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Original Article

Pulsed wave Doppler echocardiographic assessment after sedation by intravenous injection of medetomidine and xylazine hydrochloride on cardiac output and systolic time intervals in one-humped camel calves (*Camelus dromedarious*)

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Abstract

Background: Pulsed wave (PW) Doppler echocardiography provides a convenient and noninvasive tool for measuring cardiac output (CO) alternations after the administration of sedative drugs, but this is not a usual method for camelids. **Aims:** The aim of the present study was to investigate the changes of the left and right ventricular outflow tracts (LVOT and RVOT), CO, and systolic time intervals following the intravenous (IV) injection of medetomidine (M) and xylazine (X) using PW Doppler echocardiography. **Methods:** Twenty apparently healthy immature male one-humped camels (*Camelus dromedarious*) were selected and divided into four groups (five animals per group). Medetomidine and X were injected to the left jugular vein at two different doses of 10 and 20 µg/kg, and 0.2 and 0.4 mg/kg, respectively. Effects on echocardiographic parameters were assessed at 4 intervals: before, 3, 60, and 120 min after drug administrations. **Results:** Velocity time integrity (VTI), maximum/mean flow velocity (Vmax and Vmean) and maximum/mean pressure gradient (PGmax and PGmean) decreased in aortic and pulmonic valves. Left ventricular ejection time (LVET) and LVET + pre ejection period (PEP) decreased and PEP and PEP/LVET increased in all groups except the low dose X group, 3 min after drug administration ($P<0.05$). The least values of VTI, velocity (V), PG and CO were observed after 60 min in the low dose X group ($P<0.05$). **Conclusion:** A relationship was found between the intensity and the duration of changes in cardiac parameters and both types and dosages of the injected drugs. We concluded that X and M have transient depressor effects on the ventricular outflow tract and CO of healthy camels.

Key words: *Camelus dromedarious*, Cardiac output, Echocardiography

Introduction

Echocardiography is an available and straightforward imaging tool for cardiac evaluation in small animals (Thomas *et al*., 1993), equines (Reef, 1990), and ruminants (Hallowell *et al*., 2007; Buczinski and Descôteaux, 2009); while it is rarely practiced for camelids. As a result, camelids' cardiac diseases are mostly detected at slaughterhouses or incidentally discovered at postmortem examinations (Fowler, 2010). During the last recent years, pulsed wave (PW) Doppler echocardiography has developed and become a routine facility for the evaluation of heart diseases in domestic animals (Leroux *et al*., 2012). Pulsed wave Doppler echocardiography allows an accurate quantitative assessment of intracardiac blood flow velocity to diagnose regurgitant flow through the cardiac valves and intracardiac shunts (Marr and Patteson, 2010). In addition, systolic time interval indices could be measured to interpret changes in ventricular performance (Koito and Spodick, 1989; Boon, 2011). Most ultrasound units have Doppler acquisition algorithms that allow the accurate detection of returning signals during a time interval specified by a sample depth, ignoring all other signals. Blood flow movement around the chosen specific area is analyzed. It then gives information about variables that cannot be assessed without Doppler imaging including direction, velocity, character and timing of the blood flow (Boon, 2011). Therefore, Noninvasive cardiac output (CO) evaluation completes the clinical assessment of hemodynamic status in animals (McConachie *et al*., 2013), as CO is the best available variable to estimate overall cardiovascular functions (Tibby and Murdoch, 2002).

Xylazine (X) has been used commonly for sedation and general anesthesia as an α_2-adrenoceptor agonist in many species including ruminants (England and Clarke, 1996). Of all domestic animals, ruminants are the most sensitive to X (kinjavdekar *et al*., 2000) and it is still considered the most commonly used premedication in camels (Al-Mubarak *et al*., 2008). Medetomidine (M) (4(5)-[1, 2, 3-dimethylphenylethyl]-imidazole) is a newer α_2-adrenoceptor agonist with a higher affinity to α_2-adrenergic receptors than xyalzine (Cruz *et al*., 1998).

This drug stimulates type-A α_2-adrenoceptors to inhibit norepinephrine release, acting on "locus coeruleus" (Scheinin and MacDonald, 1989). It also causes vasoconstriction and subsequently increases blood pressure by stimulating type-B α_2-adrenoceptors that are located on peripheral arterioles' smooth muscles (Pypendop and Verstegen, 1998; Dugdale, 2010).

Information regarding the echocardiographic changes following the intravenous (IV) injection of X and M is limited, and to date, there is no existing data on camels in this field. This study was designed for the preliminary investigation of the quantitative echocardiographic findings of left and right ventricular outflow tracts (LVOT and RVOT), as well as CO and systolic time intervals in one-humped camel calves (*Camelus dromedarious*) under different sedative doses of X and M.

Materials and Methods

Animals

Twenty immature one-humped male camels (6-8 months of age) weighing 140-160 kg were selected for the experiment. All camels were owned by the Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, andkept in a large pen, having free access to hay and water and supplemented with concentrate. All procedures have been approved by the University of Tehran Animal Use and Care Committee (No. IR7508054/6/24). Prior to the study, camels were checked for health using clinical and hematological evaluations. All trials were conducted in the morning and the ambient temperature was variable between 25-27°C. In order to verify heart health, all animals were checked by echocardiographic examination before the sedation, based on real time B-Mode and M-Mode echocardiography. Color flow and PW Doppler imaging were also taken to check probable pulmonic, mitral, tricuspid and aortic valves regurgitation or turbulent jets. Based on previously reported methods, the most accurate blood flow recordings are obtained when the ultrasound beam is placed as parallel as possible to the direction of blood flow (Boon, 2011).

Drugs

Medetomidine hydrochloride 1 mg/ml (Jurox, Australia, 10 µg/kg group ML, 20 µg/kg group MH) and X HCL %2 (Alfasan, Holland, 0.2 mg/kg group XL, 0.4 mg/kg group XH) were adjusted to 5 ml with 0.9% sodium chloride to comfort IV administration via the jugular catheter.

Animals were randomly devided into 4 groups of . Camels were restrained (by belt and rope) in a quiet sternal position on a soft and comfortable mattress. The skin sites for the attachment of electrocardiography (ECG) electrodes were prepared by shaving and applying ultrasonographic jelly.

Echocardiography protocol

Echocardiographic examinations were performed in each camel 4 times: before injection (base), 3 (T3), 60 (T60), and 120 (T120) min after drug injections. All echocardiographic examinations were performed in sternal recumbency. To attain better contact between the probe and the intercostal space, their thoracic limbs were moved cranially to the same side where the echocardiographic examination was performed. Transthoracic echocardiography was performed using a multi-frequency (1-5 MHz) phased-array transducer connected to a portable ultrasound unit (Micro Maxx, Sono Site, 2009). A maximum depth of 160 mm was set to gain images. During echocardiographic examinations, concurrent single lead electrocardiography was recorded using a bipolar base-apex lead method, integrated into the ultrasound unit. In this method, the right hand lead (negative electrode: red colour), the left hand lead (positive electrode: yellow colour), and the wither's lead (earth electrode: black colour) are attached by clips to the lower neck (on the jugular groove), the skin of the sixth intercostal space (behind the olecranon), and the withers, respectively. The ECG was set on the interval duration of 0.02 s and the amplitude of 0.05 mV. The speed of the paper movement was 2.5 cm/s where 1 cm was equal to 1 mV.

Image orientation was performed using intracardiac landmarks to set the transducer position in order to procure standardized planes and correct measurements according to the previously recommended methods in camelids and cattle (Braun and Schweizer, 2001; Hallowell *et al*., 2007; Zarifi *et al*., 2012; Tharwat *et al*., 2012). A high quality image and accurate measurements of optimum velocity were obtained by setting the sample volume cursor size on 5 mm and changing its angle to 60 degrees. This was repeated in all camels to decrease possible miscues (Fig. 1).

In the two dimensional right parasternal short axis (RPSSAx) view at the pulmonic valve level and the straight left parasternal long axis (LPSLAx) five chamber view at the aortic valve level, PW Doppler imaging was used for the accurate evaluation of velocity time integrity (VTI), maximum velocity (Vmax), mean velocity (Vmean), maximum pressure gradient (PGmax), and mean pressure gradient (PGmean). Furthermore, a PW Doppler echocardiogram from the LPSLAx view of the aortic valve was used to evaluate systolic time interval parameters (pre-ejection period (PEP), left ventricular ejection time (LVET), PEP+LVET (QAVC), and PEP/LVET ratio). Heart rate (HR) was calculated from ECG tracings using three consecutive cardiac cycles during the echocardiographic recordings. Finally, the stroke volume (SV) and CO were determined using the following standard formulae:

$$SV = 3.14 \times VTI \times (Ao/2)^2$$

$$CO = SV \times HR$$

Where, Ao: Cross-sectional aortic diameter (cm)

Sample volume size of PW line was obtained at 5 mm for valves.

The beginning of the QRS complex was defined as the time point of end-diastole, and the end of

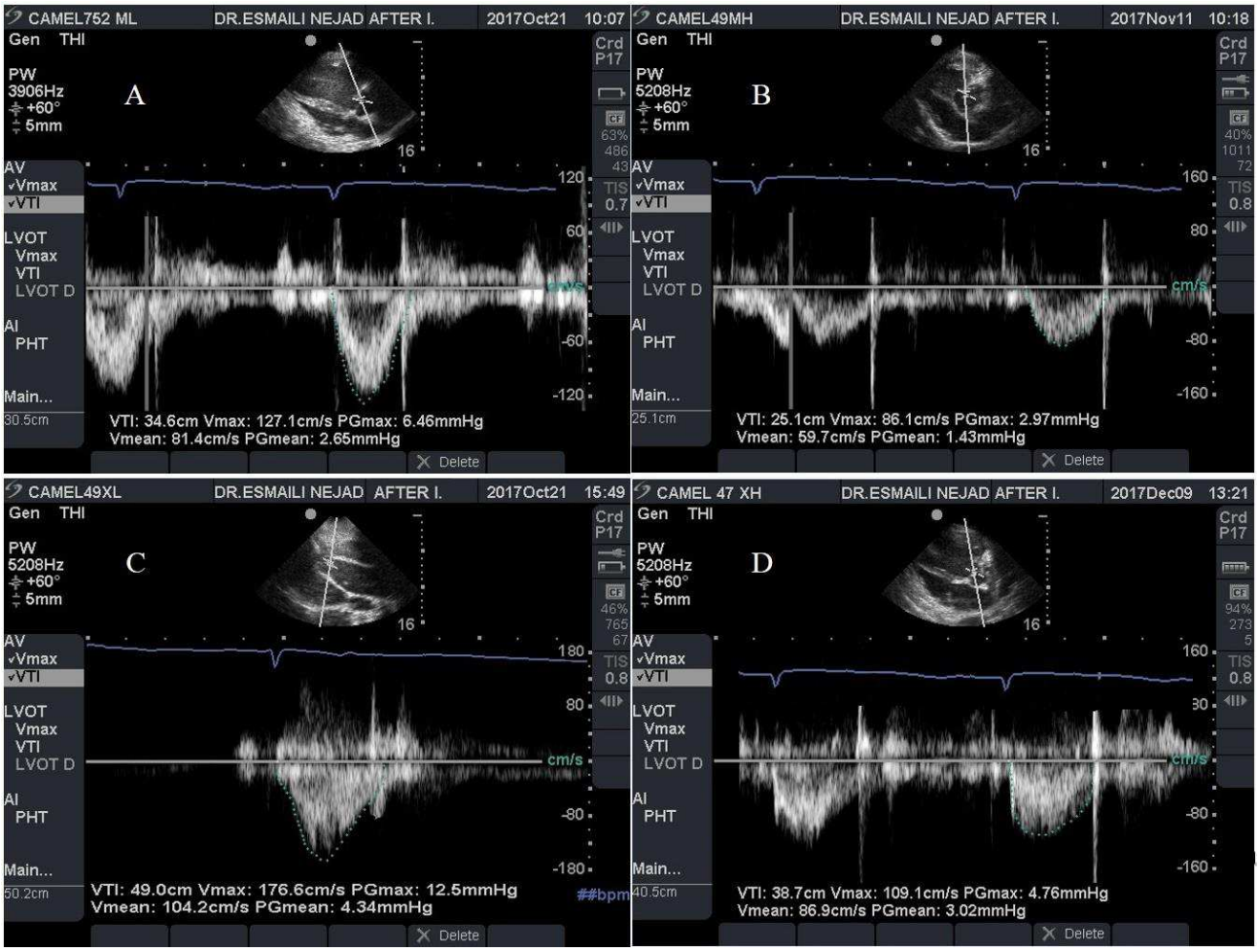

Fig. 1: Pulsed wave echocardiography of aortic valve 3 min after intravenous injection of medetomidine and xylazine in 4 groups (**A**: Low dose medetomidine, **B**: High dose medetomidine, **C**: Low dose xylazine, and **D**: High dose xylazine), multi-frequency (1-5 MHz) phased-array transducer, straight left parasternal long axis (LPSLAx) 5 chamber view at the level of aortic valve. PW: Pulsed wave, AV: Aortic valve, Vmax: Maximum flow velocity, Vmean: Mean flow velocity, VTI: Velocity time integrity, LVOT: Left ventricular outflow tract, PGmax: Maximum pressure gradient, and PGmean: Mean pressure gradient

the T-wave was set for end-systole for quantitative data measuring (Zarifi *et al*., 2012). Three cardiac cycles were measured and the mean value for each index was calculated. During examination time, images were recorded digitally, saved on a memory card and evaluated afterward.

Statistical analysis

Data analysis was carried out between groups and time points using SPSS-24 software (SPSS Inc., Chicago, USA). A repeated measures analysis of variance (ANOVA) followed by a Bonferroni's test were conducted for each group at 4 time points to detect within-group responses relative to a baseline or resting time points, and between-group differences in the responses. Before analysis, normality distribution was checked using the Kolmogorov-smirnov test, and all data sets were found to have normal distribution. Mean values and standard deviations for each variable at each time point were calculated to determine the main effect of dose and time. Differences at $P<0.05$ were considered significant.

Results

Tables 1 and 2 clarify cardiac valves' output changes from the base time (before injection) up to 120 min after the injection. In pulmonic and aortic valves, significant decreases in VTI, Vmax, Vmean, PGmax, and PGmean were noticeable 3 min after drug injection in ML, MH, and XH groups ($P<0.05$). In particular, Vmax in aortic and pulmonic valves statically decreased until 120 min, in the mentioned groups ($P<0.05$). In these groups, SV and HR parameters decreased significantly 3, 60, and 120 min after drug administration, leading to a significant decrease in CO ($P<0.05$). SV did not change statistically after 3 min in the XL group; however, similar to the other groups, the reduction of HR index ($P<0.05$) caused significant decreases in CO ($P<0.05$) (Table 3).

In addition, the PEP:LVET ratio and PEP index increment were associated with LVET and QAVC decrement 3 min after drug administrations in MH, ML and XH groups comparing to base time values ($P<0.05$). PEP:LVET ratio, PEP and LVET alterations were

Table 1: Mean±SD of PW Doppler echocardiographic parameters of aortic valve output, during 3, 60, and 120 min after administration of high (M: 20 µg/kg [MH] and X: 0.4 mg/kg [XH]) and low (M: 10 µg/kg [ML] and X: 0.2 mg/kg [XL]) doses of medetomidine and xylazine in 20 *Camelus dromedarious*

Indices	Groups															
	ML				MH				XL				XH			
	Base	3	60	120	base	3	60	120	base	3	60	120	base	3	60	120
AoVVTI (cm)	49.38 ±1.16^{a}	32.84 ±2.30^{bE}	37.76 ±2.14^{c}	40.68 ±1.12^{cE}	49.26 ±1.03^{a}	27.14 ±1.37^{bF}	38.2 ±2.40^{c}	40.8 ±4.16^{cE}	49.74 ±0.74^{a}	48.68 ±1.09^{aH}	35.12 ±1.79^{b}	48.84 ±1.28^{aH}	49.68 ±0.73^{a}	35.2 ±2.08^{bE}	39.34 ±3.75^{c}	43.7 ±4.65^{dE}
AoVVmax (cm/s)	173.14 ±2.70^{a}	124.86 ±4.70^{bE}	134.26 ±3.47^{cE}	153.98 ±3.97^{cE}	175 ±3.18^{a}	91.14 ±4.58^{bF}	108.64 ±2.78^{cF}	129.9 ±2.32^{dF}	174.5 ±3.06^{a}	170.38 ±2.70^{aH}	130.54 ±5.53^{bE}	170.3 ±4.13^{aH}	175 ±2.15^{a}	114.02 ±8.96^{bE}	132.26 ±11.28^{cE}	149.72 ±6.73^{dE}
AoVVmean (cm/s)	113.5 ±2.50^{a}	75.82 ±1.80^{bE}	84.76 ±2.85^{b}	97.84 ±2.56^{cE}	115.98 ±2.06^{a}	61.34 ±2.40^{bF}	74.54 ±2.62^{c}	83.88 ±3.52^{cF}	114.78 ±3.38^{a}	111.2 ±3.00^{aH}	73.52 ±2.14^{b}	108 ±8.13^{aE}	115.52 ±2.45^{a}	75.78 ±1.43^{bE}	88.96 ±14.58^{c}	100.4 ±5.67^{cE}
AoVPGmax (mmHg)	12.53 ±0.20^{a}	6.09 ±0.44^{bE}	6.60 ±0.23^{b}	9.97 ±0.25^{cE}	12.56 ±0.15^{a}	3.63 ±0.29^{bF}	4.80 ±0.16^{cF}	7.06 ±0.26^{dF}	12.41 ±0.09^{a}	12.03 ±0.12^{aH}	7.24 ±0.22^{bH}	11.7 ±0.88^{aH}	12.55 ±0.16^{a}	5.10 ±0.24^{bG}	6.66 ±0.30^{cE}	9.69 ±0.25^{dE}
AoVPGmean (mmHg)	5.47 ±0.13^{a}	2.4 ±0.16^{bE}	3.17 ±0.16^{c}	3.88 ±0.20^{dE}	5.55 ±0.07^{a}	2.21 ±0.07^{bE}	2.90 ±0.21^{c}	3.39 ±0.23^{dE}	5.50 ±0.09^{a}	5.23 ±0.22^{aH}	3.12 ±0.09^{b}	5.14 ±0.38^{aH}	5.39 ±0.21^{a}	2.40 ±0.07^{bE}	3.30 ±0.08^{c}	3.79 ±0.20^{dE}

PW: Pulsed wave, AoV: Aortic valve, VTI: Velocity time integral, Vmax: Maximum velocity, Vmean: Mean velocity, PGmax: Maximum pressure gradient, and PGmean: Mean pressure gradient. $^{a, b, c, d}$ Different letters indicate a significant difference between two study times within each group (P≤0.05), and $^{E, F, G, H}$ Different signs indicate a significant difference between two study groups within same time (P≤0.05). No letter indicates no significant difference. Data were expressed as mean±SD

Table 2: Mean±SD of PW Doppler echocardiographic of pulmonary valve output, during 3, 60, and 120 min after administration of high (M: 20 µg/kg [MH] and X: 0.4 mg/kg [XH]) and low (M: 10 µg/kg [ML] and X: 0.2 mg/kg [XL]) doses of medetomidine and xylazine in 20 *Camelus dromedarious*

Indices	Groups															
	ML				MH				XL				XH			
	base	3	60	120	base	3	60	120	base	3	60	120	base	3	60	120
PVVTI (cm)	25.78 ±0.69^{a}	17.56 ±0.32^{bE}	19.82 ±0.63^{cE}	22.40 ±0.73^{dE}	26.4 ±0.72^{a}	15.6 ±0.64^{bF}	20.04 ±0.90^{cE}	21.68 ±1.25^{dE}	25.74 ±0.51^{a}	25.4 ±0.54^{aH}	18.32 ±0.40^{bH}	25.26 ±0.35^{aH}	26.2 ±0.49^{a}	17.66 ±0.35^{bE}	20.06 ±0.47^{cE}	22.76 ±0.93^{dE}
PVV max (cm/s)	78.48 ±2.55^{a}	45.12 ±1.06^{b}	56.92 ±2.37^{c}	68.62 ±1.39^{d}	77.84 ±2.88^{a}	37.62 ±2.44^{b}	51.26 ±2.99^{c}	54.72 ±2.86^{c}	76.8 ±2.54^{a}	75.36 ±3.02^{a}	55.12 ±2.83^{b}	74.86 ±3.08^{a}	78.38 ±1.87^{a}	43.38 ±1.75^{b}	56.36 ±1.95^{c}	67.66 ±2.07^{d}
PVV mean (cm/s)	52.46 ±1.86^{a}	32.56 ±1.25^{bE}	38.3 ±1.18^{cE}	43.82 ±1.27^{dE}	50.04 ±2.51^{a}	26.02 ±1.88^{bF}	37 ±2.86^{cE}	40.5 ±1.89^{dE}	52.28 ±2.44^{a}	51.6 ±2.57^{aH}	32.98 ±1.69^{bH}	50.9 ±2.93^{aH}	50.04 ±2.09^{a}	32.84 ±0.91^{bE}	38.5 ±0.90^{cE}	43.86 ±1.95^{dE}
PVPGmax (mmHg)	2.59 ±0.08^{a}	1.28 ±0.04^{bE}	1.68 ±0.06^{cE}	2.19 ±0.12^{dE}	2.69 ±0.13^{a}	0.57 ±0.09^{bF}	1.18 ±0.17^{cF}	1.29 ±0.20^{cF}	2.63 ±0.07^{a}	2.60 ±0.07^{aH}	1.57 ±0.05^{bE}	2.58 ±0.04^{aH}	2.57 ±0.06^{a}	1.22 ±0.05^{bE}	1.66 ±0.09^{cE}	2.18 ±0.11^{dE}
PVPGmean (mmHg)	1.19 ±0.06^{a}	0.61 ±0.05^{bE}	0.7 ±0.06^{cE}	1.11 ±0.08^{dE}	1.11 ±0.06^{a}	0.26 ±0.04^{bF}	0.53 ±0.08^{cF}	0.61 ±0.07^{cF}	1.17 ±0.07^{a}	1.14 ±0.08^{aH}	0.63 ±0.05^{b}	1.13 ±0.09^{aE}	1.12 ±0.06^{a}	0.55 ±.032^{bE}	0.71 ±0.04^{cE}	1.01 ±0.07^{dE}

PW: Pulsed wave, PV: Pulmonary valve, VTI: Velocity time integral, Vmax: Maximum velocity, Vmean: Mean velocity, PGmax: Maximum pressure gradient, and PGmean: Mean pressure gradient. $^{a, b, c, d}$ Different letters indicate a significant difference between two study times within each group (P≤0.05), and $^{E, F, H}$ Different signs indicate a significant difference between two study groups within same time (P≤0.05). No letter indicates no significant difference. Data were expressed as mean±SD

Table 3: Mean±SD of PW Doppler echocardiographic of systolic time intervals parameters of aortic valve, HR, SV, and CO, during 3, 60, and 120 min after administration of high (M: 20 µg/kg [MH] and X: 0.4 mg/kg [XH]) and low (M: 10 µg/kg [ML] and X: 0.2 mg/kg [XL]) doses of medetomidine and xylazine in 20 *Camelus dromedarious*

Indices	Groups															
	ML				MH				XL				XH			
	base	3	60	120	base	3	60	120	base	3	60	120	base	3	60	120
PEP (s)	0.08 ±0.00^{a}	0.11 ±0.00^{bE}	0.10 ±0.00^{bE}	0.09 ±0.00^{cE}	0.08 ±0.00^{a}	0.11 ±0.00^{bF}	0.11 ±0.00^{cE}	0.10 ±0.00^{dF}	0.08 ±0.00^{a}	0.08 ±0.00^{aH}	0.1 ±0.00^{bH}	0.09 ±0.00^{bE}	0.08 ±0.00^{a}	0.1 ±0.00^{bE}	0.10 ±0.00^{bE}	0.1 ±0.00^{cE}
LVET (s)	0.36 ±0.00^{a}	0.28 ±0.01^{bE}	0.30 ±0.00^{c}	0.33 ±0.00^{dE}	0.36 ±0.00^{a}	0.25 ±0.01^{bF}	0.28 ±0.01^{c}	0.31 ±0.01^{dF}	0.35 ±0.00^{a}	0.34 ±0.00^{aH}	0.30 ±0.00^{b}	0.34 ±0.00^{aE}	0.36 ±0.00^{a}	0.29 ±0.00^{bE}	0.30 ±0.01^{c}	0.34 ±0.00^{dE}
QAVC (s)	0.44 ±0.00^{a}	0.39 ±0.01^{bE}	0.40 ±0.00^{b}	0.43 ±0.00^{a}	0.44 ±0.01^{a}	0.37 ±0.01^{bF}	0.39 ±0.01^{c}	0.42 ±0.01^{dF}	0.44 ±0.00^{a}	0.43 ±0.00^{aH}	0.40 ±0.00^{b}	0.44 ±0.01^{aH}	0.44 ±0.00^{a}	0.40 ±0.00^{bE}	0.42 ±0.01^{c}	0.44 ±0.00^{a}
PEP/LVET	0.23 ±0.01^{a}	0.38 ±0.01^{bE}	0.35 ±0.01^{cE}	0.29 ±0.01^{dE}	0.23 ±0.01^{a}	0.45 ±0.01^{bF}	0.39 ±0.02^{cF}	0.33 ±0.02^{dF}	0.24 ±0.01^{a}	0.24 ±0.01^{aH}	0.33 ±0.00^{bE}	0.26 ±0.01^{aE}	0.23 ±0.01^{a}	0.37 ±0.01^{bE}	0.34 ±0.02^{cE}	0.29 ±0.00^{dE}
HR (b/min)	59 ±2.91^{a}	38.4 ±1.14^{bE}	43.4 ±2.07^{cE}	50 ±1.58^{dE}	58.6 ±2.70^{a}	30 ±2.55^{bF}	36.6 ±2.07^{cF}	41.4 ±2.07^{dF}	58.2 ±2.86^{a}	45 ±1.58^{bH}	50.4 ±2.07^{cH}	58 ±2.82^{aH}	58 ±2.55^{a}	39.6 ±2.07^{bE}	44.4 ±1.94^{cE}	50.6 ±2.07^{dE}
SV (ml)	104.76 ±2.06^{a}	86.9 ±1.51^{bE}	94.04 ±1.93^{cE}	99.02 ±1.06^{dE}	103.16 ±1.87^{a}	74.78 ±2.43^{bF}	79.76 ±1.73^{cF}	91.46 ±2.46^{dF}	104.68 ±0.65^{a}	105.08 ±0.93^{aH}	99.98 ±1.35^{bH}	104.66 ±0.58^{aH}	103.58 ±1.35^{a}	88.14 ±2.47^{bE}	95.74 ±4.00^{cE}	99.48 ±2.92^{dE}
CO (L/min)	6.17 ±0.25^{a}	3.33 ±0.12^{bE}	4.08 ±0.19^{cE}	4.95 ±0.12^{dE}	6.04 ±0.20^{a}	2.24 ±0.17^{bF}	2.91 ±0.13^{cF}	3.78 ±0.17^{dF}	6.09 ±0.29^{a}	4.68 ±0.15^{bH}	5.03 ±0.19^{cH}	6.07 ±0.29^{aH}	6.00 ±0.22^{a}	3.48 ±0.16^{bE}	4.24 ±0.18^{cE}	5.03 ±0.26^{dE}

PW: Pulsed wave, PEP: Pre ejection period, LVET: Left ventricular ejection time, QAVC: Quiet automatic volume control, HR: Heart rate, SV: Stroke volume, and CO: Cardiac output. $^{a, b, c, d}$ Different letters indicate a significant difference between two study times within each group (P≤0.05), and $^{E, F, H}$ Different signs indicate a significant difference between two study groups within same time (P≤0.05). No letter indicates no significant difference. Data were expressed as mean±SD

persistent until 120 min in MH, ML and XH groups ($P<0.05$), but the reduction of QAVC was significant up to 120 min, only in the MH group ($P<0.05$) (Table 3). On the other hand, in the XL group, the increase of the PEP:LVET ratio and PEP index and the reduction of LVET and QAVC parameters were seen 60 min after the drug administration compared to the base time ($P<0.05$). At time 120 min, only PEP index remained lower than the base time in XL group ($P<0.05$).

Discussion

To our knowledge, this is the first study investigating echocardiographic parameters after the administration of α_2-adrenoceptor agonist drugs in camelids. Overall, the results of the current study demonstrated that IV injection of X or M at different sedative doses provides mild to moderate cardiovascular depression over 2 h with good to excellent recovery in all treatments. The intensity and duration of these effects were proved to be dose-dependent.

Following the IV administration of M and X, significant decreases in CO were observed in all test subjects. Changes in PW Doppler echocardiographic parameters in the XL group were significantly lower in intensity and shorter in duration than the other groups. Cardiac parameters returned to the normal state 120 min post injection in this group; however, the animals that received 20 µg/kg of M had significant changes in most echocardiographic factors, even up to 120 min post injection. Decrease in the HR index after the sedation with X and M is a typical effect of α_2-adrenoceptor agonist drugs due to sympathetic blockage and vagal stimulation (Maze and Tranquili, 1991; Wagner and Hinchcliff, 1991). It is interesting to note that, the decrease of HR index correlates with the decrease of norepinephrine release and subsequent binding of M to α_2-adrenoceptors (Sinclair, 2003).

In the present experiment, the mean HR remained steady at lower values in all groups during treatment and returned to the baseline in the XL group. As mentioned before, the significant reduction of SV and HR was noted 3 min after drug administrations in ML, MH and XH groups, leading to a significant decrease in CO. Although SV did not change after 3 min in the XL group, the reduction of the heart rate index caused significant decrease in CO in this group, similar to that of the ML, MH and XH groups. This means that even if contraction ability does not change, bradycardia may reduce CO.

In small animals, the best imaging method for quantitative measurement of aortic valve flow is obtained from the left apical long axis view (Boon, 2011). This imaging procedure offers the best possible alignment with the Doppler beam. Given that there is a thick fat pad in the ventral aspect of the thoracic cavity of camels (extending from the manubrium to the sternum), the above-mentioned imaging method is not executable in this species. Pressure gradient depends on transvalvular flow as well as the valve areas. For example, valvular stenosis and decrease in valve outflow have a direct relationship with transvalvular PG changes and consequently decrease CO (Otto *et al*., 1989). Decrease in LVOT and RVOT's PGmax as a result of the decline in transaortic and transpulmonary volume flow was noticeable after injecting both types of α_2-adrenoceptor agonist drugs in the present study.

In one study on equines, CO significantly decreased after the administration of M (4 µg/kg, IV), but significantly increased after the administration of X (0.4 mg/kg, IV) (Bueno *et al*., 1999). Nonetheless, in our study of camels, CO decreased in response to both drugs. Another study in equine medicine revealed that M injection decreased heart rate and cardiac index (CI) during the first 20 min. In addition, SV reduced for the first 5 min. (Bettschart-Wolfensberger *et al*., 1999). In 2005, Regula Bettschart-Wolfensberger confirmed that the maintenance of prolonged anesthesia with medetomidine-propofol was suitable for heavy horses in a variety operations, in order to provide adequate cardiovascular function and a high quality recovery without requiring sympathomimetic drugs (Bettschart-Wolfensberger *et al*., 2005). The cardiopulmonary changes in sheep were very similar to those in ponies after the administration of M, but they were not dose-related. The SV also decreased after the administration of the higher dose of M in both ponies and sheep (Bryant *et al*., 1996). In the literature, several studies have investigated the cardiovascular effects of the administration of M in dogs. Saponaro *et al*. in 2013 reported that although M or acepromazine alone provides similar and satisfactory levels of sedation and good recovery, M, in combination with acepromazine, produce a significant reduction of HR and CO compared with acepromazine alone (Saponaro *et al*., 2013).

As a heart-dependent index for the evaluation of cardiac function, the pre-ejection period is affected by heart loading alterations, in addition to the contraction capacity of myocardium (Borow, 1989). Myocardial contractility is known to be inversely correlated with PEP and PEP/LVET (Boon, 1996). In the present PW Doppler findings, the increase in PEP and PEP/LVET and decrease in LVET and QAVC were visible 3 min after the drug injection. This was statistically significant compared to the base time in MH, ML, and XH groups and remained significant until 120 min in all parameters except in QAVC. In echocardiographic studies, the lower the PEP and PEP/LVET indices, the better the cardiac systolic function and vice versa (Sousa *et al*., 2007). Therefore, it is likely that myocardial contractility was reduced in the present experiment.

In conclusion, the present study documented that IV injection of α_2-adrenoceptor agonist drugs produces a dose dependent and temporary effect in cardiac systolic time intervals, and this has a direct relationship with the decrease in cardiac valve outflow, SV (contraction ability), HR (bradycardia) and consequently CO. This result was consistent with the depression of both systolic and diastolic functions.

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Conflict of interest

The authors do not have any conflicts of interest to disclose.

References

Al-Mubarak, AI; Abdin-Bey, MR and Ramadan, RO (2008). Evaluation of xylazine/ketamine total intravenous anaesthesia (TIVA) in dromedary camels, a clinical retrospective study. J. Camel. Pract. Res., 15: 201-203.

Bettschart-Wolfensberger, R; Bettschart, RW; Vainiom, O; Marlin, D and Clarke, KW (1999). Cardiopulmonary effects of a two hour medetomidine infusion and its antagonism by atipamezole in horses and ponies. J. Vet. Anaesth., 26: 8-12.

Bettschart-Wolfensberger, R; Kalchofner, K; Neges, K; Kästner, S and Furst, A (2005). Total intravenous anaesthesia in horses using medetomidine and propofol. Vet. Anaesth. Analg., 32: 348-354.

Boon, JA (1996). *Manual of veterinary echocardiography*. 1st Edn., Philadelphia, USA, Williams and Wilkins. PP: 151-236.

Boon, JA (2011). *Veterinary echocardiography*. 2nd Edn., Chichester, UK, Wiley-Blackwell. PP: 106-116.

Borow, KM (1989). An integrated approach to the noninvasive assessment of left ventricular systolic and diastolic performance. In: *Textbook of adult and pediatric echocardiography and Doppler*. (1st Edn.), Cambridge, UK, Blackwell Scientific Publications. PP: 97-155.

Braun, U and Schweizer, T (2001). Determination of heart dimensions in cattle via 2-D mode echocardiography. Berl. Munch. Tierarztl. Wochenschr., 114: 46-50.

Bryant, CE; Clarke, KW and Thompson, J (1996). Cardiopulmonary effects of medetomidine in sheep and in ponies. Res. Vet. Sci., 60: 267-271.

Buczinski, S and Descôteaux, L (2009). *Echographie des bovins.* 1st Edn., Paris, France, Point Veterinaire. PP: 47-67.

Bueno, AC; Cornick-Seahorn, J; Seahorn, TL; Hosgood, G and Moore, RM (1999). Cardiopulmonary and sedative effects of intravenous administration of low doses of medetomidine and xylazine to adult horses. Am. J. Vet. Res., 60: 1371-1376.

Cruz, JI; Loste, M and Burzaco, OH (1998). Observations on the use of medetomidine/ketamine and its reversal with atipemazole for chemical restraint in the mouse. Lab. Anim., 32: 18-22.

Dugdale, A (2010). *Veterinary anaesthesia. Principle to practice*. 1st Edn., Oxford, UK, Wiley-Blackwell. PP: 39-45.

England, G and Clarke, KW (1996). Alpha 2 adrenoreceptor agonists in the horse. A review. Br. Vet. J., 152: 641-657.

Fowler, ME (2010). Cardiovascular system. In: *Medicine and surgery of camelids*. (3rd Edn.), Ames, IA, USA, Wiley-Blackwell. PP: 423-427.

Hallowell, G; Potter, TJ and Bowen, IM (2007). Methods and normal values for echocardiography in adult dairy cattle. J. Vet. Cardiol., 9: 91-98.

Kinjavdekar, P; Singh Amarpal, GR; Aithal, H and Pawde, AM (2000). Physiologic and biochemical effects of subarachnoidally administrated xylazine and medetomidine in goats. Small Rum. Res., 38: 217-228.

Koito, H and Spodick, D (1989). Optimal Doppler measurement of left ventricular ejection time. Am. J. Cardiol., 63: 257-259.

Leroux, AA; Farnir, F; Moonen, ML; Sandersen, CF; Deleuze, S and Amory, H (2012). Repeatability, variability and reference values of pulsed wave Doppler echocardiographic measurements in healthy Saanen goats. BMC Vet. Res., 8: 190-200.

Marr, CM and Patteson, MW (2010). Echocardiography. In: *Cardiology of the horse*. 2nd Edn., Philadelphia, USA, Elsevier. PP: 105-126.

Maze, M and Tranquili, W (1991). Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. Anesthesiology. 74: 581-605.

McConachie, E; Barton, MH; Rapoport, G and Giguere, S (2013). Doppler and volumetric echocardiographic methods for cardiac output measurement in standing adult horses. J. Vet. Intern. Med., 27: 324-330.

Otto, CM; Pearlman, AS and Gardner, CL (1989). Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J. Am. Coll. Cardiol., 13: 545-550.

Pypendop, BH and Verstegen, JP (1998). Hemodynamic effects of medetomidine in the dog: a dose titration study. Vet. Surg., 27: 612-622.

Reef, VB (1990). Echocardiographic examination in the horse: the basics. Compend. Contin. Educ. Pract. Vet., 12: 1312-1319.

Saponaro, V; Crovace, A; DeMarzo, L; Centonze, P and Staffieri, F (2013). Echocardiographic evaluation of the cardiovascular effects of medetomidine, acepromazine and their combination in healthy dogs. Res. Vet. Sci., 95: 687-692.

Scheinin, M and MacDonald, E (1989). An introduction to the pharmacology of A2-adrenoceptors in the central nervous system. Acta Vet. Scand., 85: 11-19.

Sinclair, MD (2003). A review of the physiological effects of A2-agonists related to the clinical use of medetomidine in small animal practice. Can. Vet. J., 44: 885-897.

Sousa, MG; Carareto, R; De-Nardi, AB; Brito, FL; Nunes, N and Camacho, AA (2007). Effects of isoflurane on Tei-index of myocardial performance in healthy dogs. Can. Vet. J., 48: 277-282.

Tharwat, M; Al-Sobayil, F; Ali, A and Buczinski, S (2012). Echocardiography of the normal camel (*Camelus dromedaries*) heart: technique and cardiac dimensions. BMC Vet. Res., 8: 130-138.

Thomas, W; Gaber, C; Jacobs, GJ; Kaplan, PM; Lombard, CW; Moise, NS and Moses, BL (1993). Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. J. Vet. Inter. Med., 7: 247-252.

Tibby, SM and Murdoch, IA (2002). Measurement of cardiac output and tissue perfusion. Curr. Opin. Pediatr., 14: 303-309.

Wanger, AE; Muir, WW and Hincheliff, KW (1991). Cardiovascular effects of xylazine and detomidine in horses. Am. J. Vet. Res., 52: 651-657.

Zarifi, M; Buczinski, S; Rezakhani, A; Dezfouli, MR and Khonsha, A (2012). Effect of lactation on functional and morphological echocardiographic variables in adult dairy cows. J. Vet. Cardiol., 14: 415-421.