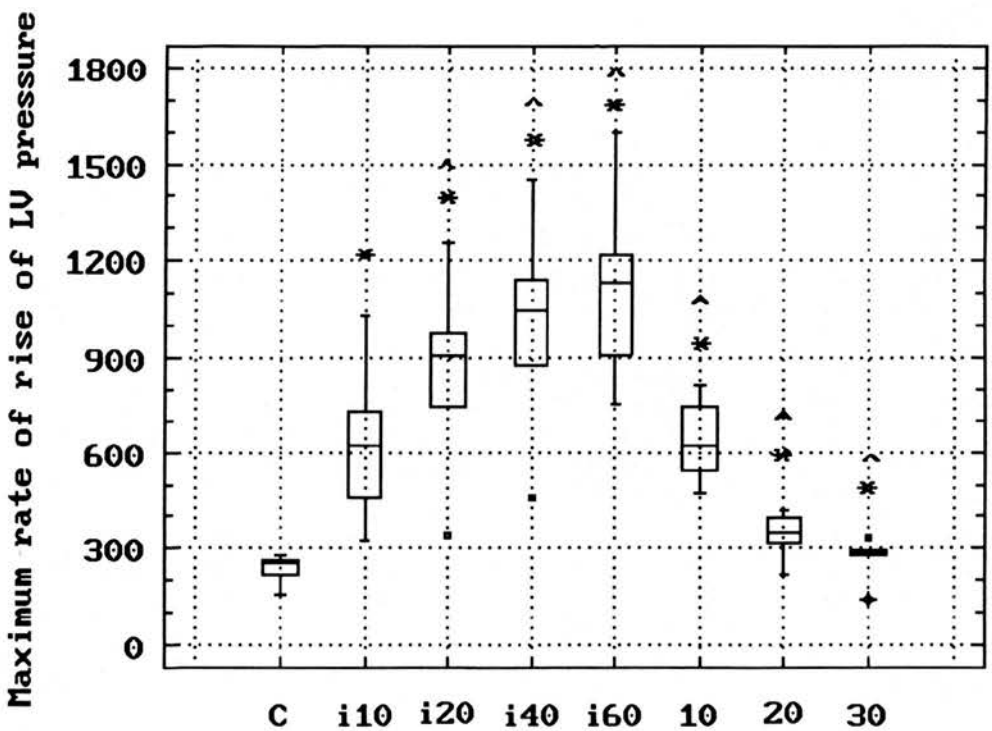
The vertical whiskers are drawn from the smallest, or largest data point, within 1.5 interquartile ranges from either quartile

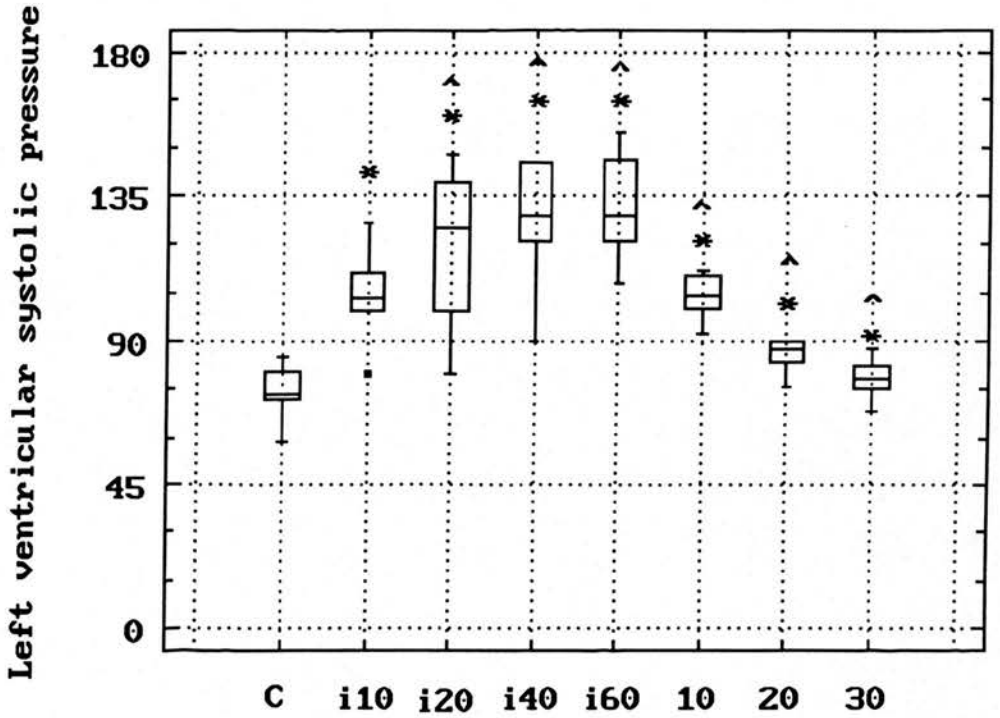
Outlying points are shown by a point. Special data points (e.g. crosses or elipses) are used to indicate far outlying data, more than three interquartile ranges from the upper, or lower, quartile

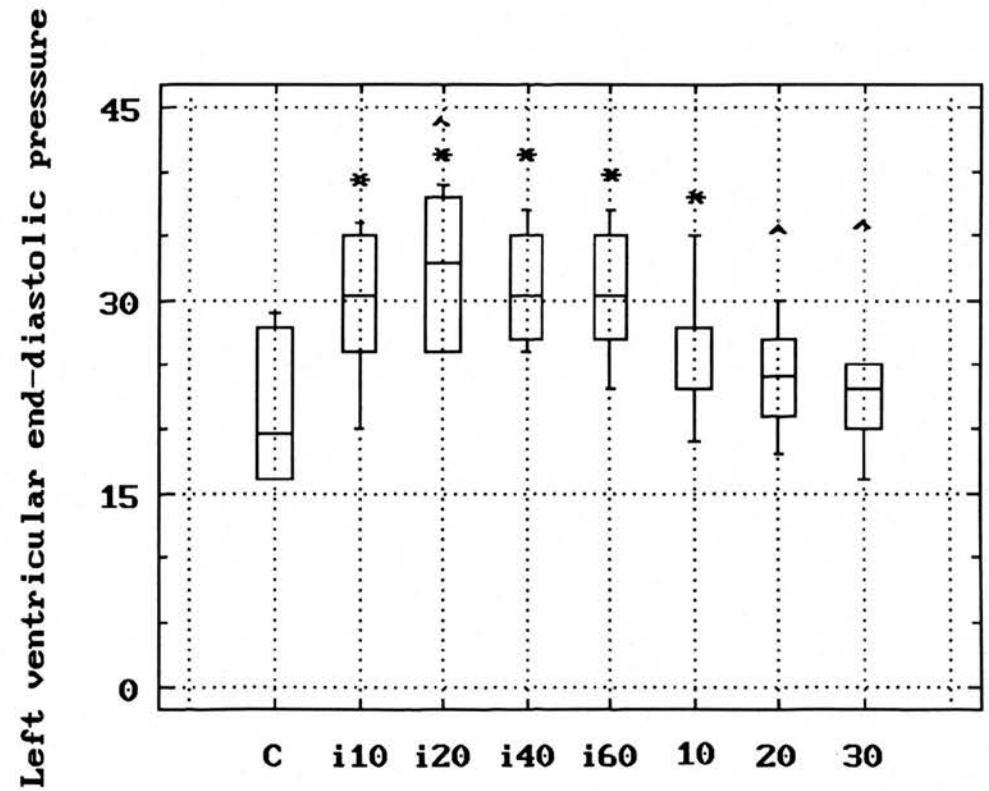
* Indicates a significant difference from control values ($p < 0.05$) by a paired Wilcoxon Test

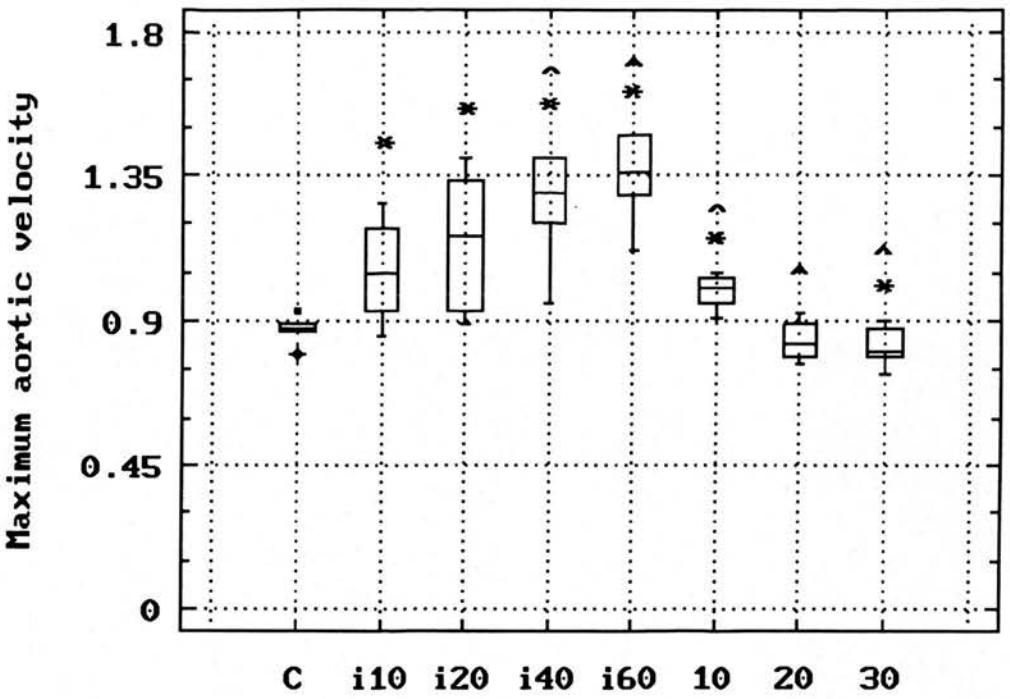
^ Indicates a significant difference from the preceding value ($p < 0.05$) by a paired Wilcoxon Test

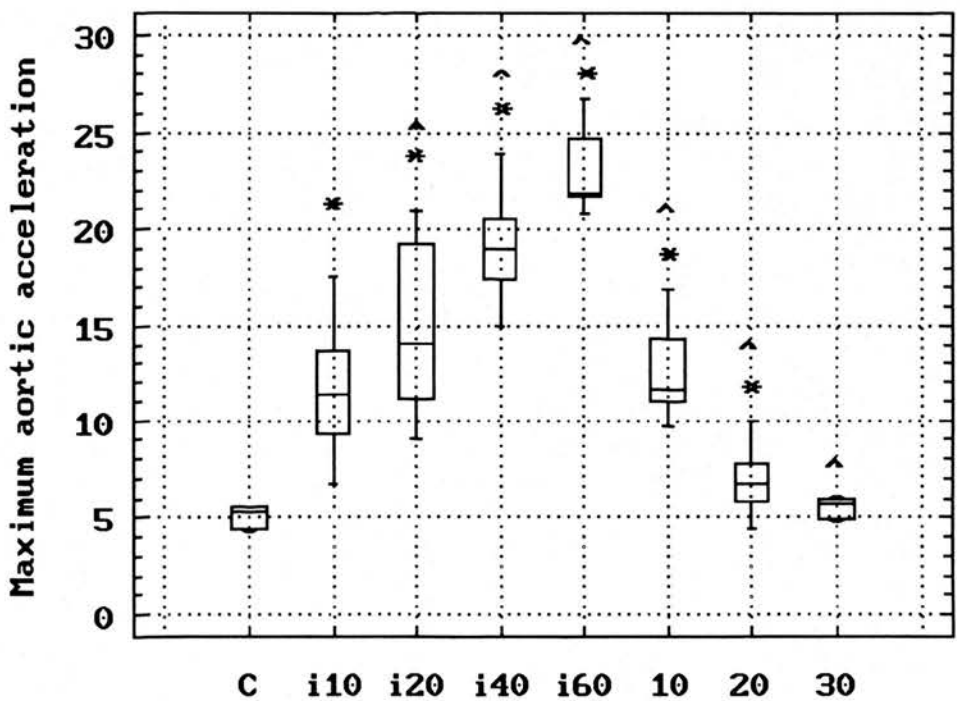

Heart rate
50
40
30
20
10
0
C
i10
i20
i40
i60
10
20
30

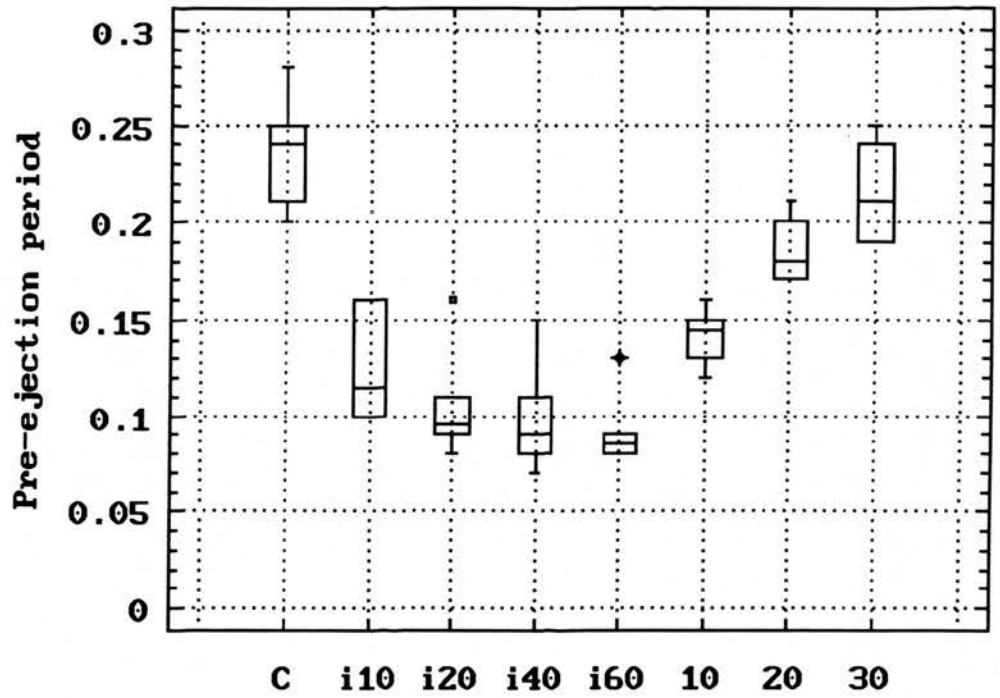

Maximum rate of rise of LV pressure
1800
1500
1200
900
600
300
0
C
i10
i20
i40
i60
10
20
30

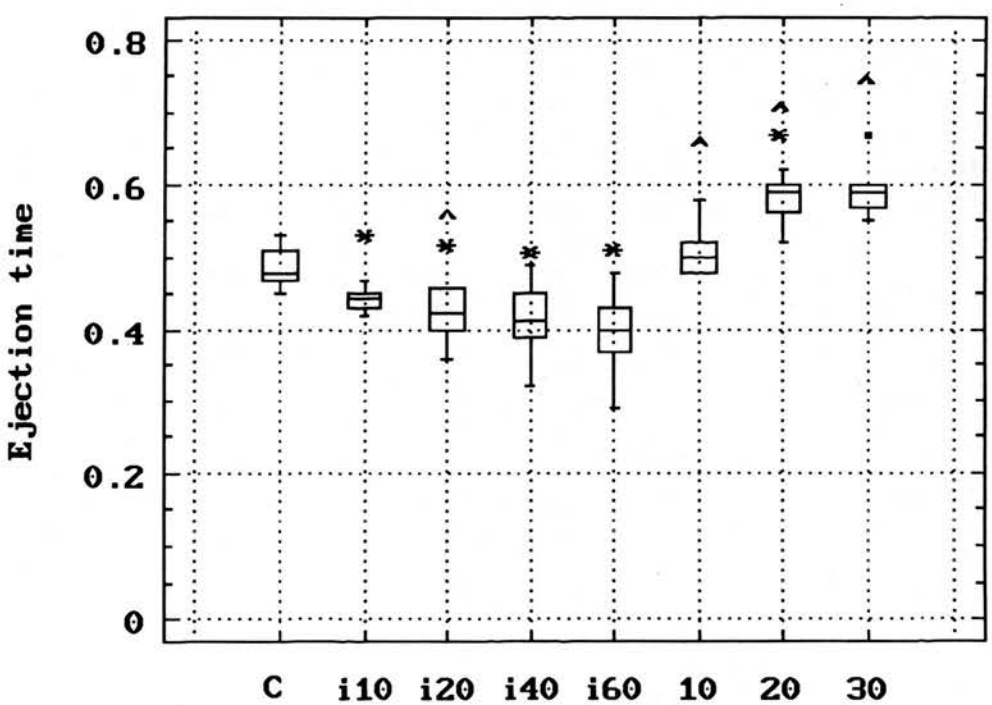

Left ventricular systolic pressure
180
135
90
45
0
C
i10
i20
i40
i60
10
20
30

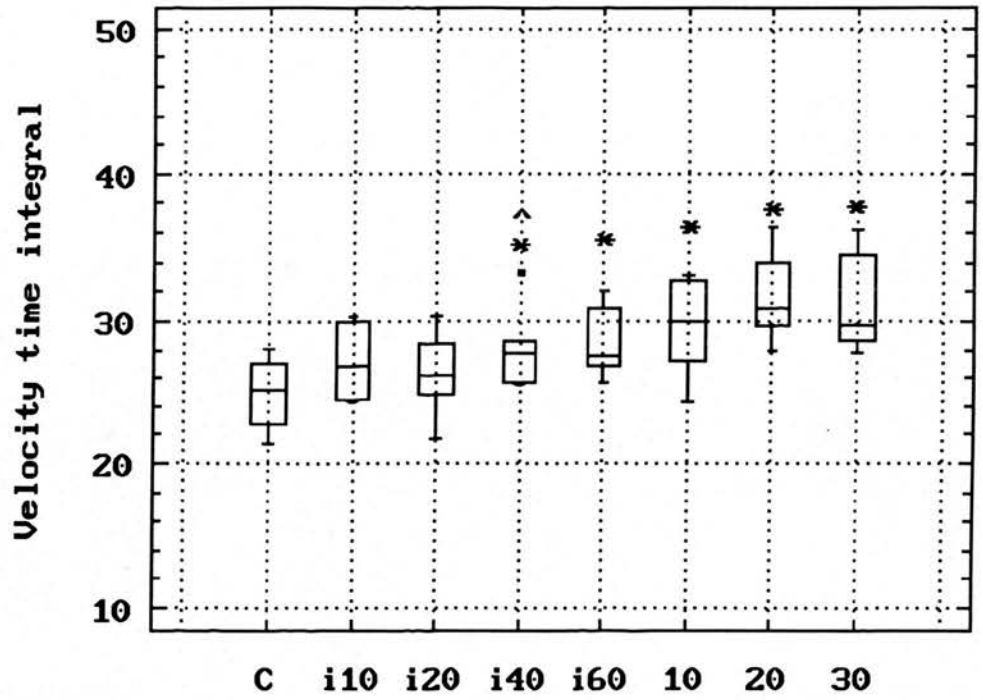

Left ventricular end-diastolic pressure
45
30
15
0
C
i10
i20
i40
i60
10
20
30

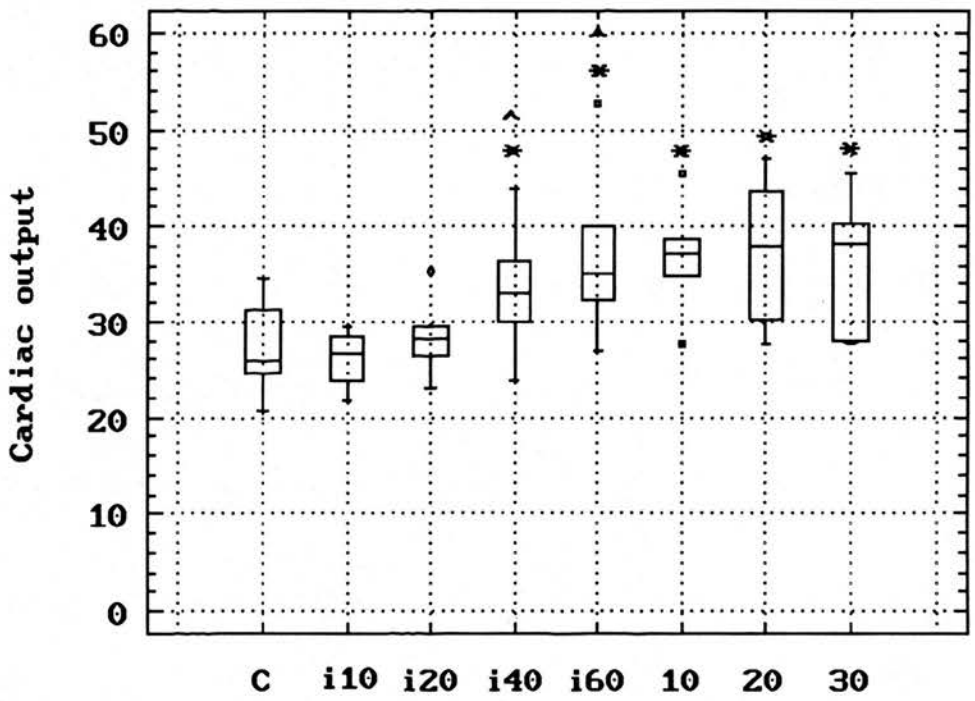

Maximum aortic velocity
1.8
1.35
0.9
0.45
0
C
i10
i20
i40
i60
10
20
30

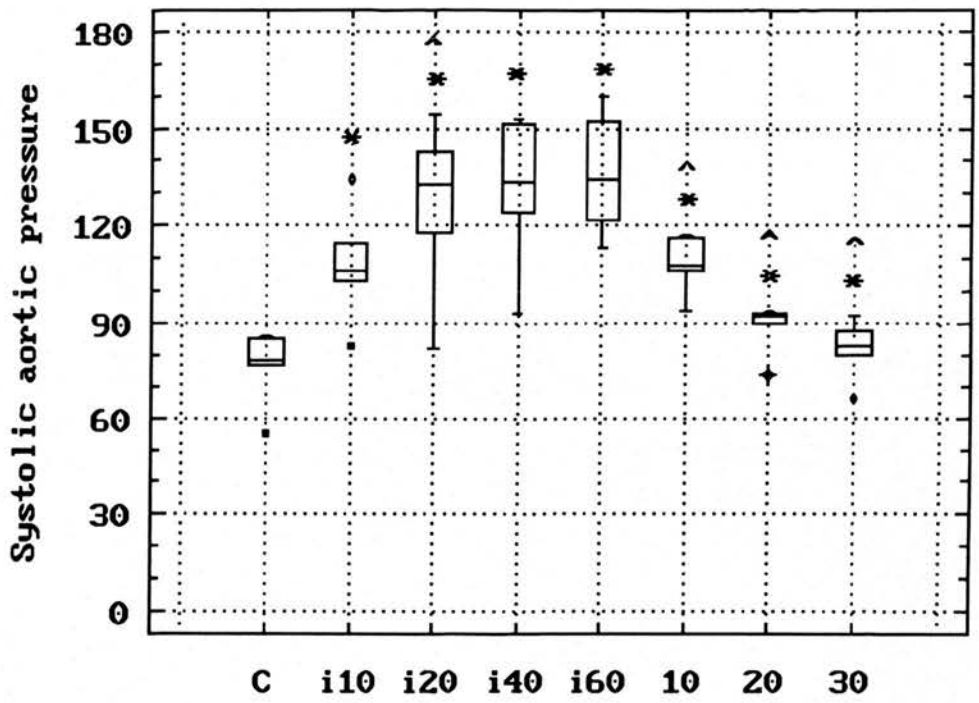

Maximum aortic acceleration
30
25
20
15
10
5
0
C
i10
i20
i40
i60
10
20
30

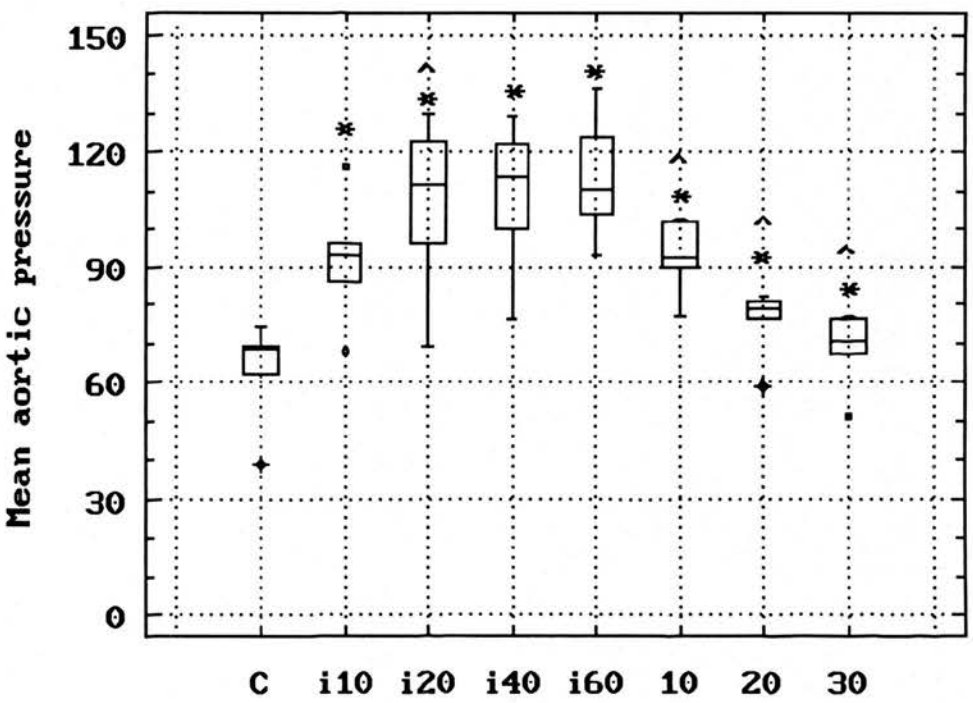

Pre-ejection period
0.3
0.25
0.2
0.15
0.1
0.05
0
C
i10
i20
i40
i60
10
20
30

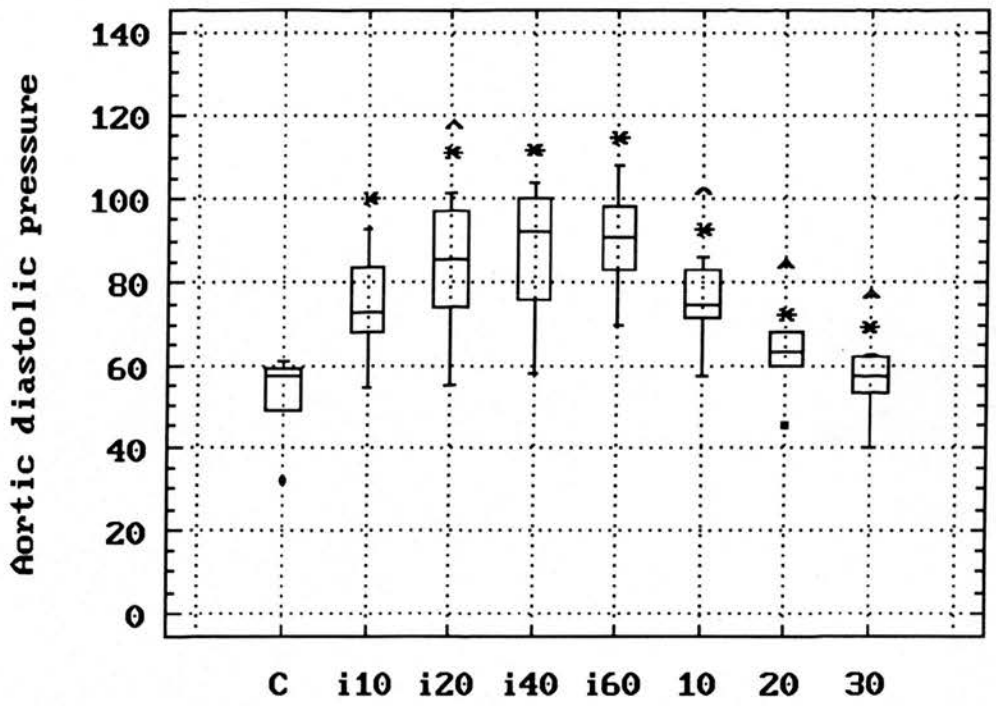

Ejection time
0.8
0.6
0.4
0.2
0
C
i10
i20
i40
i60
10
20
30


Velocity time integral
50
40
30
20
10
C
i10
i20
i40
i60
10
20
30


Cardiac output
60
50
40
30
20
10
0
C
i10
i20
i40
i60
10
20
30


Systolic aortic pressure
180
150
120
90
60
30
0
C
i10
i20
i40
i60
10
20
30


Mean aortic pressure
150
120
90
60
30
0
C
i10
i20
i40
i60
10
20
30


Aortic diastolic pressure
140
120
100
80
60
40
20
0
C
i10
i20
i40
i60
10
20
30

CHAPTER 5 APPENDIX

DOPEXAMINE

In all box and whisker plots the central horizontal lines in the boxes represent the median value.

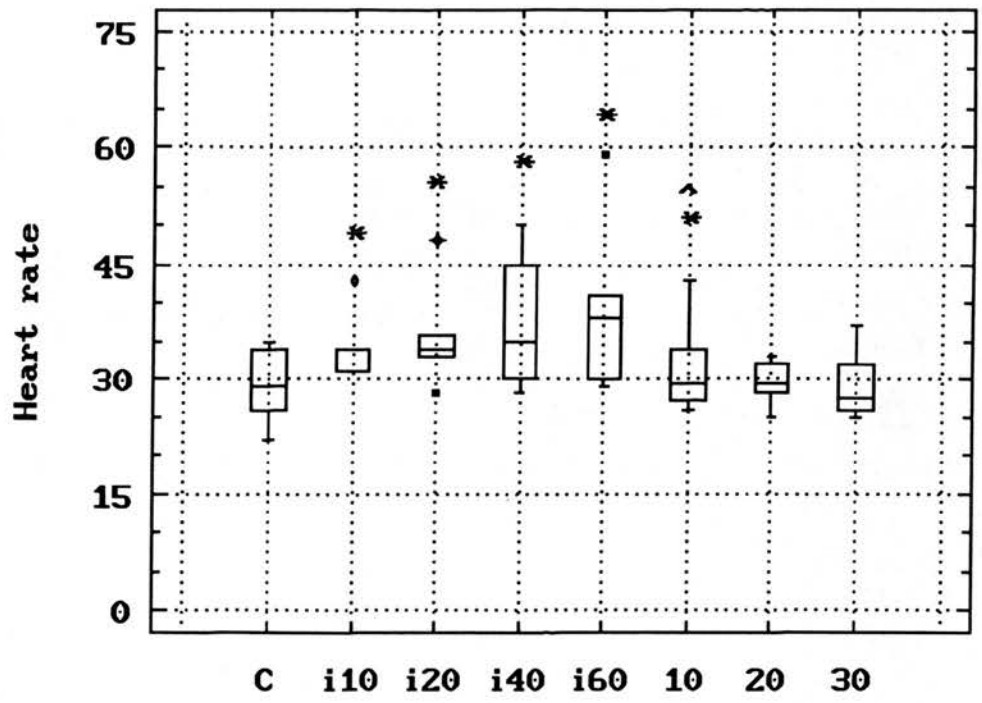
The upper and lower horizontal box boundaries are the upper and lower quartiles.

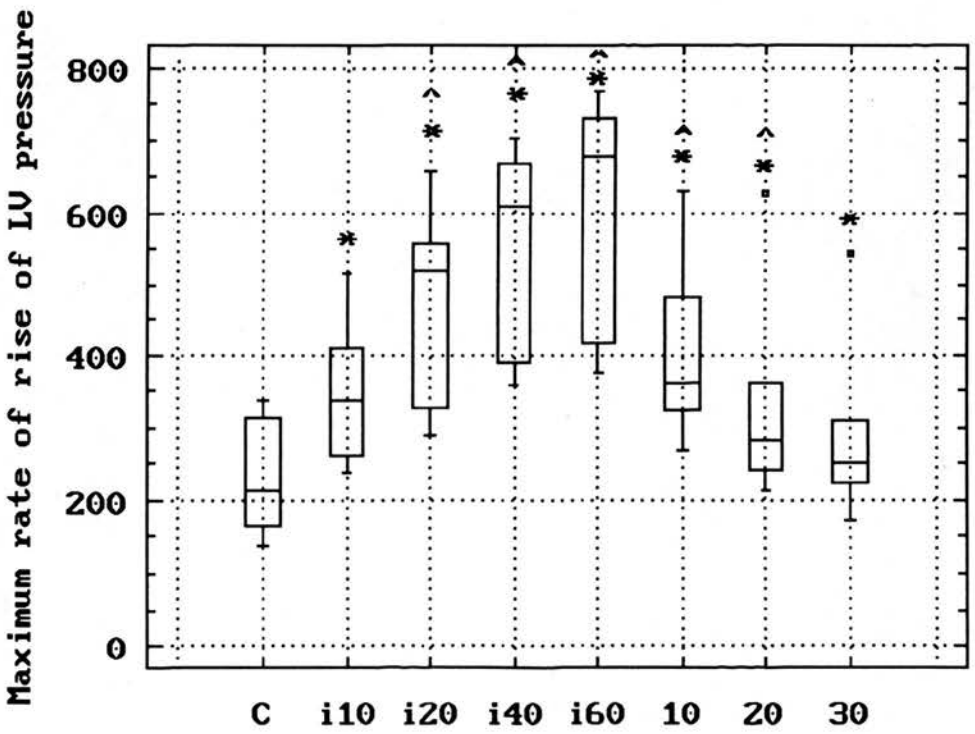
The vertical whiskers are drawn from the smallest, or largest data point, within 1.5 interquartile ranges from either quartile

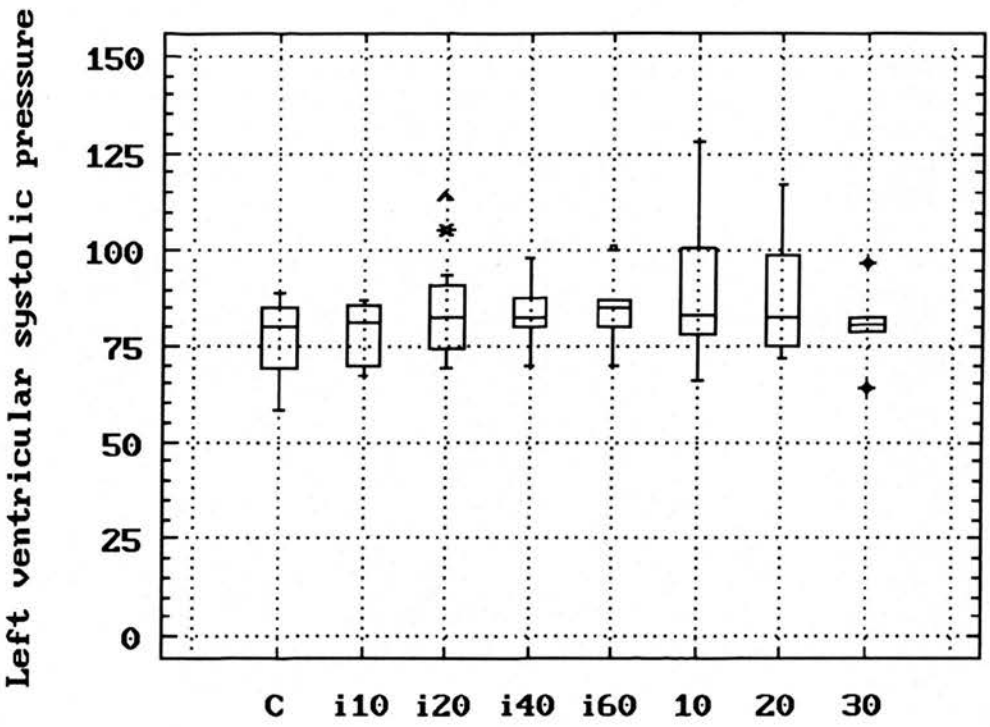
Outlying points are shown by a point. Special data points (e.g. crosses or elipses) are used to indicate far outlying data, more than three interquartile ranges from the upper, or lower, quartile

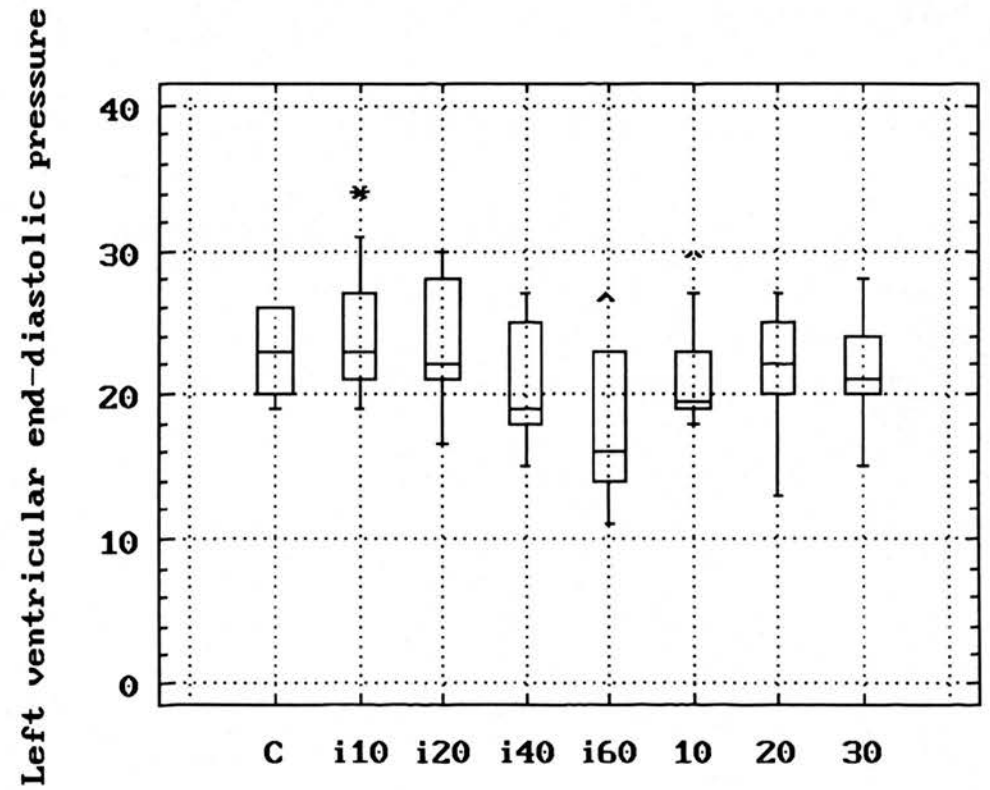
* Indicates a significant difference from control values ($p < 0.05$) by a paired Wilcoxon Test

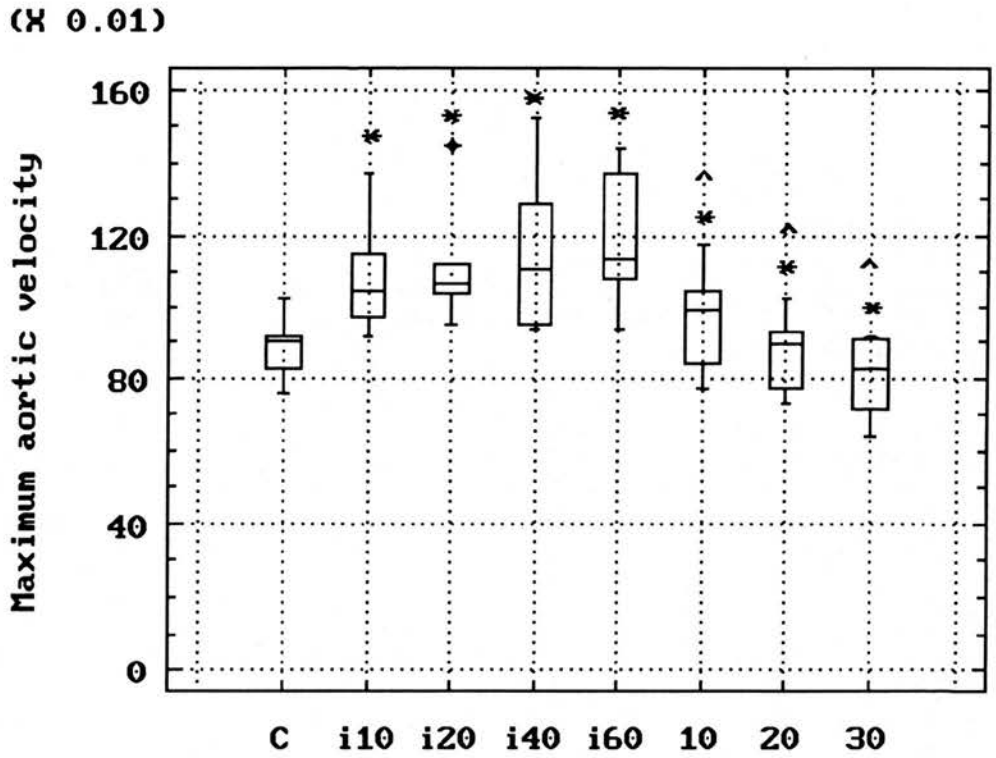
^ Indicates a significant difference from the preceding value ($p < 0.05$) by a paired Wilcoxon Test

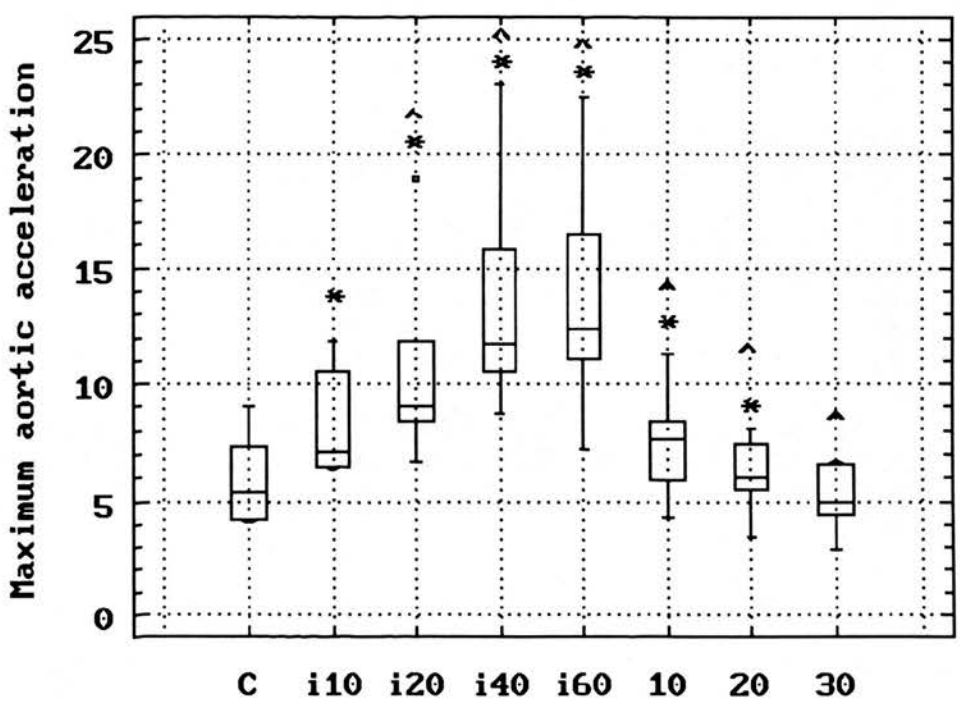

Heart rate
75
60
45
30
15
0
C
i10
i20
i40
i60
10
20
30

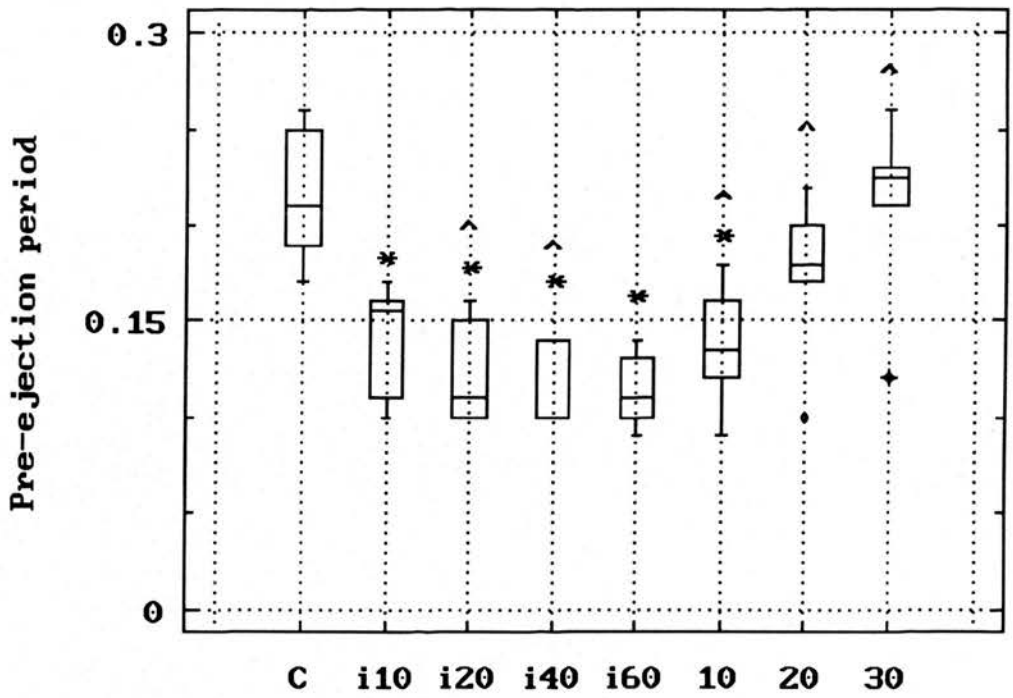

Maximum rate of rise of LV pressure
800
600
400
200
0
C
i10
i20
i40
i60
10
20
30

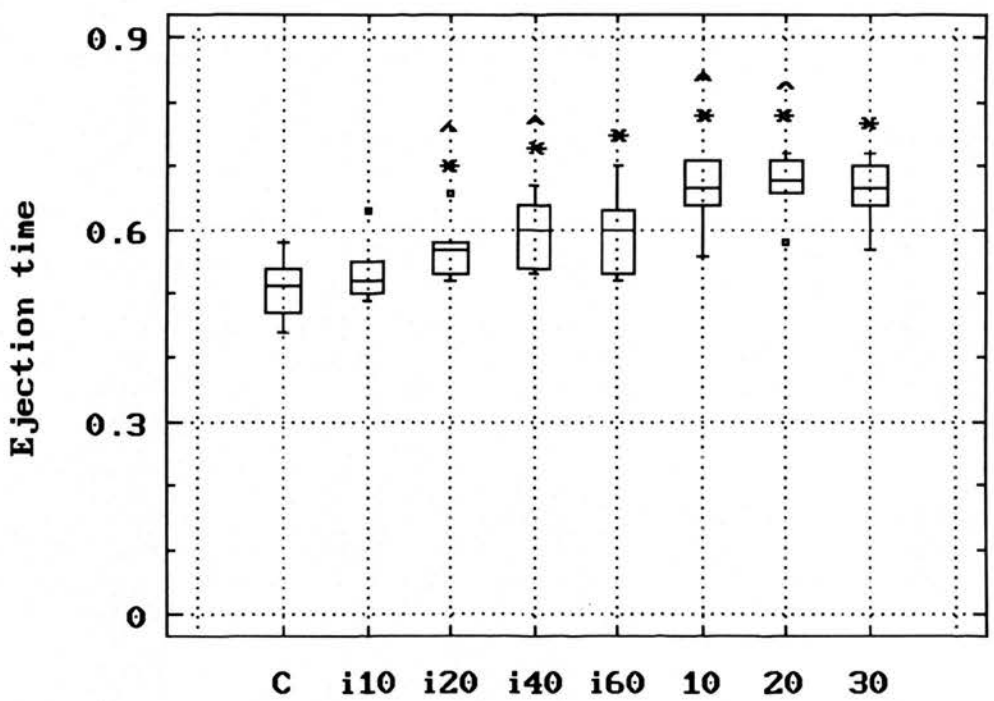

Left ventricular systolic pressure
150
125
100
75
50
25
0
C
i10
i20
i40
i60
10
20
30

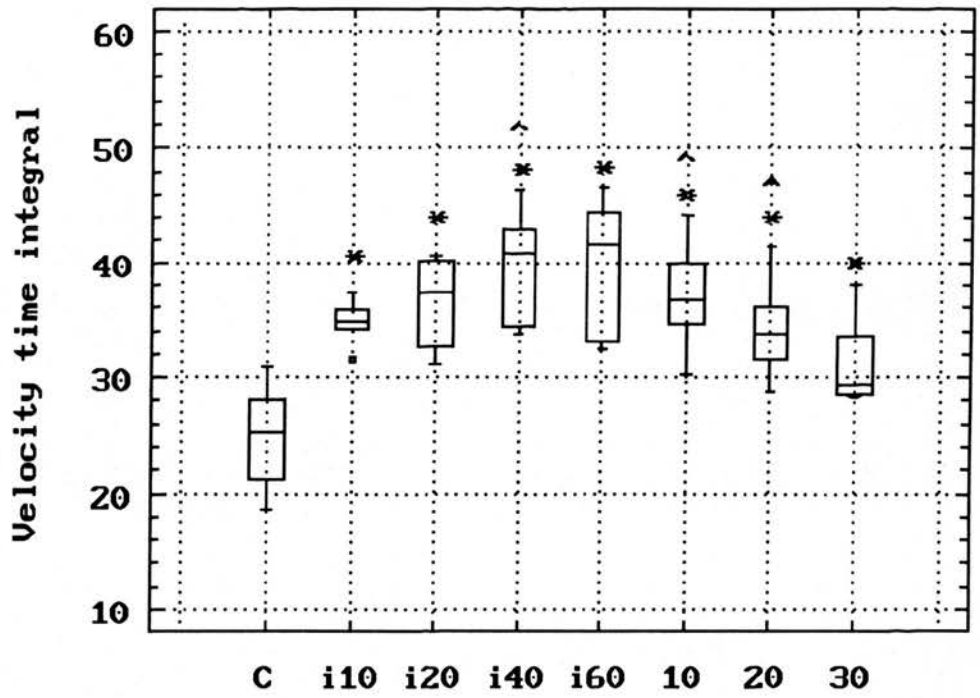

Left ventricular end-diastolic pressure
40
30
20
10
0
C
i10
i20
i40
i60
10
20
30

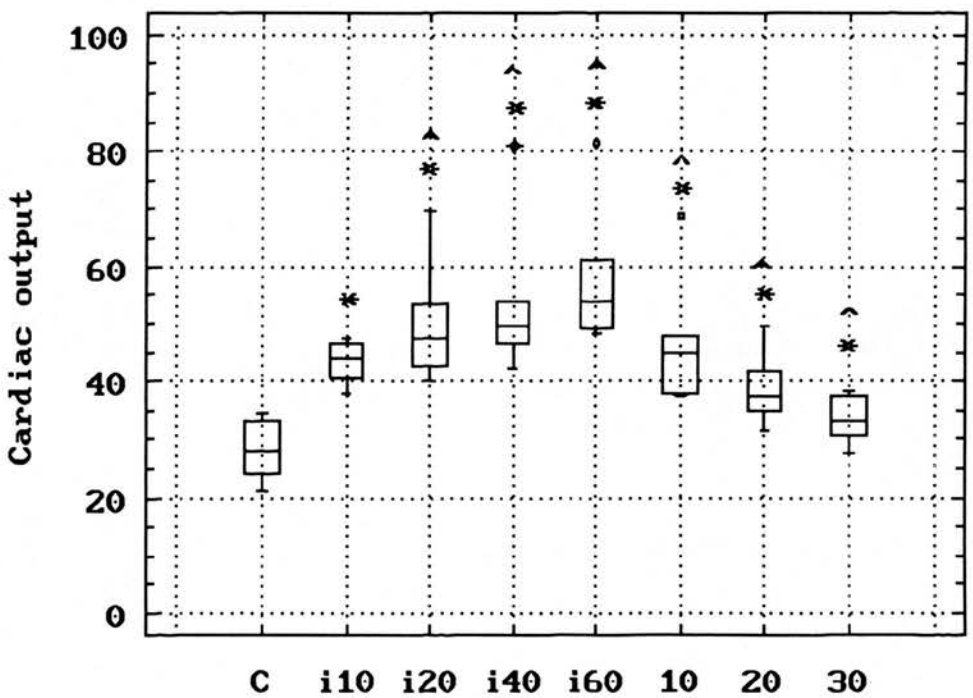

(X 0.01)
Maximum aortic velocity
160
120
80
40
0
C
i10
i20
i40
i60
10
20
30

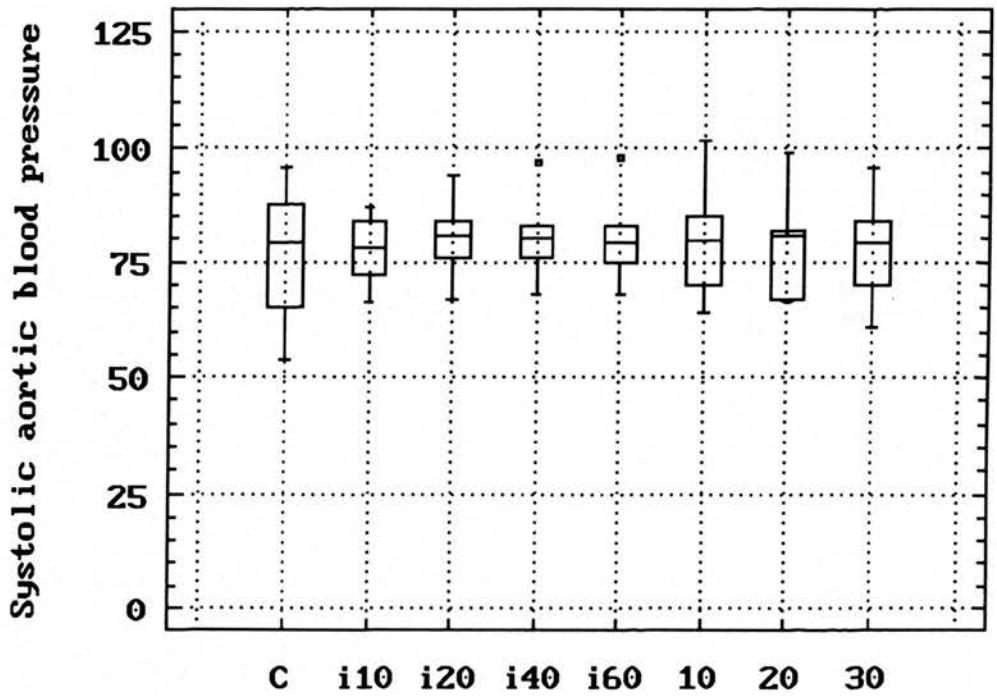

Maximum aortic acceleration
25
20
15
10
5
0
C
i10
i20
i40
i60
10
20
30

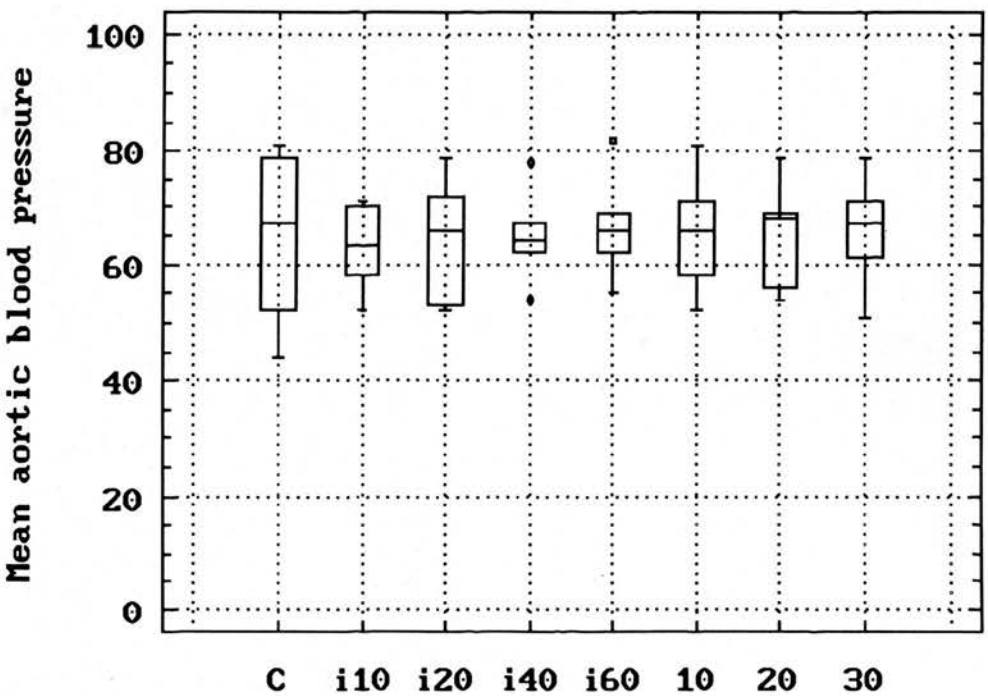

Pre-ejection period
0.3
0.15
0
C
i10
i20
i40
i60
10
20
30

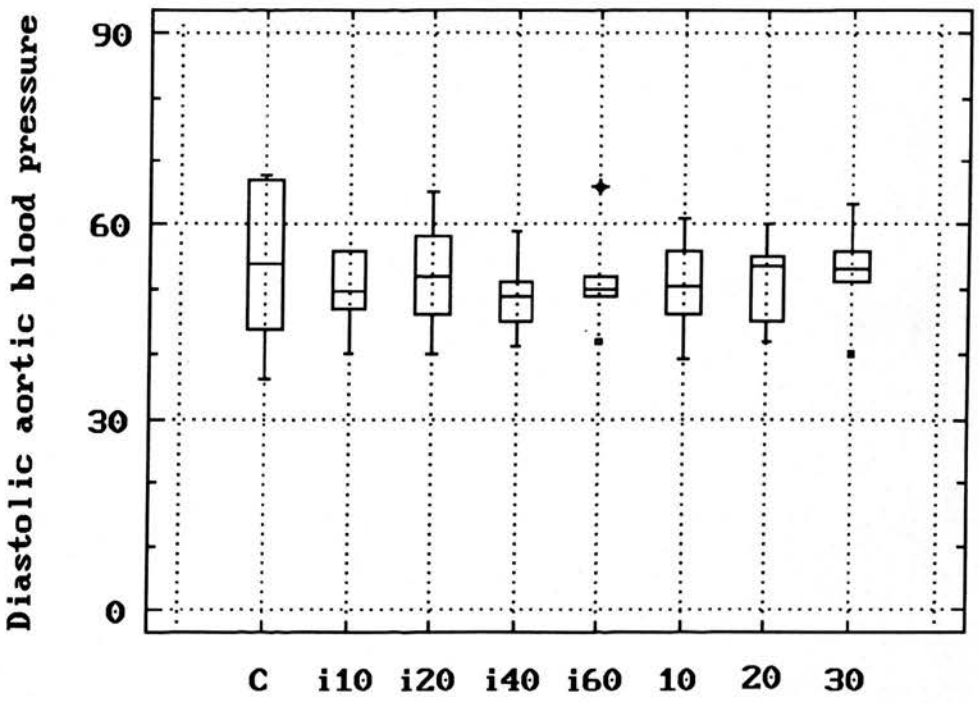

Ejection time
0.9
0.6
0.3
0
C
i10
i20
i40
i60
10
20
30


Velocity time integral
60
50
40
30
20
10
C
i10
i20
i40
i60
10
20
30


Cardiac output
100
80
60
40
20
0
C
i10
i20
i40
i60
10
20
30


Systolic aortic blood pressure
125
100
75
50
25
0
C
i10
i20
i40
i60
10
20
30


Mean aortic blood pressure
100
80
60
40
20
0
C
i10
i20
i40
i60
10
20
30


Diastolic aortic blood pressure
90
60
30
0
C
i10
i20
i40
i60
10
20
30

CHAPTER 5 APPENDIX

DOPAMINE

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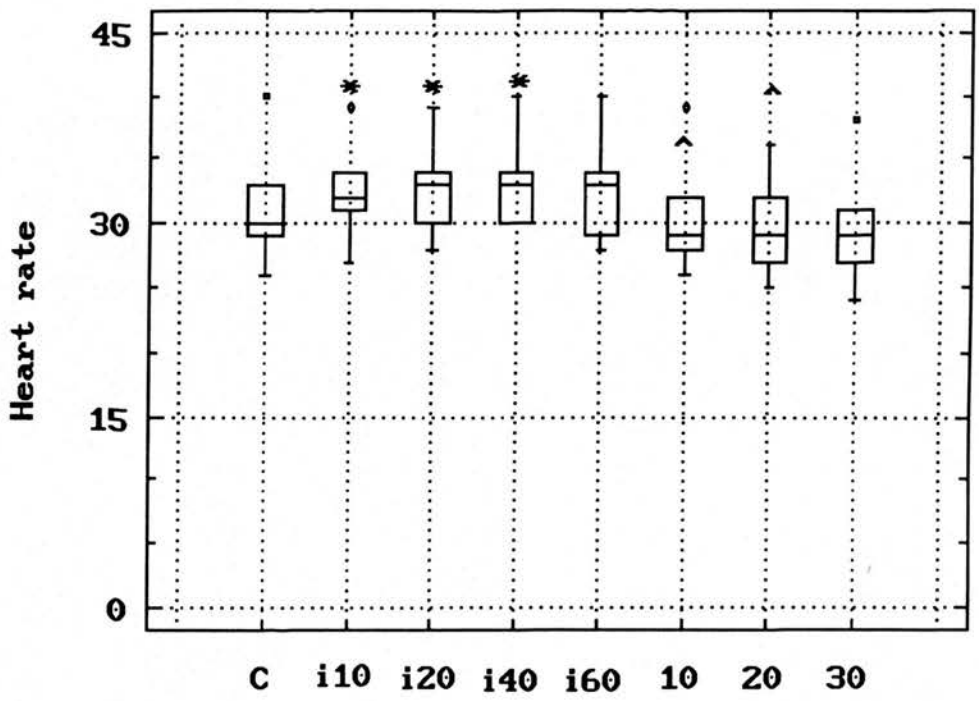
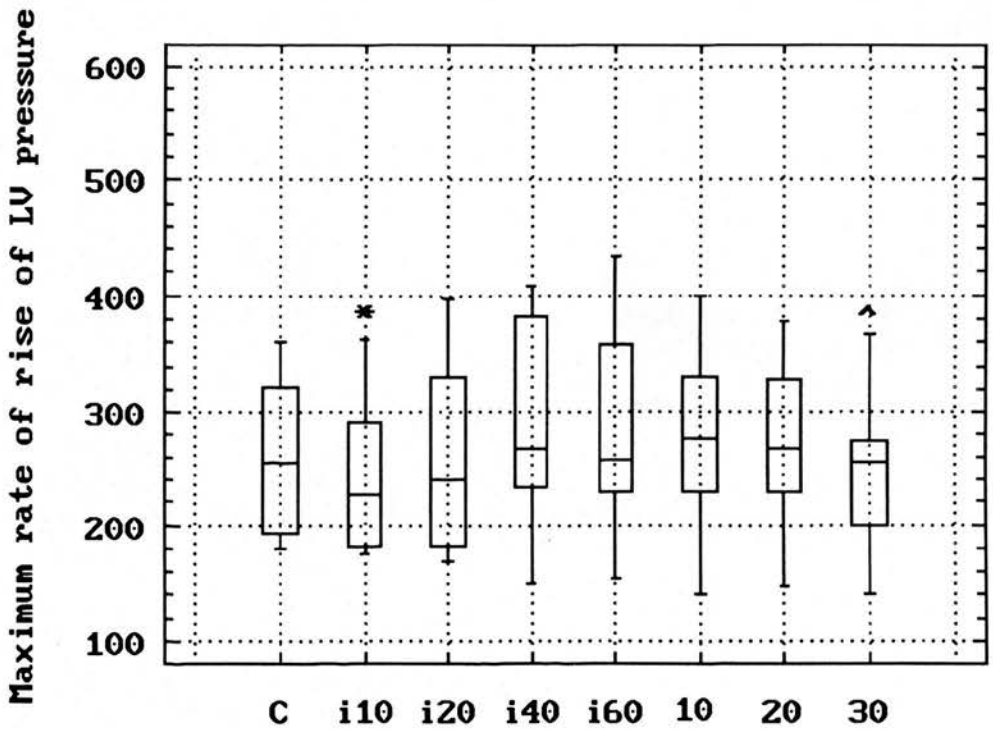
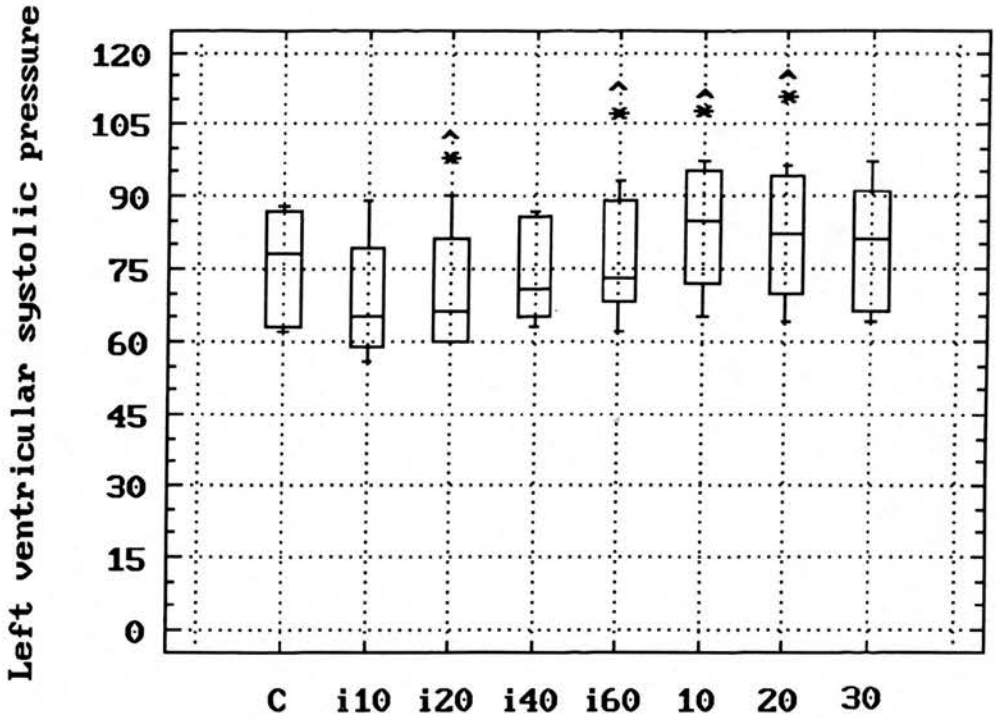
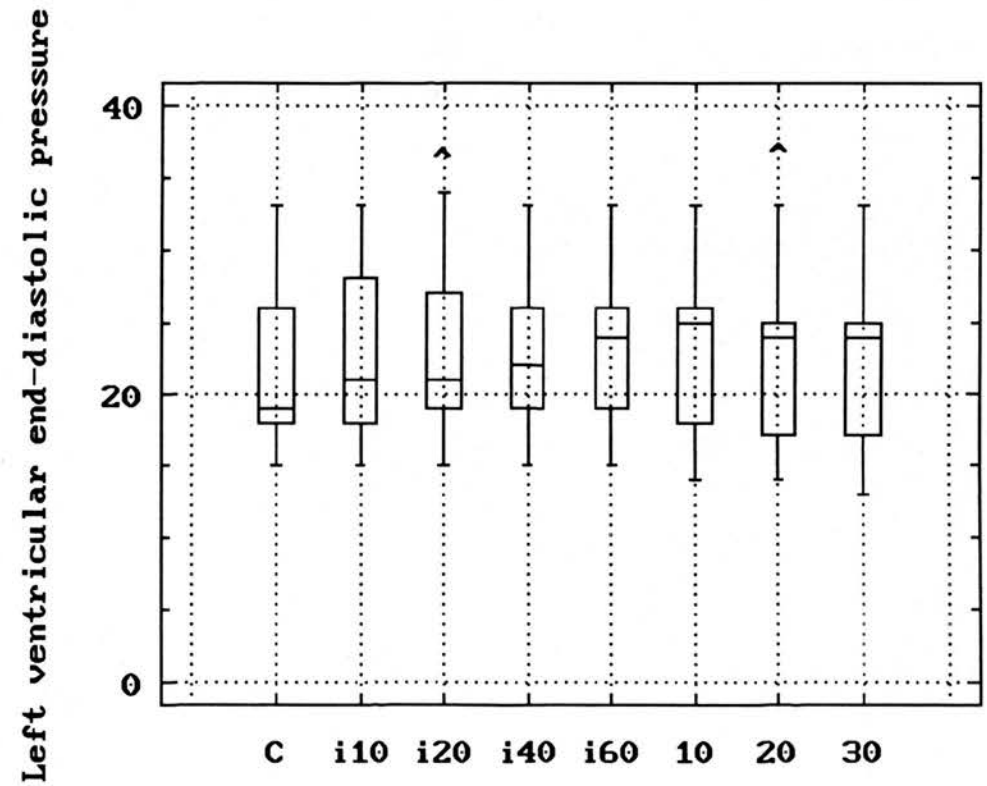
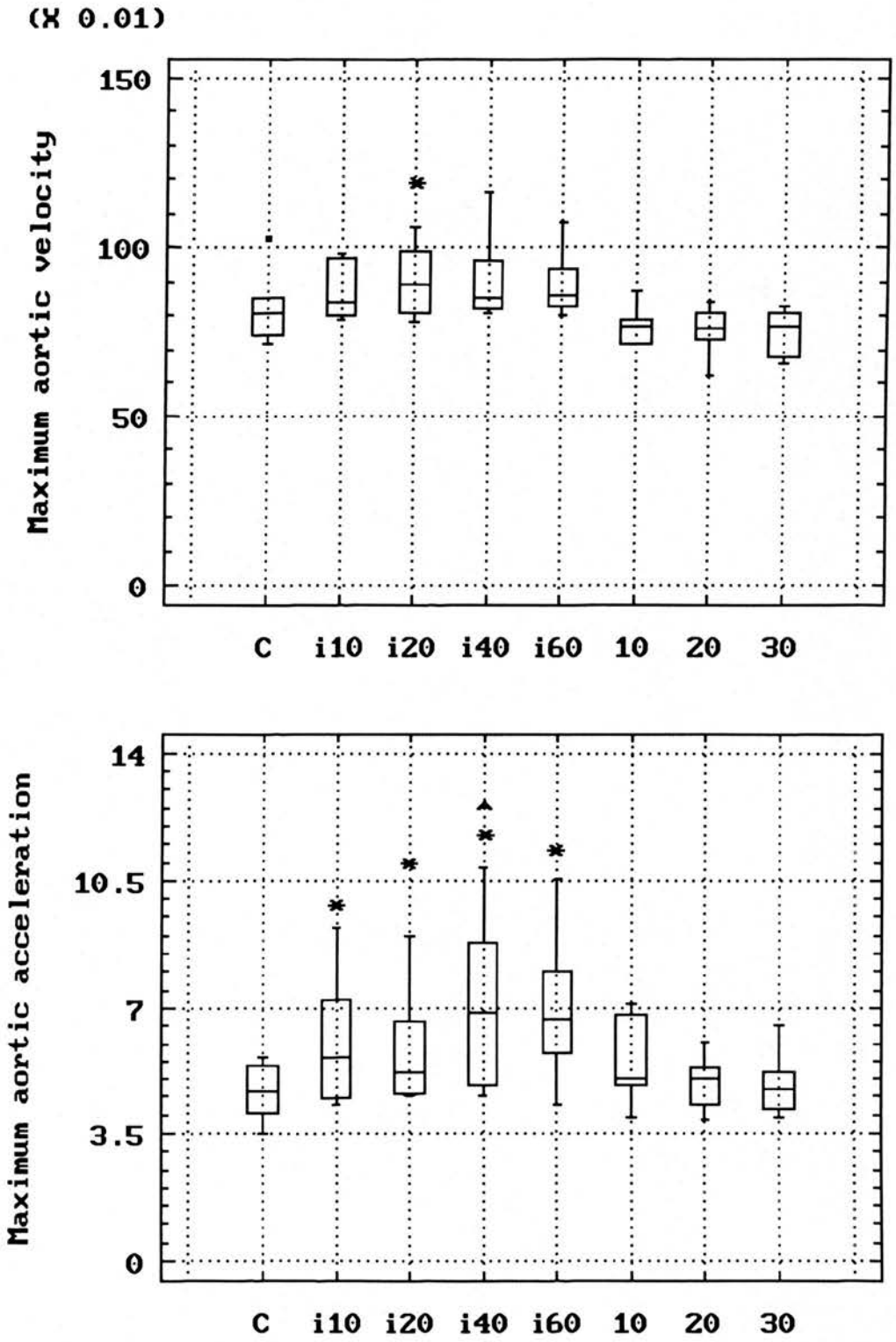
^ Indicates a significant difference from the preceding value ($p < 0.05$) by a paired Wilcoxon Test

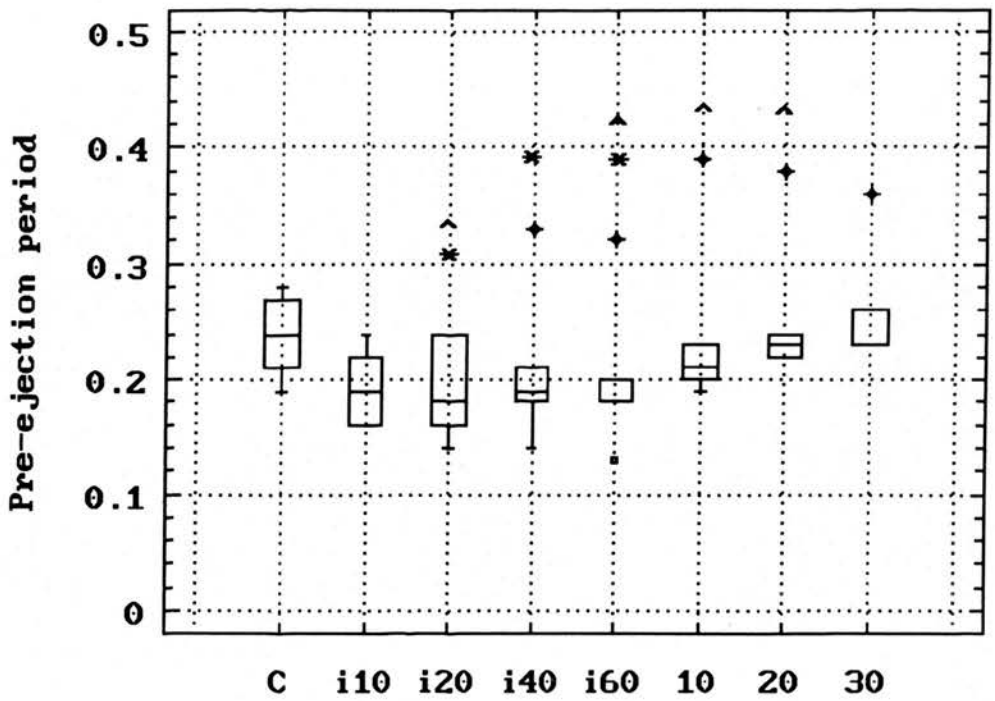

Heart rate
45
30
15
0
C
i10
i20
i40
i60
10
20
30

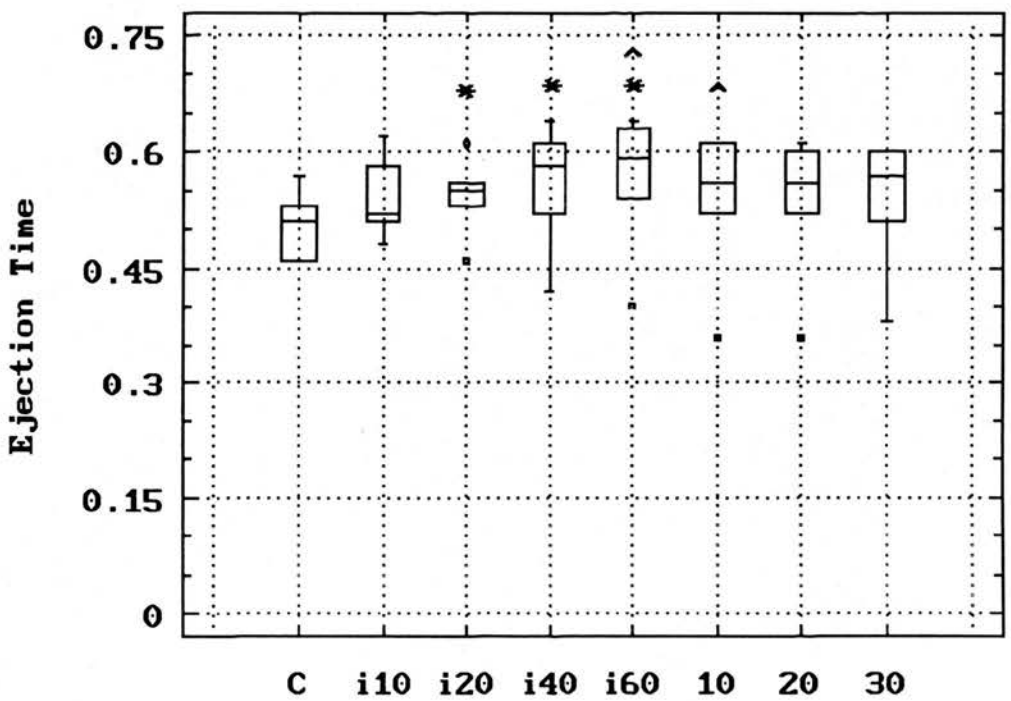

Maximum rate of rise of LV pressure
600
500
400
300
200
100
C
i10
i20
i40
i60
10
20
30

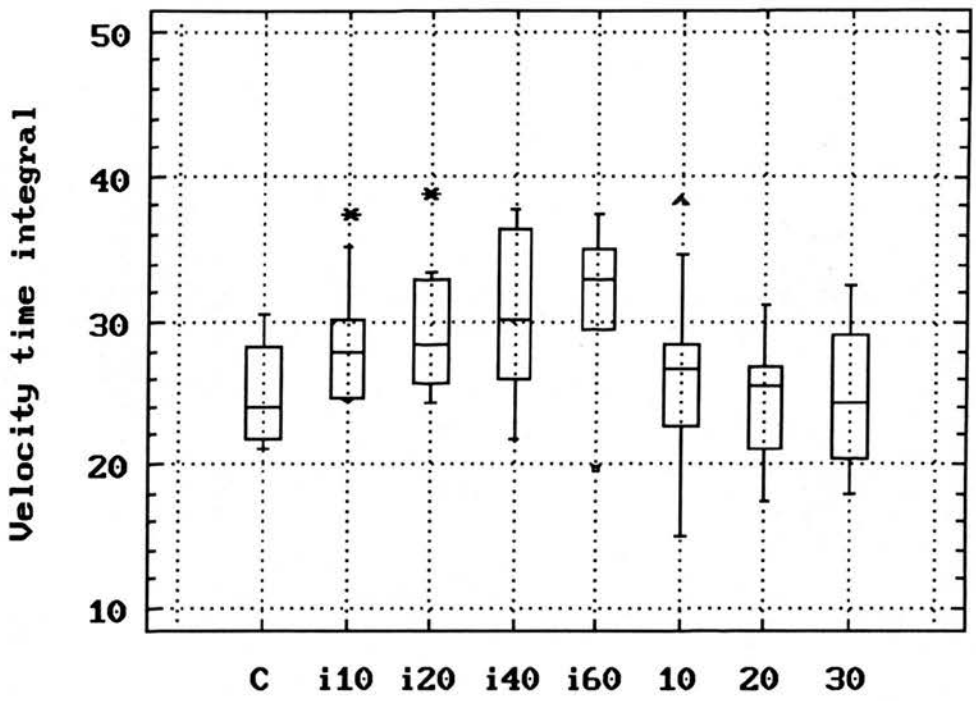

Left ventricular systolic pressure
120
105
90
75
60
45
30
15
0
C
i10
i20
i40
i60
10
20
30

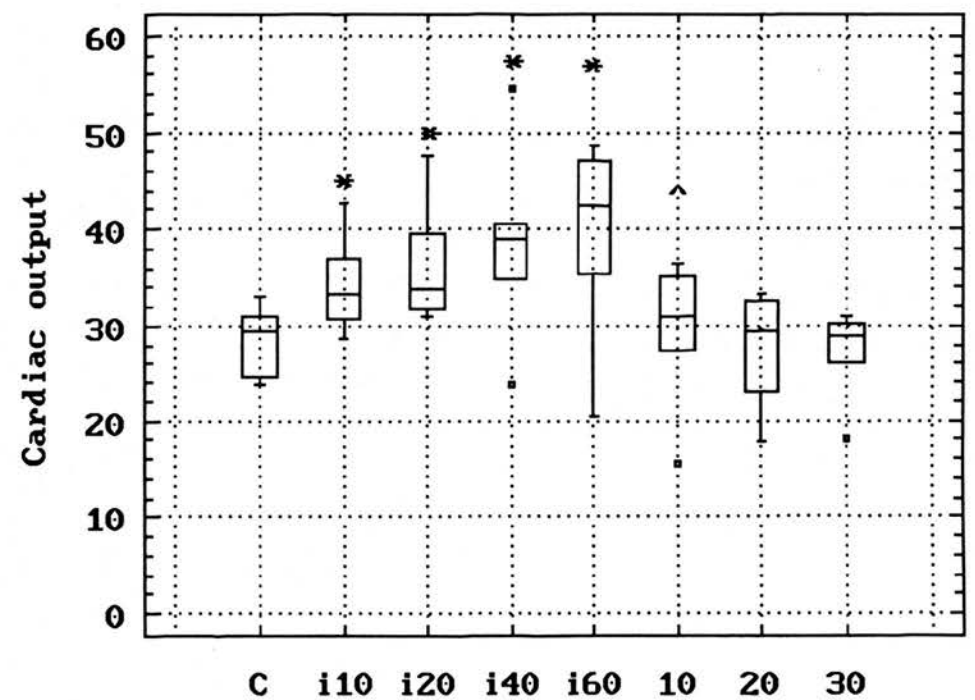

Left ventricular end-diastolic pressure
40
20
0
C
i10
i20
i40
i60
10
20
30

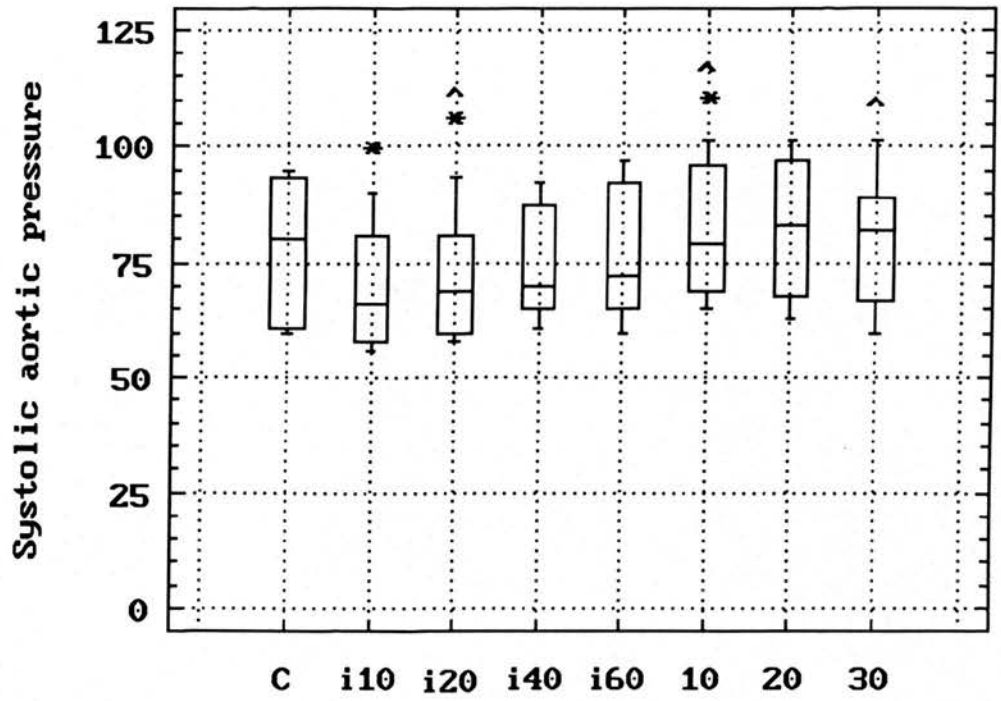

(X 0.01)
Maximum aortic velocity
150
100
50
0
C
i10
i20
i40
i60
10
20
30
Maximum aortic acceleration
14
10.5
7
3.5
0
C
i10
i20
i40
i60
10
20
30

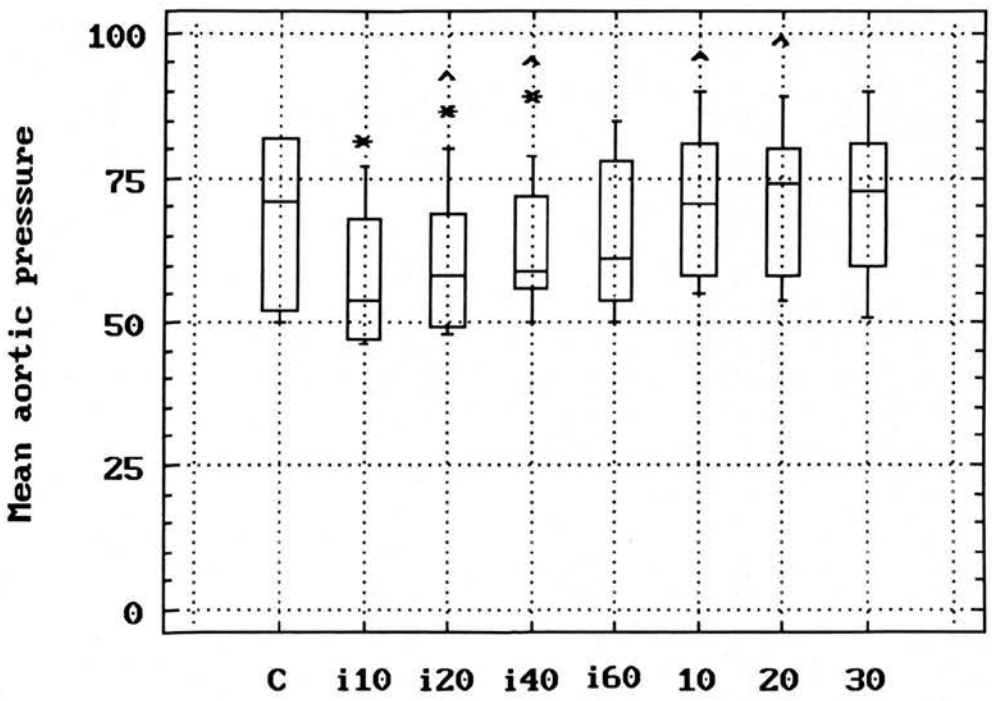

Pre-ejection period
0.5
0.4
0.3
0.2
0.1
0
C
i10
i20
i40
i60
10
20
30

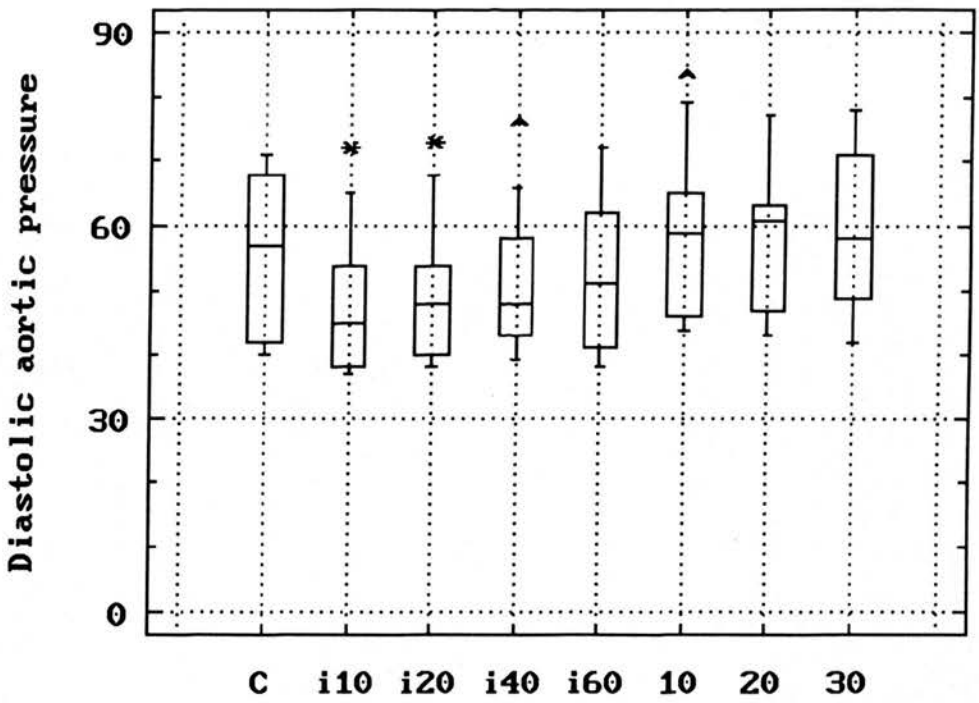

Ejection Time
0.75
0.6
0.45
0.3
0.15
0
C
i10
i20
i40
i60
10
20
30


Velocity time integral
50
40
30
20
10
C
i10
i20
i40
i60
10
20
30


Cardiac output
60
50
40
30
20
10
0
C
i10
i20
i40
i60
10
20
30


Systolic aortic pressure
125
100
75
50
25
0
C
i10
i20
i40
i60
10
20
30


Mean aortic pressure
100
75
50
25
0
C
i10
i20
i40
i60
10
20
30


Diastolic aortic pressure
90
60
30
0
C
i10
i20
i40
i60
10
20
30

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Equine vet. J., Suppl. **19** (1995) 63-70

Feasibility of transoesophageal echocardiography for evaluation of left ventricular performance in anaesthetised horses

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Keywords: horse; anaesthesia; transoesophageal echocardiography

Summary

Transoesophageal Doppler echocardiography was performed in 7 Thoroughbred horses anaesthetised with halothane. The procedure was performed on 4 occasions under standard conditions. On one occasion dobutamine hydrochloride was infused at 4 μg/kg/min for 20 min. Recordings of aortic blood velocity, obtained using high pulsed repetition frequency Doppler echocardiography (HPRF), were used to derive maximum acceleration (dv/dt_{max}), maximum velocity (V_{max}), left ventricular ejection time (ET), pre-ejection period (PEP), velocity time integral (VTI) and cardiac output (CO).

The coefficient of variation and 95% confidence intervals were narrower for the Doppler variables than for those obtained from cardiac catheterisation. For each horse the anaesthetic to anaesthetic repeatability of the Doppler indices of left ventricular function, exceeded that of maximum rate of rise of left ventricular pressure ($LVdp/dt_{max}$). The horse to horse variability was significant for heart rates V_{max}, dv/dt_{max}, and VTI. After dobutamine infusion there were signifcant changes in all measured variables except heart rate, VTI and CO. The % change that occurred exceeded the predicted 95% confidence intervals for single measurements in all significantly affected variables. This suggests Doppler indices of cardiac performance may be useful to assess changes in haemodynamic function.

Passage of the probe into the oesophagus was not associated with serious adverse effects. Mild serous nasal discharge was visible for up to 24 h after the horses recovered from anaesthesia. Mild nasal haemorrhage occurred on 5 occasions during probe insertion. It is concluded that transoesophageal Doppler echocardiography provides a minimally invasive, continuous method for monitoring left ventricular systolic performance in anaesthetised horses.

Introduction

Transoesophageal ultrasonography was first developed in human cardiology to enable cardiac imaging of patients with obesity, pulmonary disease or prosthetic valves (Frazin *et al.* 1976). The close anatomical proximity of the oesophagus to the heart enabled the use of near-focused, high frequency transducers, resulting in superior images of many intracardiac structures (Schluter *et al.* 1982). In transoesophageal echocardiography the transducer is fixed in the oesophagus and controlled from a site distant to the patient; and the technique is, therefore, ideal for the intensive care unit or operating theatre (Bjerke 1992).

Measurement of aortic blood flow velocity enables left ventricular systolic performance to be assessed. It has been shown that the peak acceleration and maximum velocity of blood flow in the ascending aorta are sensitive indices of left ventricular contractile function (Rushmer 1964; Lambert *et al.* 1983). Studies performed in dogs in which noninvasive Doppler measurements were compared with conventional invasive indices of contractility have shown a close correlation over a range of contractile states and over a wide range of preload and afterload (Wallmeyer *et al.* 1988).

Doppler echocardiography plots blood velocity against time in targeted areas of the heart and great vessels. Peak velocity and maximum acceleration are readily obtained from blood velocity spectra recorded from the aortic root during ventricular ejection. These indices, derived from transthoracic echocardiography, have been used to evaluate ventricular function in dogs (Brown 1992) and adult horses, and are sensitive to changes in inotropic state (Young *et al.* 1993).

Integration of the velocity-time curve gives an area which represents the summated distance travelled by the blood with each heartbeat, the velocity time integral (VTI). If the VTI is multiplied by the cross sectional area of the vessel and the heart rate, a measure of cardiac output is obtained (Haites *et al.* 1984). When transthoracic echocardiography was used to obtain the aortic velocity recordings, cardiac output estimations compared favourably with thermodilution measurements in man (Huntsman *et al.* 1983), dogs (Bonagura *et al.* 1990) and horses (Long *et al.* 1992). Doppler echocardiography is now available on commercial transoesophageal ultrasound transducers and has been used for intraoperative measurement of cardiac output in man (Haude *et al.* 1989; Gorcsan *et al.* 1992; Ryan *et al.* 1992).

General anaesthesia in horses is known to produce cardiac depression and systemic hypotension (Eberly *et al.* 1968; Gillespie *et al.* 1969) and this has been linked to the development of post operative morbity and lameness (Grandy *et al.* 1987; Lindsay *et al.* 1989; Richey *et al.* 1990). Steffey and Howland (1978) showed that the equine cardiovascular system is more susceptible to the depressant effects of halothane than that of other species. The assessment of cardiac performance in horses has been restricted to measurement of cardiac output (Muir *et al.* 1976) or intracardiac and arterial pressures (Brown and Holmes 1979). However, use of these techniques is limited to research applications due to risks associated with cardiac catheterisation (Cournand 1975; Schlipf *et al.* 1994). The need for a noninvasive

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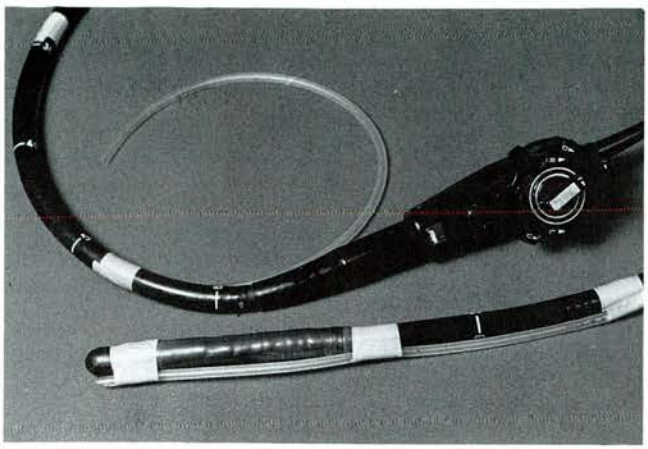

Fig 1: Equine transoesophageal probe. A 3.0 MHz, dynamically steered, annular phased array transducer, mounted at the distal end of a 150 cm human colonoscope. Note that the end has been stiffened, so that the controls are no longer operational and an external lubrication system has been applied.

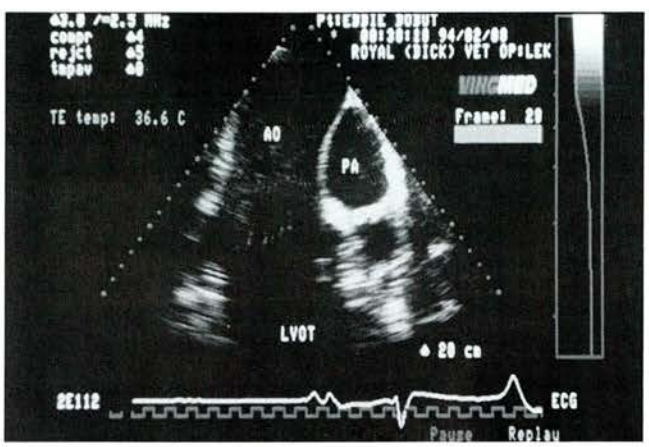

Fig 2: Standard 2-D view of the left ventricular outflow tract and aorta, obtained by transoesophageal echocardiography (AO = aorta, PA = pulmonary artery, LVOT = left ventricular outflow tract).

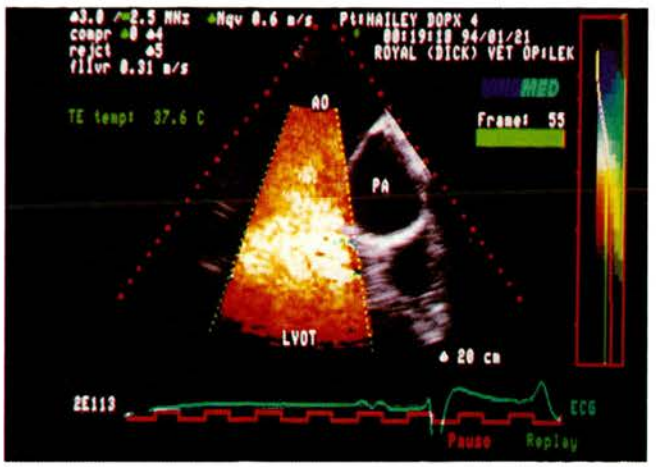

Fig 3: Colour flow mapping applied to the aorta to facilitate placement of the Doppler sample volume. The flash of red colour shows flow from the left ventricular outflow tract to the aorta during systole. The lighter shades of red represent a central core of faster flowing blood in the centre of the vessel. The timing of this frame is represented by the ECG in the far right of the figure (AO = aorta, PA = pulmonary artery, LVOT = left ventricular outflow tract).

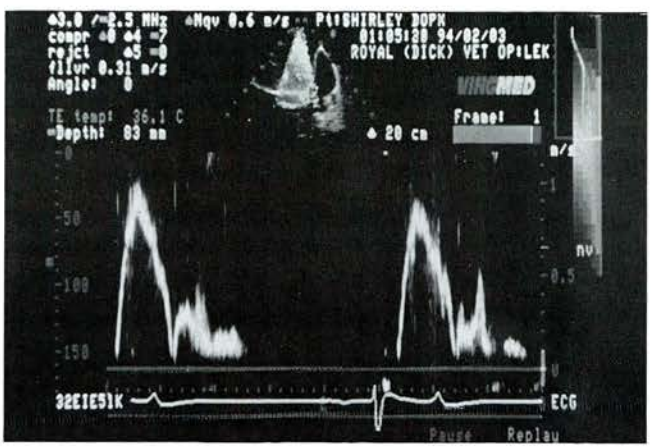

Fig 4: Pulse-wave Doppler study of aortic blood flow. The frozen 2-D image, used to position the sample volume can be seen in the top of the figure. The velocity scale in m/s is depicted on the right of the figure. Blood is flowing towards the ultrasound transducer and is depicted above the baseline.

technique to evaluate cardiac function in horses led the authors to investigate transoesophageal echocardiography. The aims of this particular study were to examine the feasibility of transoesophageal echocardiography in anaesthetised adult horses, and assess the repeatability of the derived indices of left ventricular performance. The sensitivity of the Doppler indices to inotropic intervention was also assessed by administration of the β1 adrenoreceptor agonist, dobutamine.

Materials and methods

Echocardiography

A transoesophageal probe, suitable for use in horses, was developed by Vingmed Sound (Horten, Norway) in association with the Royal (Dick) School of Veterinary Studies. The probe was used in conjunction with a Vingmed CFM 700 ultrasound machine (Diasonics, Sonotron, Bedford, UK). The images were obtained using a 3.0 MHz transducer mounted at the end of a 150 cm human colonoscope (Fig 1). The transducer was a mechanically steered, 6 ringed annular phased array, with dynamic focussing. The ultrasound system had the capacity for two-dimensional (2-D) and M-mode imaging, colour flow mapping and spectral Doppler (HPRF) and continuous wave (CW) modes.

The maximum depth for 2-D and M-mode imaging was 24 cm. The frame update rate was between 19 and 55 frames/s, dependent upon the sector angle selected and the imaging depth. The maximum depth for colour flow mapping and spectral Doppler studies was 20 cm. Spectral Doppler studies were conducted using the transducer in HPRF mode, with ultrasound emitted at a frequency of 2.5 MHz.

The first equine transoesophageal transducer was similar to a standard human transoesophageal probe. The distal end was flexible for 15cm beyond the transducer, which could be rotated, using the endoscopic controls. Flexibility of the end of the probe is important in human cardiology to allow acquisiton of the multiple standard transoesophageal images (Fisher *et al.* 1991). However, during early studies, advancing the probe against

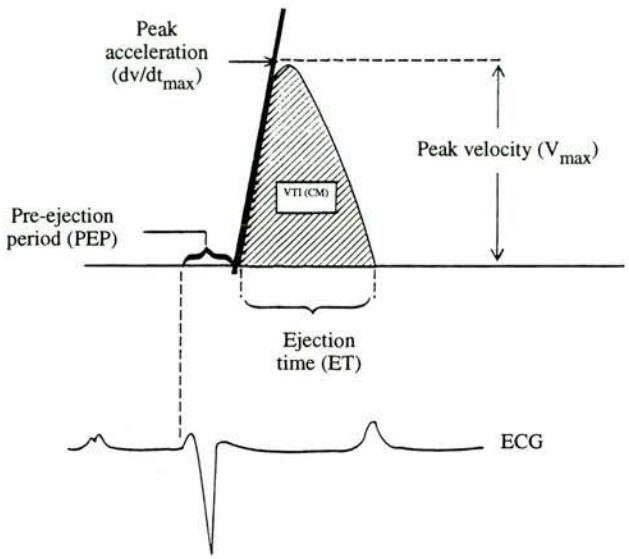

Fig 5: Diagram representing the ventricular outflow velocities recorded by Doppler echocardiography. Peak velocity (V_{max}) is measured in m/s. Peak acceleration (dv/dt_{max}), in m/s/s, is measured from the middle of the upstroke of the spectral envelope to the peak velocity. The area under the curve (VTI) is measured in cm and is derived by integrating below a line traced around the brightest line of the spectral envelope (modal velocity). PEP is measured from the start of the 'Q' wave of the ECG to the start of ejection. The pre-ejection period (PEP) and the ejection time (ET) are both measured in seconds.

resistance in the horses' pharynx caused it to bend and retroflex before entering the oesophagus. This resulted in irreversible damage. This complication, although rare, has also been reported in man (Kronzon 1992). Subsequent pilot studies showed that suitable transoesophageal images were obtained in horses with the endoscopic controls in the locked position. The end of the probe was then stiffened using heat seal material (Fig 1). To facilitate lubrication of the oesophagus and to ensure good echocardiographic contact, a length of vinyl tubing (800/101/250/800, Portex, Hythe, UK) was affixed to the body of the colonoscope by adhesive tape (Sleek, Smith and Nephew Medical Limited, Hull, UK). Before insertion the tubing was pre-filled with lubricating fluid (Vet-Lubigel, Millpledge, Retford, Herts, UK).

Horses and preparation

Seven Thoroughbred horses (4 mares and 3 geldings), aged 3–6 years and weighing 490–600 kg were used in the study. The horses were healthy, housed indoors, and kept in moderate work. No less than 3 months before these studies began, a 3 cm portion of the right carotid artery in the mid-cervical area was raised to a subcutaneous position with the horses under general anaesthesia.

Food, but not water, was withheld from the horses from 0800 h of the day preceding the study. In a padded induction area 100 µg/kg romifidine (Sedivet, Boehringer Ingelheim (Vetmedica), Bracknell, UK) were administered i.v. through a pre-placed jugular catheter. Anaesthesia was induced by administration of 2.2 mg/kg bwt ketamine (Vetalar, Parke Davis, Pontypool, UK). The trachea was intubated with a 25 or 30 mm cuffed endotracheal tube which was adapted to allow collection of gas from its distal end. Anaesthesia was subsequently maintained by halothane. Initially the horses breathed spontaneously from a large animal circle system.

Each horse was anaesthetised on 4 separate occasions, separated by a period of not less than 28 days

Transoesophageal probe insertion

Within 15 min of induction of anaesthesia, with the horses in lateral recumbency, the transoesophageal probe was inserted into the uppermost nostril and advanced through the ventral nasal meatus into the pharynx. Once the probe reached the pharynx, the endotracheal tube was removed. One operator then placed a hand into the pharynx through the horse's mouth, which was held open using a Varnell's gag. From this postion the end of the probe could be guided into the oesophagus and advanced at the nares by a second operator. The endotracheal tube was then reintroduced and its cuff inflated. As soon as the airway was secure, 60 ml of lubricating fluid was introduced through the lubrication tubing. The probe was then advanced down the oesophagus until the endoscopic controls reached the nostrils.

General anaesthetic protocol

The horse was transferred to a padded operating table and respiration was controlled using intermittent positive pressure ventilation (Large Animal Control Center, Drager, Germany). Ventilation rate and tidal volume were adjusted to maintain arterial partial pressure of CO_2 ($PaCO_2$) between 35 and 45 mmHg. Halothane concentration was measured from end-expired

TABLE 1: Mean values and coefficients of variation of measured haemodynamic variables derived from pooled data (7 anaesthetised Thoroughbreds in 4 separate anaesthetic episodes). Intraclass correlation coefficient is also shown (where applicable P<0.05 in ANOVA)

	Mean (n=28)	Coefficient of variation	95% CI as % of mean value	Intraclass correlation coefficient
Heart rate (beats/min)	28	14%	20%	0.43
Maximum aortic velocity V_{max} (m/s)	0.84	11%	23%	0.75
Maximum aortic acceleration dv/dt (m/s/s)	5.12	23%	22%	NA
Pre-ejection period PEP (s)	0.23	12%	17%	NA
Ejection time (ET) (s)	0.51	9%	15%	NA
Velocity time integral VTI (cm)	24.8	14%	19%	0.47
Cardiac output (l/min)	27.8	14%	24%	NA
Aortic systolic pressure (mmHg)	78	18%	35%	NA
Aortic mean pressure (mmHg)	66	20%	42%	NA
Aortic diastolic pressure (mmHg)	55	22%	45%	NA
Maximum rate of rise of LV pressure (mmHg/s)	246	26%	52%	NA

CI = confidence interval; n = number of measurements; NA = Not applicable.

TABLE 2: Mean values of measured haemodynamic variables in individual horses (H) from 4 separate episodes of 0.9% end-tidal halothane anaesthesia (values in parenthesis indicate coefficient of variation)

	H1	H2	H3	H4	H5	H6	H7
Heart rate (beats/min)	28.0 (14%)	26.7 (8%)	29.7 (6%)	37 (7%)	28.2 (5%)	27.5 (14%)	30.5 (8%)
Maximum aortic velocity V_{max} (m/s)	0.93 (8%)	0.86 (5%)	0.75 (8%)	0.80 (14%)	0.84 (5%)	0.87 (8%)	0.86 (15%)
Maximum aortic acceleration dv/dt (m/s/s)	5.91 (37%)	5.62 (18%)	4.64 (17%)	5.1 (13%)	4.74 (14%)	5.71 (22%)	4.14 (14%)
Pre-ejection period PEP (s)	0.22 (18%)	0.21 (14%)	0.24 (4%)	0.22 (9%)	0.24 (13%)	0.22 (9%)	0.26 (8%)
Ejection time (ET) (s)	0.49 (8%)	0.56 (11%)	0.48 (13%)	0.51 (2%)	0.53 (6%)	0.50 (6%)	0.48 (8%)
Velocity time integral VTI (cm)	26.8 (10%)	29.5 (12%)	21.1 (9%)	23.7 (13%)	26.2 (11%)	24.8 (5%)	21.3 (7%)
Cardiac output (l/min)	27.6 (13%)	29.06 (10%)	23.0 (11%)	32.4 (8%)	27.1 (10%)	28.1 (14%)	26.7 (17%)
Aortic systolic pressure (mmHg)	77 (19%)	75 (21%)	76 (17%)	84 (19%)	67 (21%)	76 (12%)	89 (13%)
Aortic mean pressure (mmHg)	64 (20%)	63.2 (30%)	65 (18%)	72 (24%)	58 (22%)	66 (13%)	77 (14%)
Aortic diastolic pressure (mmHg)	53 (22%)	51.8 (32%)	54 (20%)	61 (27%)	47 (23%)	54 (14%)	65 (16%)
Maximum rate of rise of LV pressure (mmHg/s)	238 (32%)	225 (24%)	242 (18%)	289 (33%)	206 (29%)	278 (17%)	244 (22%)

gas sampled from the end of the endotracheal tube, using an anaesthetic gas monitor (Servo Gas Monitor 120, Siemens plc, Cumberauld, UK). The out-of-circuit vaporiser was continually adjusted throughout the procedure to maintain an end-tidal halothane concentration of 0.9%. A base-apex electrocardiogram (ECG) was displayed on an oscilloscope (Datascope 500, Datascope Medical Company Ltd, Cambridge, UK).

Transoesophageal probe postioning

The transoesophageal ultrasound probe was positioned by slowly withdrawing it, until a standard long-axis view of the aorta, left ventricular outflow tract, and pulmonary artery (Fig 2) was obtained. The probe occasionally had to be rotated to bring this image into view. Once optimal alignment along the long-axis of the aorta was obtained, colour flow mapping of aortic blood flow was performed (Fig 3). The Doppler sample volume was then placed in the centre of the vessel above the aortic valve in the area where the colour flow Doppler study had revealed the fastest flow of blood (Blissitt *et al.* 1995). Once the sample volume had been positioned, the colour flow Doppler image was frozen, allowing the transducer to be dedicated to the acquisition of Doppler information. Adequate alignment with aortic blood flow was assumed from the clarity of the audible signal and when a complete velocity envelope containing minimal spectral dispersion was obtained (Fig 4).

Intravascular pressure measurement

Left ventricular and aortic pressure measurements were made using strain gauge transducers (Gaeltec Ltd, Dunvegan, Skye, UK), mounted on a size 8F, woven Dacron catheter. One manometer was sited at the distal end, and one 12 cm more proximal. The bridge excitation voltage from each manometer was monitored with a high gain amplifier (Series 5000, Lectromed, Letchworth Garden City, UK). The output from each high gain amplifier was recorded simultaneously by 1 channel of a 4 channel chart recorder and a data acquisition system on a Macintosh 11VI microcomputer. Each transducer was calibrated against 100 mmHg, using a mercury manometer before being inserted and again on removal. In this study for both transducers, zero lay within 2.5 mmHg of their pre-insertion zero reading with 95% confidence. Recorded pressures were not adjusted when baseline drift occurred.

Catheters were introduced into the the left heart through an 8 French introducer (Haemaquet, Bard Ltd, Crawley, UK) placed in the raised right carotid artery. The catheter was advanced through the introducer until the pressure traces recorded indicated the distal transducer was located in the left ventricle and the proximal transducer in the aorta. Pressure data was displayed throughout each study on the chart recorder and on the screen of the microcomputer.

Data collection and measurement

Data was collected after 60 min of anaesthesia maintained at 0.9% end-tidal halothane concentration. In anaesthetic episode 3, after initial data collection, dobutamine hydrochloride (Dobutrex, Eli Lilley and Co, Basingstoke, UK) was infused at 4 μg/kg bwt/min. Additional data was collected at 20 min and the infusion was discontinued. Mechanical ventilation was stopped at each measurement point and data was therefore recorded during apnoea. In each recording period, 20 s of pressure data from each strain gauge transducer was stored on the hard disk of the microcomputer. This was analysed off-line using a purpose written analysis programme (Labview 2.2.1, National Instruments, Texas, USA). The average mean, systolic and diastolic pressures for the aortic transducer were derived. The left ventricular pressure waveform was differentiated to obtain maximum rate of rise of left ventricular pressure ($Lvdp/dt_{max}$). Average heart rate was also determined from the left ventricular pressure waveform.

Doppler velocity spectra were recorded onto VHS videotape for analysis. All Doppler derived data was measured by a single observer by manual planimetry using electronic callipers. Measurements from the spectra comprised; velocity time integral

TABLE 3: Mean values of measured haemodynamic variables in 7 anaesthetised Thoroughbreds after 60 min of 0.9% end-tidal halothane concentration in each of 4 separate anaesthetic episodes (values in parenthesis indicate coefficient of variation)

	Episode 1	Episode 2	Episode 3	Episode 4
Heart rate (beats/min)	31 (14%)	29 (14%)	28 (13%)	30 (14%)
Maximum aortic velocity V_{max} (m/s)	0.82 (12%)	0.89 (9%)	0.88 (5%)	0.78 (12%)
Maximum aortic acceleration dv/dt (m/s/s)	4.69 (16%)	5.89 (31%)	5.18 (10%)	4.74 (19%)
Pre-ejection period PEP (s)	0.22 (14%)	0.24 (12%)	0.24 (13%)	0.24 (4%)
Ejection time (ET) (s)	0.51 (8%)	0.51 (10%)	0.48 (6%)	0.53 (11%)
Velocity time integral VTI (cm)	24.6 (14%)	25.1 (16%)	24.8 (10%)	24.5 (19%)
Cardiac output (l/min)	28.4 (9%)	28.6 (17%)	26.6 (18%)	27.0 (11%)
Aortic systolic pressure (mmHg)	78 (18%)	76 (19%)	75 (15%)	82 (20%)
Aortic mean pressure (mmHg)	68 (20%)	64 (21%)	62 (20%)	72 (22%)
Aortic diastolic pressure (mmHg)	55 (22%)	53 (22%)	51 (20%)	61 (24%)
Maximum rate of rise of LV pressure (mmHg/s)	257 (26%)	237 (34%)	234 (18%)	257 (26%)

(VTI), maximum acceleration (dv/dt_{max}), maximum velocity (V_{max}), left ventricular ejection time (ET) and pre-ejection period (PEP) (Fig 5). Five consecutive velocity spectra, coinciding with the period of blood pressure data acquisition, were averaged for each anaesthetic episode. Cardiac output was calculated using the equation:

Cardiac output = VTI x aortic cross sectional area x heart rate

Aortic cross sectional area was calculated using the equation:

Aortic cross sectional area = 3.14 x $(radius)^2$

Aortic radius was measured from a 2-D standard transoesophageal image (Fig 2), using the leading edge to leading edge method (Wyatt *et al.* 1983). The vessel was measured above the sinus of Valsalva at the vertical level of the Doppler sample volume. To obtain the radius, 3 measurements were taken during systole from 3 consecutive cardiac cycles and an average figure obtained. These 2-D images were recorded onto videotape immediately before the spectral Doppler recordings. Heart rate was derived from left ventricular pressure measurements recorded by the Macintosh 11VI.

Statistical analysis

Differences between anaesthetic episodes and horses were assessed using analysis of variance. When the f ratio was significant ($P<0.05$) an estimate of the day to day variability and within horse variability was determined by calculating the intraclass correlation coefficient, using the method described by Sokal and Rohlf (1969). In this method the added variance between groups, s_A^2, is first calculated using the equation:

$$s_A^2 = \frac{s_B^2 - s_W^2}{n}$$

s_A^2 = measure of the variability between individual horses. (an estimate of the variance due to error-free variability of different horses)
s_B^2 = the between group mean square (measure of the variance between horses)
s_W^2 = the within group mean square (measure of the variance in individual horses)
n = number of horses

The intraclass correlation coefficient (r_I) is calculated from the equation

$$r_I = \frac{s_A^2}{s_W^2 - s_A^2}$$

The intraclass correlation coefficient represents the fraction of the overall variability of the measurement that arises due to variability between individual horses. It therefore varies from 0 to 1. The more repeatable a measurement is in an individual the closer r_I will be to 1.

Coefficient of variation was calculated for each variable from pooled data by dividing the mean value by the standard deviation and expressing the result as a percentage. Ninety-five % confidence intervals for the error-free (or true) value of a measured variable in a single subject was calculated using the methods described by Moulinier *et al*, (1991). The square root of s_W^2 is used to obtain the standard deviation (s.d.) within individuals.

95% confidence interval for a single measurement = 2 x s_W

s_W = s.d. within individuals.

This value was then expressed as a percentage of the mean. The percentage difference between 2 measurements in a single individual must therefore exceed the 95% confidence interval, if the observed difference reflects a real change ($P<0.05$)

Measurements before and after dobutamine infusion were compared using a paired Student's *t* test. A probability of less than 0.01 was considered significant.

Results

The probe was placed in the oesophagus successfully in each horse on every occasion. The stiffened distal portion of the colonoscope made it difficult to place in the ventral meatus. Inadvertent introduction into the middle meatus resulted in nasal haemorrhage on 5 occasions. Haemorrhage was usually short lived and had always resolved before the horse recovered from anaesthesia. If the probe entered the middle meatus, resistance was detected before it reached the pharynx. When this occurred the probe was withdrawn and reintroduced into the ventral nasal meatus.

Once the oesophageal probe was fully inserted the standard 2-D view (Fig 1) was always obtained within 5 min. The required view was obtained at a depth of 130–145 cm in all horses studied, a depth that was repeatable for each horse. A long-axis view of the left atrium and left ventricular inflow was also observed, but this was not specifically studied. Spectral Doppler recordings taken from aortic blood flow were of uniform high quality, only minor adjustment or rotation of the probe being required to maintain clear audible signals and velocity spectra.

Table 1 shows the pooled data for all measured variables. There were significant differences for heart rate, V_{max} and VTI

TABLE 4: Measured variables before and 20 min after infusion of 4 µg/kg bwt/min dobutamine hydrochloride. Change expressed as percentage of control values (mean value and standard deviation in parenthesis)

	Control	Dobutamine	% Change from control
Heart rate (beats/min)	28 (3.5)	29 (4.7)	1%
Maximum aortic velocity V_{max} (m/s)	0.88 (0.04)	1.15 (0.21)[a]	39%
Maximum aortic acceleration dv/dt (m/s/s)	5.18 (0.61)	14.7 (4.7)[a]	175%
Pre-ejection period PEP (s)	0.24 (0.03)	0.1 (0.03)[a]	-60%
Ejection time (ET) (s)	0.48 (0.03)	0.42 (0.04)[a]	-12%
Velocity time integral VTI (cm)	24.8 (0.05)	26.3 (3.0)	7%
Cardiac output (l/min)	26.6 (4.7)	28.4 (4.12)	7%
Aortic systolic pressure (mmHg)	75 (11.4)	127 (25.9)[a]	59%
Aortic mean pressure (mmHg)	62 (12.2)	106 (22)[a]	67%
Aortic diastolic pressure (mmHg)	51 (10.5)	83 (16.8)[a]	55%
Maximum rate of rise of LV pressure (mmHg/s)	234 (43.1)	856 (303)[a]	250%

[a]Statistically significant difference from control values $P<0.01$. Tested using a paired Student's *t* test.

only. Table 2 shows data from each anaesthetic episode averaged for each horse, the coefficient of variation reflects variability within individual horses. In Table 3 the data are averaged for all horses for each anaesthetic episode. The coefficients of variation therefore reflect the between horse variability.

Table 4 shows the variables before and after administration of dobutamine, and the percentage change from control values. Aortic dv/dt_{max}, V_{max}, LV systolic and end-diastolic pressures, mean, systolic and diastolic aortic pressures and $LVdp/dt_{max}$, were all significantly increased from control values. Left ventricular ET and PEP were significantly decreased. There was no significant change in heart rate or VTI, or the related variable CO.

Discussion

The present study shows that transoesophageal echocardiography is well tolerated in anaesthetised Thoroughbred horses and although the number of 2-D images obtained was limited compared to human studies, a long-axis view of the left ventricular outflow tract and aorta was always obtained. The axial alignment of the aorta and left ventricular outflow tract with the ultrasound beam in this view was ideal for Doppler echocardiography. High quality velocity spectra, which were suitable for derivation of ejection phase indices of left ventricular function, were readily obtained using high pulse repetition frequency Doppler insonation. Management of the horses in the study was controlled with respect to diet, exercise and environment. Anaesthetic technique was standardised, and intraoperative arterial blood gas tensions were maintained within fixed limits. The effects of these sources of variance on the measured haemodynamic variables within each study, should therefore have been minimised.

All measured variables showed marked overall variation, indicated by coefficients of variation greater than 10% and wide 95% confidence intervals (Table 1). Since variation in a biological measurement made on a particular animal on different occasions dictates its sensitivity for detecting serial changes, allowance must be made for this when it is proposed to use the measurement to detect responses to treatment. Variation between individuals also influences the normal range of a measurement and must be defined, if the measurement is to be used to help define disease or abnormal function. For physiological data these two sources of variation can be of differing relative importance. When haemodynamic data are considered, the situation is complex because measurement errors can also contribute additional sources of variation to biological data. As a result reliability of any new measurement technique is an important consideration.

In this study significant differences in measured variables between individual horses was assessed using analysis of variance. Statistically significant differences were detected in heart rate, V_{max} and VTI. The intraclass correlation coefficient, r_I, has been used as an index of measurement technique reliability (Landis and Koch 1977). It provides a number between 0–1, for which 1 which indicates perfect repeatability. Moulinier *et al.* (1991) performed a very similar study of day to day reliability of Doppler derived VTI measurements in 7 conscious human volunteers kept under tight environmental control. They used transthoracic echocardiography to obtain the aortic velocity spectra and also measured heart rate and arterial blood pressure. If calculation of the correlation coefficient, r_I described by Moulinier *et al.* (1991) is used on data from the present study, the values obtained for heart rate are very similar (0.60 cf 0.57), but r_I for VTI was considerably higher in the Moulinier study (0.87 cf 0.51). Similarly arterial blood pressure values were much more repeatable in human subjects compared to anaesthetised horses. If the errors in blood pressure measurement are similar in both studies it can be concluded that general anaesthesia in horses interferes with normal homeostatic control of arterial blood pressure. A similar effect may also be responsible for the increased variation of VTI, an index which reflects stroke volume.

In the present study, heart rate, V_{max}, and VTI were the only variables for which significant differences were detected between individual horses. The source of this variation is more clearly illustrated in Table 2 . The coefficients of variation of heart rate, in 2 horses (*Horses 1* and *6*) show much higher individual variation than the rest of the group. *Horse 1* was noted to have second degree atrioventricular block and a heart rate of 22 during anaesthetic episode 2. In the other 3 episodes, the horse was in normal sinus rhythm with a rate of 30 beats/min. Dysrhythmias have important effects on indices of myocardial contractility and, in this horse, were probably responsible for aberrant high values for dv/dt_{max} and $LVdp/dt_{max}$ and their very high coefficients of variation. In *Horse 6* the high coefficient of variation was not associated with a single anaesthetic episode. Marked variation of heart rate between horses is illustrated by *Horse 4* who persistently maintained a higher heart rate in all anaesthetic episodes.

The main source of error in the measurement of linear velocity by Doppler echocardiography arises from poor alignment of the ultrasound beam with the direction of blood flow. The measured velocity of blood flow is proportional to the cosine of the angle between the direction of blood flow and the insonating beam. If this angle is less than 18° this gives a maximum error of ± 5% in velocity measurement. The standard 2-D image obtained

by transoesophageal echocardiography in horses permitted good alignment with anatomical structures (Fig 2). Alignment in the other plane is difficult to assess, but the clarity of the audible signals indicated that the beam was well aligned to blood flow. It is therefore considered unlikely that poor alignment provided a significant source of error in the present study.

Operator errors associated with measurement of the Doppler indices are a possible source of error in this study, but most variation was associated with variables derived from aortic and left ventricular pressure measurement. The high fidelity micromanometers and the recording system used were calibrated frequently and are considered to have measured pressure accurately. Since the greatest coefficient of variation and widest 95% confidence intervals are associated with the index of left ventricular contractility $LVdp/dt_{max}$, it is probable that ventricular performance indices derived simultaneously from Doppler echocardiography are also subject to a similar amount of true physiological variation. In this study the coefficient of variation and 95% confidence intervals are narrower for the Doppler variables than for those obtained by cardiac catheterisation. Doppler indices of ventricular performance are ejection phase indices, occurring after the aortic valve has opened. In contrast $LVdp/dt_{max}$ is an isovolumic index of left ventricular contractility. This difference may explain the different variability found for these indices.

Ideally the error of a new measurement technique can be established by first comparing it with a pre-existing technique taken to be an absolute standard. Transoesophageal Doppler derived cardiac output measurements have been compared with simultaneous measurements made by thermodilution in anaesthetised Thoroughbred horses (Long *et al.* 1994), the 2 techniques showed good agreement and the results of this study will be published in full later. The remaining Doppler derived variables, dv/dt_{max}, V_{max}, ET, PEP and VTI have not been compared directly with measurements made by other techniques.

Peak aortic velocity, acceleration and $LVdp/dt_{max}$ were demonstrated to have similar inotropic sensitivity to dobutamine infusions in a study in thoracotomised dogs (Lambert *et al.* 1983). $LVdp/dt_{max}$ is the most frequently used index for assessment of myocardial contractility in horses (Brown and Holmes 1979; Muir, 1992; Wagner *et al.* 1990). In the present study dobutamine infusion caused significant increases in dv/dt_{max}, V_{max} and $LVdp/dt_{max}$. $LVdp/dt_{max}$ showed the greatest percentage increase in response to infusion of the inotrope, but the increases in dv/dt_{max} and V_{max} significantly exceeded their 95% confidence intervals, indicating that all 3 variables show sufficient sensitivity to dobutamine administration to be useful markers of ventricular contractile performance. The 3 indices, $LVdp/dt_{max}$, dv/dt_{max} and V_{max}, all have differing sensitivities to changes in afterload. The Doppler derived measurements, dv/dt_{max} and V_{max} being ejection phase indices are highly sensitive to afterload changes whereas $LVdp/dt_{max}$, an isovolumic index is less influenced by afterload. These differing sensitivities to ventricular loading may explain the quantitative differences in variable response to dobutamine infusion.

Maximum aortic acceleration (dv/dt_{max}) showed much higher variation than the peak velocity (V_{max}). This is in agreement with a study performed in experimental dogs (Wallmeyer *et al.*1988). In a study in man, Gardin *et al.* (1984) attributed this to technical difficulties in defining dv/dt_{max} from the velocity spectra. Peak velocity is much easier to identify and small errors in identifying dv/dt_{max} are magnified by differentiation (Figures 4 and 5).

Pre-ejection period and ET also showed sensitivity to dobutamine infusion, both were reduced significantly from preinfusion values. This reduction in PEP is expected when ventricular contractility increases; the increased contractility results in an increase in the rate of left ventricular pressure generation during isovolumic systole, luminal pressure exceeds aortic pressure faster, so that the aortic valve opens and ejection commences sooner after electrical activation of the ventricle. Increases in afterload and contractility reduce ventricular ejection times (Braunwald 1988) and this may explain the significant falls in ET after infusion of dobutamine.

In the present study, increased peak aortic velocity was offset by reduction in ejection time (ET), as a result VTI, which directly reflects stroke volume, remained unchanged. Although arterial blood pressure was significantly increased by dobutamine at 4 µg/kg/bwt/min, cardiac output remained unchanged after 20 min of infusion. These results are in agreement with those from standing horses, when dobutamine failed consistently to raise cardiac output despite elevating cardiac contractility (Hinchcliffe *et al.* 1991; Young *et al.* 1993). Increased arterial blood pressure, with no change in cardiac output implies that systemic vascular resistance has increased. This contrasts the drug's activity in man and dogs, when augmentation of cardiac output is not accompanied by elevation of arterial blood pressure or systemic vascular resistance (Tuttle and Mills 1975; Bendersky *et al.* 1981).

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