RESEARCH PAPER

The effects of detomidine, romifidine or acepromazine on echocardiographic measurements and cardiac function in normal horses

Rikke Buhl* DVM, **Annette K Ersbøll*** MSc, PhD, **Nanna H Larsen*** DVM, **Lis Eriksen*** DVM, DVSc & **Jørgen Koch†** DVM, PhD

*Department of Large Animal Sciences, The Royal Veterinary and Agricultural University, Frederiksberg C, Denmark
†Department of Small Animal Diseases, The Royal Veterinary and Agricultural University, Frederiksberg C, Denmark

Correspondence: Rikke Buhl, Department of Large Animal Sciences, The Royal Veterinary and Agricultural University, 88 Dyrlægevej, DK-1870 Frederiksberg C, Denmark. E-mail: rib@kvl.dk

Abstract

Objective To evaluate by echo- and electrocardiography the cardiac effects of sedation with detomidine hydrochloride, romifidine hydrochloride or acepromazine maleate in horses.

Study design An experimental study using a crossover design without randomization.

Animals Eight clinically normal Standardbred trotters.

Materials and methods Echocardiographic examinations (two-dimensional, guided M-mode and colour Doppler) were recorded on five different days. Heart rate (HR) and standard limb lead electrocardiograms were also obtained. Subsequently, horses were sedated with detomidine (0.01 mg kg^{-1}), romifidine (0.04 mg kg^{-1}) or acepromazine (0.1 mg kg^{-1}) administered intravenously and all examinations repeated.

Results Heart rate before treatment with the three drugs did not differ significantly ($p = 0.98$). Both detomidine and romifidine induced a significant decrease ($p < 0.001$) in HR during the first 25 minutes after sedation; while acepromazine had a varying effect on HR. For detomidine, there was a significant increase in LVIDd (left ventricular internal diameter in diastole; $p = 0.034$) and LVIDs (left ventricular internal diameter in systole; $p < 0.001$). In addition, a significant decrease was found in IVSs (the interventricular septum in systole; $p < 0.001$), LVFWs (the left ventricular free wall in systole; $p = 0.002$) and FS% (fractional shortening; $p < 0.001$). The frequency of pulmonary regurgitation was increased significantly ($p < 0.001$). Romifidine induced a significant increase in LVIDs ($p < 0.001$) and a significant decrease in IVSs ($p < 0.001$) and FS% ($p = 0.002$). Acepromazine had no significant effect upon any of the measured values.

Conclusions and clinical relevance The results indicate that sedation of horses with detomidine and to a lesser extent romifidine at the doses given in this study has a significant effect on heart function, echocardiographic measurements of heart dimensions and the occurrence of valvular regurgitation. Although the clinical significance of these results may be minimal, the potential effects of sedative drugs should be taken into account when echocardiographic variables are interpreted in clinical cases.

Keywords acepromazine, detomidine, echocardiography, horses, romifidine.

Introduction

Echocardiography is a valuable and noninvasive procedure, which is increasingly used in the assessment of congenital and acquired heart diseases in

horses (Bonagura & Blissitt 1995). Echocardiography is well tolerated by most horses (Patteson et al. 1995); but it may be necessary to restrain nervous and restless horses with sedative drugs. Those most commonly used in horses are the α_2-agonists detomidine, romifidine and the phenothiazine derivative acepromazine (Ballard et al. 1982; Clarke & Taylor 1986; England et al. 1992; Kannegieter 1993; Marroum et al. 1994). These sedatives all have a dose-dependent effect on cardiovascular function. Detomidine and romifidine induce bradycardia, sino-atrial block (SA-block), atrio-ventricular block (AV-block) and initial hypertension followed by hypotension (Clarke & Taylor 1986; Sarazan et al. 1989; Clarke et al. 1991; Wagner et al. 1991). Administration of detomidine and romifidine leads to a decrease in cardiac output and stroke volume (Sarazan et al. 1989; Wagner et al. 1991), whereas administration of acepromazine leads to either an increase or a decrease in cardiac output (Muir et al. 1979; Steffey et al. 1985). Acepromazine induces hypotension but a varying effect on heart rate (HR) has been reported (Parry et al. 1982; Steffey et al. 1985; Hashem & Keller 1993; Marroum et al. 1994).

Despite the importance of sedative agents on cardiac function, only one investigation of the effect of detomidine on echocardiographic measurements in horses has been published (Patteson et al. 1995). Patteson et al. (1995) showed that detomidine mostly results in changes in the systolic dimensions of the heart. An effect on the diastolic dimensions was not found and valvular competence was not examined.

The aim of the present study was to determine whether echocardiographic measures were significantly affected by detomidine, romifidine or acepromazine and to consider the clinical significance of any echocardiographic changes.

Materials and methods

Horses

All experimental procedures and animal protocols were carried out in accordance with the requirements of The Danish Animal Experimentation Inspectorate. Eight untrained Standardbred trotters were used. They were all mares aged 3–8 years and weighing 477–540 kg. All horses were stabled at the Large Animal Hospital, The Royal Veterinary and Agricultural University and were accustomed to the surroundings and the experimental procedures prior to the study. All horses underwent a general clinical examination before each experiment to ensure that they were healthy.

Drugs

Two α_2-agonists and one phenothiazine derivative tranquilizing drug were used. All drugs were administered intravenously through a needle into the jugular vein: 0.01 mg kg^{-1} detomidine hydrochloride (10 mg ml Domosedan; Orion Pharma Animal Health, Kvistgård, Denmark); 0.04 mg kg^{-1} romifidine hydrochloride (10 mg ml Sedivet; Boehringer Ingelheim Danmark A/S, Copenhagen, Denmark); 0.1 mg kg^{-1} acepromazine maleate (10 mg ml Plegicil; Pharmacia Animal Health, Copenhagen, Denmark). A period of at least 3 days was allowed between treatments to allow washout time for the drugs.

Experimental design

Before the experimental procedure, the horses were placed in stocks equipped with a rubber matted floor. The horses were allowed to settle and not examined until the HR was near resting levels. Heart rate was obtained by auscultation counting heart beats over 30 seconds. The same trained operator (RB) performed all echocardiograms. Five control echocardiograms without sedation were recorded on five different days for each horse before administration of the first drug. The measurements obtained on the fifth day were used for control values, as this examination was temporally closest to the sedation studies and because each sedative was only evaluated on 1 day. The three drugs were then tested in the following order, which was randomly chosen: detomidine, romifidine, acepromazine. Standard limb lead electrocardiograms (ECG; Schiller AT-4, Simonsen & Weel, Taastrup, Denmark) of 20 heart cycles were recorded before and during the experiment at a speed of 25 mm second^{-1}, amplitude 10 mm mV^{-1}.

The ECG and HR were recorded before (0 minutes) and at 2, 5, 15, 25 and 35 minutes after administration of each drug. Echocardiography was started 10 minutes after drug administration and lasted for 20–25 minutes.

Echocardiographic measurements

The echocardiographic measurements were recorded with a 1.5 MHz phased arrayed sector transducer

with harmonic imaging (Vivid 3 Vingmed; G.E. Healthcare, Brøndby, Denmark). A base apex ECG was superimposed for timing of echocardiographic measurements. Cardiac cycles after SA-block or second-degree AV-block (2°AV-block) were not used for measurements. All images were recorded at a depth of 26–28 cm. Two-dimensional short-axis images of the left ventricle (LV) were recorded from the right parasternal view as described by Long et al. (1992). The M-mode curser was placed across the LV, and care was taken to ensure that the plane of section was perpendicular to the interventricular septum (IVS) and that the cursor bisected the ventricle. Motion mode echocardiograms were recorded at the chordal level between the mitral valve and papillary muscles such that a short border of the opened anterior mitral valve was seen during the beginning of ventricular filling (Sampson et al. 1999). The leading edge methodology was used in all M-mode measurements (Sahn et al. 1978). Care was taken not to include the septomarginal trabecule located in the right ventricle when measuring the IVS. End diastolic measurements were timed with the point of the Q-wave on the simultaneously recorded ECG. End systolic measurements were made at the time of maximal IVS thickness. Left ventricular internal diameter in systole (LVIDs) and diastole (LVIDd), the IVS in systole and diastole (IVSd) as well as the left ventricular free wall in systole (LVFWs) and diastole (LVFWd) were obtained from the same image. Five separate cardiac cycles (five frames) were measured and an average was calculated. These measurements were recorded in the order as they were described from 10 and 15 minutes after drug administration. Fractional shortening (FS%) was calculated from LVIDs and LVIDd using the formula (Pipers & Hamlin 1977):

$$FS\% = \frac{LVIDd - LVIDs}{LVIDd} \times 100.$$

From 15 to 30 minutes after drug administration, the pulmonary, tricuspid, mitral and aortic valve areas were all examined in the described order using colour flow mapping, to identify valvular regurgitation jets. During the colour Doppler examinations, efforts were made to evaluate all parts of the valves. The tricuspid valve was examined in the right parasternal long-axis and long-axis tipped view (Long et al. 1992). The pulmonary valve was examined in the right parasternal angled view, and the mitral valve in the left parasternal long-axis

view and in the long-axis apical view (Long et al. 1992). Finally, the aortic valve was examined in the left parasternal long-axis view and in the five-chambered view (Long et al. 1992). If a regurgitant blood flow was present, the imaging plane was angled to show the maximal size of the regurgitation. This procedure was repeated five times. The equipment zoom feature was not used. Signals were ignored if they were of very short duration and immediately after valve closure. These signals were attributed to either valve closure artefacts or simply the movement of blood in front of the closing valves. Based on the area of the jet in comparison with the approximate size of the atrium for the mitral (MIT) and tricuspid (TRI) regurgitation, four groups were defined: 'very small jet' (<10% of the area of the atrium), 'small jet' (>10–30%), 'medium jet' (>30–50%) and 'large jet' (>50%) (Pedersen et al. 1999). For the aortic (AO) and pulmonary (PUL) regurgitation, the maximal jet diameter just below the aortic/pulmonary valves was measured in centimetres (Willems et al. 1997). For further statistical analysis, the regurgitation for all four valves were only classified as present or absent, with regurgitation defined as present whenever the area or diameter could be measured.

Statistical analyses

The study design used was a cross-over study. However, the order of treatment was not randomized. In order to show that there was no carry-over effect of drugs, differences in HR before administration of the drugs were tested. An analysis of variance (ANOVA) was used with HR before sedation as the outcome. Differences between the drugs were tested with drugs as a fixed effect.

The effect of each drug (detomidine, romifidine, acepromazine) across time on HR was evaluated. This was done with repeated measurements ANOVA using a general linear mixed model, with HR as the outcome. An analysis was performed for each drug, separately. The fixed effect of time after administration of the drug (0, 2, 5, 15, 25 minutes) and the random effect of horse were included in the model. The autocorrelation between repeated measures on the same horse and treatment was taken into account by including an autoregressive structure. Pairwise comparison of differences between time as administration of the drug and the HR before administration of the drug was performed, using a test of least square means differences.

Differences in echocardiographic measures between drugs and control were compared, using a general linear mixed model (ANOVA). Type of drug was included as a fixed effect and horse as a random effect. The assumptions for using ANOVA were evaluated using Shapiro–Wilk's test for normality as well as visual evaluation of residual plots. Pairwise comparison between each drug and the control was performed using a test of least square means differences with Dunnett's adjustment.

Fisher's exact test was used to test the association between the presence of valvular regurgitations (AO, PUL, TRI, MIT) for each of the drugs *versus* the control.

A 5% significance level was used. Data were analysed using Statistical Analysis System (SAS Institute, version 8.2, Cary, NC, USA). The repeated measurements ANOVA of HR and the ANOVA of echocardiographic measures using a general linear mixed model were performed with the MIXED procedure. Fisher's exact test of valvular regurgitation was performed, using the FREQ procedure.

Results

All horses remained healthy throughout the experiment.

ECG evaluation

Differences in HR before drug administration between the three drugs were tested in order to show no carry-over effect of the drugs. The resting HR before drug administration (baseline levels) did not differ significantly before administration of the three sedatives ($p = 0.98$). No arrhythmias were recorded.

Within 2 minutes of detomidine administration, HR decreased significantly ($p < 0.001$) to 16–32 beats minute^{-1}. Heart rates stayed significantly below baseline levels throughout the time course (35 minutes). Within two minutes after administration of detomidine, four horses acquired both SA-block and 2°AV-block and three horses showed 2°AV-block. The arrhythmia was most pronounced within the first 5–15 minutes after drug administration. The recovery of SA-block and 2°AV-block was gradual and after 35 minutes only one horse showed 2°AV-block.

After romifidine administration, HR decreased significantly ($p < 0.001$), within 2 minutes, to 16–40 beats minute^{-1}. Heart rate stayed below baseline levels for 25 minutes after drug administration. Within two minutes of drug administration, three horses had 2°AV- as well as SA-block. One horse showed SA-block and four horses had 2°AV-block alone. The occurrence of SA-block in general had a duration of 5 minutes. Recovery from 2°AV-block was gradual and after 35 minutes only one horse had 2°AV-block.

Acepromazine induced a considerable variation in HR (28–62 beats minute^{-1}) in the first few minutes after drug administration. There were no significant changes from baseline HR ($p = 0.53$) and no arrhythmia was observed.

Echocardiographic examination

The repeatability of the five control echocardiographic examinations obtained on five separate days has been published elsewhere (Buhl et al. 2004). Only the measurements of the fifth examination were used as control data in the present study. The echocardiographic variables (Table 1) showed that

Table 1 Effects of detomidine, romifidine or acepromazine on echocardiographic measurements compared with the controls

Drug	LVIDd (cm)	LVIDs (cm)	IVSd (cm)	IVSs (cm)	LVFWd (cm)	LVFWs (cm)	FS%
Control	11.4 ± 0.53	7.75 ± 0.60	2.56 ± 0.17	3.44 ± 0.25	2.33 ± 0.17	3.48 ± 0.26	33 ± 3
95% CI†	11.38–11.56	7.56–7.74	2.52–2.60	3.46–3.54	2.36–2.42	3.42–3.52	32.9–33.4
Romifidine	11.6 ± 0.79	8.41 ± 0.66*	2.46 ± 0.13	3.00 ± 0.35*	2.24 ± 0.19	3.27 ± 0.35	28 ± 4*
Detomidine	11.8 ± 0.60*	8.63 ± 0.43*	2.48 ± 0.08	3.02 ± 0.25*	2.29 ± 0.19	3.02 ± 0.31*	27 ± 4*
Acepromazine	11.1 ± 0.57	7.52 ± 0.51	2.61 ± 0.16	3.35 ± 0.28	2.39 ± 0.20	3.48 ± 0.44	33 ± 3

The results are given as mean ± SD. The *p*-value is given for Dunnett's adjusted test for comparison of the sedative to the control. Asterisk (*) indicates a significant difference ($p < 0.05$) between the treatment group and the control group.
95% CI†, 95% confidence interval for the mean (with permission from Buhl et al. 2004); LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVSd, interventricular septum in diastole; IVSs, interventricular septum in systole; LVFWd, left ventricular free wall in diastole; LVFWs, left ventricular free wall in systole; FS%, fractional shortening.

Table 2 The number of horses (*n*) with valvular regurgitations after sedation with detomidine, romifidine or acepromazine

Drug	Total	AO	PUL	MIT	TRI
Control	8	3	0	1	0
Romifidine	8	7 (0.12)	4 (0.077)	3 (0.57)	4 (0.077)
Detomidine	8	6 (0.31)	8 (<0.001)	2 (1.00)	4 (0.077)
Acepromazine	8	1 (0.57)	1 (1.00)	2 (1.00)	1 (1.00)

The *p*-value is shown in brackets for the association between valvular regurgitation and each of the drugs *versus* the control. AO, Aortic regurgitation; PUL, pulmonary regurgitation; TRI, tricuspid regurgitation; MIT, mitral regurgitation.

treatment with detomidine resulted in a significant increase in LVIDd and LVIDs ($p = 0.034$ and $p < 0.001$, respectively), and a significant decrease in IVSs, LVFWs and FS% ($p < 0.001$, $p = 0.002$ and $p < 0.001$, respectively) was also observed. No significant change was found for IVSd and LVFWd. Romifidine resulted in a significant increase in LVIDs ($p < 0.001$) and a significant decrease in IVSs and FS% ($p < 0.001$ and $p = 0.002$, respectively) in comparison with the controls (Table 1). For the remaining measurements, significant differences between treatment and control were not observed. No significant changes were found in the echocardiographic measurements after acepromazine administration compared with the control measurements (Table 1).

Valvular regurgitation was demonstrated by colour flow Doppler echocardiography in four of the eight horses on the day 5 control examination (Table 2). Three horses revealed AO regurgitations, and another horse showed MIT regurgitation. None of the regurgitations were detectable by auscultation during the clinical examination. The MIT regurgitation was classified as 'very small' occupying <10% of the atria. The average diameter of the AO regurgitation jets was 0.91 cm ± 0.39 cm. After detomidine administration, a significant increase in the frequency of PUL regurgitation was observed ($p < 0.001$). The AO regurgitation also appeared to increase in frequency, but this increase was not statistically significant. The increased incidence of AO and PUL regurgitation after romifidine administration was also not significant increase. No significant changes in regurgitation jets were observed after acepromazine administration. The size of the MIT and TRI regurgitation was

classified as 'very small'. Also the size of the AO regurgitation remained unchanged (0.82 ± 0.32 cm), compared with the control echocardiograms. The diameters of the PUL regurgitation jets after administration of drugs were 0.72 ± 0.25 cm.

Discussion

The present study included eight normal untrained horses and demonstrated that detomidine and to a lesser extent romifidine influenced heart function and dimensions as measured by ECG and echocardiography at the doses given. Acepromazine did not appear to have these effects at the dose administered in the present study.

Heart rate was recorded simultaneously with the ECG obtained from echocardiography. 'Blinding' of the investigation was, therefore, impractical because of the pronounced treatment effect on the HR (Sinclair et al. 2003).

The drugs were administered in the same order during the study period. Ideally, the order of drug administration should have been randomized. In a standard cross-over design with randomized order of treatments, it is possible to evaluate the effect of period and the effect of treatment by period effect (carry-over effect). However, because of the lack of randomized treatment order in the present study, these effects could not be estimated. However, the ultrasonographer was experienced and no learning effect across time was expected. The horses were very familiar with the echocardiographic procedures before initiation of the study with echocardiography being performed very often during the previous year. Therefore, it is unlikely that any changes in measured variables were caused by horses becoming more familiar with the procedure. At least, three days were allowed between treatments to ensure washout of the drugs administered. The study showed no significant differences in HR before administration of the three drugs; therefore, a treatment by period effect could probably be neglected.

The study design did not allow the clinical sedative effect of the drugs to be tested. Therefore, we can only evaluate the echocardiographic effect of the sedatives at the doses given in this study. The doses chosen were doses generally accepted as those producing 'light' sedation although their equipotency – in terms of sedation – is impossible to establish (Ballard et al. 1982; England et al. 1992; Hamm et al. 1995).

In the present study, the change in HR was significant within 2 minutes after IV administration of romifidine and detomidine, and reached the lowest level after 2 minutes, which is consistent with results reported previously (Clarke & Taylor 1986; Sarazan et al. 1989; Clarke et al. 1991; England et al. 1992). No changes in HR were observed after acepromazine administration. However, within the first 5 minutes, a significant variation in HR was observed. In general, there is discrepancy between reports about the effect of acepromazine on HR after IV administration in horses. Some reports reveal a significant increase (Hashem & Keller 1993), while others find no changes in HR (Marroum et al. 1994). These differences may be because of the different dosages used.

In a study involving 26 horses of different breeds, a dose of 0.01 mg kg^{-1} detomidine induced significant changes in echocardiographic measurements (Patteson et al. 1995). There was a significant increase in LVIDs and with this a significant decrease in FS%. In addition, wall thickness measured as IVSs and LVFWs were significantly decreased, indicating a reduction in systolic left ventricular performance. Only a small change in left ventricular diameter in end-diastole (LVIDd) was shown, which indicated that pre-load was not substantially increased despite the marked reduction in HR. The results of the present study are in agreement with the results reported by Patteson et al. (1995). However, we also observed a significant increase in LVIDd, which indicates an increased pre-load. The diastolic dimensions of the LV is also dependent on the filling time and a slow HR will increase the filling time and the size of LVIDd (DeMaria et al. 1979). Wagner et al. (1991) also found a reduction in the left ventricular performance in a study with six horses. After administration of romifidine, only a significant increase in LVIDs and a decrease in IVSs and FS% were observed. The aforementioned changes in echocardiographic parameters indicate that stroke volume is decreased after sedation with the two sedatives. In combination with the bradycardia, this results in a reduction in cardiac output. Noninvasive echocardiographic measurements of cardiac function do not differentiate between direct myocardial inotropic effect and abnormalities of myocardial contractility because of alterations in afterload and pre-load (Vuille & Weyman 1994). A direct negative inotropic effect of sedation with detomidine or romifidine can, therefore, not be concluded from the present study.

In the present study, each horse was only sedated once with each drug. A previously reported repeatability study of the five control echocardiographic examinations showed that the day-to-day variation for some of the measurements were of a considerable magnitude (Buhl et al. 2004). The total variation in the echocardiographic measurements was split into three levels: the variation between horses, the day-to-day variation within individual horses and finally the variation within the horse on the same day of examination. For IVSd and IVSs, the day-to-day variation was <10%; for LVIDd, LVIDs and FS%, it was between 15% and 22% and finally for LVFWd and LVFWs, it was between 26% and 43% (Buhl et al. 2004).

With colour flow Doppler echocardiography, small regurgitant jets are detectable in clinically normal horses (Blissitt & Bonagura 1995; Marr & Reef 1995), humans (Yoshida et al. 1988) and dogs (Nakayama et al. 1994). The control echocardiographic examinations of the horses showed that the repeatability for especially MIT and TRI regurgitations was quite low, because of instrumental, physiological as well as operator dependent factors (Buhl et al. 2004). As mentioned previously, we only used the results of the fifth day of the control echocardiographic examination. On that day four, horses showed valvular regurgitation, but during the previously four control examinations two horses showed TRI and one horse MIT regurgitation. No horses showed PUL regurgitation during the repeatability study and the repeatability of PUL regurgitation was, therefore, not calculated (Buhl et al. 2004). In the present study, the MIT regurgitation was classified as 'very small', and the diameter of the AO and PUL regurgitation was <1 cm. After administration of detomidine and romifidine, an increased frequency of valvular regurgitation, especially by the aortic and pulmonary valves, was observed. This may be because of an increased afterload and bradycardia. However, the fact should not be ignored that the repeatability of the AO regurgitation can influence the results as we have shown previously that 15% of the AO regurgitation does not persist during consecutive examination days (Buhl et al. 2004). Acepromazine on the other hand generally decreased the incidence of valvular regurgitation. The different effects of the drugs on HR in the present study may be the indirect cause of the occurrence of valvular

regurgitation. This also explains the observation that the increase in regurgitation jets after detomidine and romifidine administration was more pronounced at the aortic and pulmonary valves. Regurgitation jets at the pulmonary and aortic valves were recorded during diastole. After the administration of detomidine and romifidine, the duration of the diastole is increased (Sarazan et al. 1989; Wagner et al. 1991). This may contribute to the increased occurrence of regurgitation jets. In contrast, increased HR after acepromazine administration may have diminished the existence of regurgitation jets at either site.

The order in which the echocardiographic measurements were recorded in the present study could have an influence on the results. The measurements recorded shortly after drug administration may be altered more than those recorded later. The regurgitation jets were obtained between 15 and 30 minutes after drug administration. By the end of this time, the HR after romifidine administration was no longer significantly decreased. A further study to investigate the coherence of the heart dimensions and valvular regurgitation according to time after drug administration would be interesting.

The results of this study indicate that acepromazine would be the most appropriate sedative to use, because the echocardiographic measurements were not affected. As we did not evaluate the behavioural signs of sedation, statements of the sedative effect of the three drugs cannot be made. However, the dose of acepromazine used was very low and probably inadequate for sedation (Muir et al. 1979; Ballard et al. 1982). Sedation with detomidine and romifidine resulted in significant changes in echocardiographic measurements. The changes were very small and in the light of considerable day-to-day variation in repeatability (Buhl et al. 2004), the clinical significance of the changes is probably minimal. However, sedation of horses for echocardiographic examination should be avoided if possible, and the potential effects of sedative drugs on the echocardiographic variables should always be considered when echocardiographic variables are interpreted in clinical cases.

References

Ballard S, Shults T, Kownacki AA et al. (1982) The pharmacokinetics, pharmacological responses and behavioral effects of acepromazine in the horse. J Vet Pharmacol Therap 5, 21–31.

Blissitt KJ, Bonagura JD (1995) Colour flow Doppler echocardiography in normal horses. Equine Vet J Suppl 19, 47–55.

Bonagura JD, Blissitt KJ (1995) Review article: echocardiography. Equine Vet J Suppl 19, 5–17.

Buhl R, Ersbøll AK, Eriksen L et al. (2004) Sources and magnitude of variation of echocardiographic measurements of normal standardbred horses. Vet Radiol Ultrasound 45, 505–512.

Clarke KW, Taylor PM (1986) Detomidine: a new sedative for horses. Equine Vet J 18, 366–370.

Clarke KW, England GCW, Goosens L (1991) Sedative and cardiovascular effects of romifidine, alone and in combination with butorphanol in the horse. J Vet Anaes 18, 25–29.

DeMaria AN, Neumann A, Schubart PJ et al. (1979) Systematic correlation of cardiac chamber size and ventricular performance determined with echocardiography and alteration in heart rate in normal persons. Am J Cardiol 43, 1–9.

England GCW, Clarke KW, Goosens L (1992) A comparison of the sedative effects of three α_2-adrenoceptor agonists (romifidine, detomidine and xylazine) in the horse. J Vet Pharmacol Therap 15, 194–201.

Hamm D, Turchi P, Jöchle W (1995) Sedative and analgesic effects of detomidine and romifidine in horses. Vet Rec 136, 324–327.

Hashem A, Keller H (1993) Disposition, bioavailability and clinical efficacy of orally administered acepromazine in the horse. J Vet Pharmacol Therap 16, 359–368.

Kannegieter NJ (1993) The use of romifidine as a sedative in the horse. Aust Equine Vet 11, 92–93.

Long KJ, Bonagura JD, Darke PGG (1992) Standardized imaging technique for guided M-mode and Doppler echocardiography in the horse. Equine Vet J 24, 226–235.

Marr CM, Reef VB (1995) Physiological valvular regurgitation in clinically normal young racehorses: prevalence and two-dimensional colour flow Doppler echocardiographic characteristics. Equine Vet J Suppl 19, 56–62.

Marroum PJ, Aeschbacher G, Curry SH (1994) Pharmacokinetics and pharmacodynamics of acepromazine in horses. Am J Vet Res 55, 1428–1433.

Muir WW, Skarda RT, Sheehan W (1979) Hemodynamic and respiratory effects of xylazine-acetylpromazine drug combination in horses. Am J Vet Res 40, 1518–1522.

Nakayama T, Wakayo Y, Takyguchi S et al. (1994) Prevalence of valvular regurgitation in normal beagle dogs detected by colour Doppler echocardiography. J Vet Med Sci 56, 973–975.

Parry BW, Anderson GA, Gay CC (1982) Hypotension in the horse induced by acepromazine malelate. Aust Vet J 59, 148–152.

Patteson MW, Gibbs CC, Wotton PR et al. (1995) Effects of sedation with detomidine hydrochloride on echocardiographic measurements of cardiac dimensions and

indices of cardiac functions in horses. Equine Vet J 19, 33–37.

Pedersen HD, Häggström J, Falk T et al. (1999) Auscultation in mild mitral regurgitation in dogs: observer variation, effects of physical maneuver and agreement with color Doppler echocardiography and phonocardiography. J Vet Intern Med 13, 56–64.

Pipers FS, Hamlin RL (1977) Echocardiography in the horse. J Am Vet Med Assoc 170, 815–819.

Sahn DJ, DeMaria A, Kisslo J et al. (1978) Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58, 1072–1083.

Sampson SN, Jacobson RL, Sande RD et al. (1999) Reproducibility and repeatability of M-mode echocardiographic measurements collected from 25 normal horses. J Equine Vet Sci 19, 51–57.

Sarazan RD, Starke WA, Krause GF et al. (1989) Cardiovascular effects of detomidine a new α_2-adrenoceptor agonist, in the conscious pony. J Vet Pharmacol Therap 12, 378–388.

Sinclair MD, O'Grady MR, Kerr CL et al. (2003) The echocardiographic effects of romifidine in dogs with and without prior or concurrent administration of glycopyrrolate. Vet Anaesth Analgesia 30, 211–219.

Steffey EP, Kelly AB, Farver TB et al. (1985) Cardiovascular and respiratory effects of acetylpromazine and xylazine on halothane anesthetized horses. J Vet Pharmacol Therap 8, 290–302.

Vuille C, Weyman AE (1994) Left ventricle I: general considerations, assessment of chamber size and function. In: Principles and Practice of Echocardiography (2nd edn). Vuille C, Weyman AE (eds). Williams & Wilkins, Philadelphia, PA, USA, pp. 575–611.

Wagner AE, Muir WW, Hinchcliff KW (1991) Cardiovascular effects of xylazine and detomidine in horses. Am J Vet Res 52, 651–657.

Willems TP, Steyerberg EW, van Herwerden LA et al. (1997) Reproducibility of colour Doppler flow quantification of aortic regurgitation. J Am Soc Echocardiography 10, 899–903.

Yoshida K, Yoshikawa J, Shakudo M et al. (1988) Colour Doppler evaluation of valvular regurgitation in normal subjects. Circulation 78, 840–847.