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Echocardiographic assessment of intravenous administration of medetomidine and xylazine hydrochloride at different sedative doses in one-humped camel calves (*Camelus dromedarious*)

Mohammad Reza Esmailinejad[1], Majid Masoudifard[1]*, Omid Azari[2], Ehsanollah Sakhaee[2], Nima Ghalekhani[3]

[1] Department of Surgery and Radiology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran; [2] Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran; [3] HIV/STI Surveillance Research Center, WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran.

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Abstract

Echocardiography illustrates a convenient and noninvasive tool for measuring cardiac output (CO) changes after administration of sedative drugs, but it is unknown in camelids practice. The aim of present study was to investigate echocardiographic effects of intravenous (IV) injection of medetomidine and xylazine in camel calves. Twenty apparently healthy immature male one-humped camel calves (*Camelus dromedarious*) were divided into four groups (five animals in each treatment). Medetomidine and xylazine were injected into the left jugular vein at two different doses of 10.00 and 20.00 μg kg^{-1} and 0.20 and 0.40 mg kg^{-1}, respectively. Effects on some selected echocardiographic parameters were recorded at different intervals, before drug administrations (baseline) and after 3, 60 and 120 min. Data were analyzed by repeated measure, ANOVA test, then relevance and significance were taken as $p \leq 0.05$. Significant decrease in fractional shortening percentage (FS%), ejection fraction percentage (EF%), stroke volume (SV), heart rate (HR) and subsequent CO were noticeable 3 min after drug administration in medetomidine high dose (MH), medetomidine low dose (ML) and xylazine high dose (XH) groups ($p \leq 0.05$), furthermore at this time significant decrease in left ventricular mass (LVmass) and left ventricular systolic time intervals were seen in these groups, however, in xylazine low dose (XL) group, the lowest level of most echocardiographic parameters were detectable after 60 min. High dose IV injection of medetomidine was associated with significant decrease in most echocardiographic parameters without echocardiographic arrhythmia. Although, ML and XH groups had the same effects on echocardiographic indices but the intensity and duration were less than MH group.

Introduction

Since some camels are restless and they may bite, spit, kick or even rut, chemical sedation and sometimes general anesthesia is a necessity for restraining and handling and prior to some surgical procedures.

Xylazine (X), an α_2-adrenoceptor agonist has been used commonly for sedation and general anesthesia in many species including ruminants.[1] Of all domestic animals, ruminants are the most sensitive to xylazine[2] but it is considered the most common premedication used in camels.[3] Medetomidine (M) 4-(1-(2,3-Dimethylphenyl) ethyl)-1H-imidazoleis a new α_2-adrenoceptor agonist with a higher affinity for α_2-adrenergic receptor than xylazine.[4] This drug stimulates pre-synaptic type A α_2-adrenoceptors, thus inhibits norepinephrine to be released.[5] Therefore, sedation is induced by medetomidine acting its mechanism on 'locus coeruleus' which is the principal site for brain synthesis of norepinephrine. It also causes vasoconstriction and subsequence increases blood pressure by stimulation of post- and extra-synaptic type B α_2-adrenoceptors that are located on peripheral arterioles smooth muscle.[6,7] The α_2-adrenoceptor agonist drugs have synergistic effect in combination with other sedatives or tranquilizers, on the other hand, their effects are reversible by specific antagonists. They produce dose dependent

***Correspondence:**

Majid Masoudifard. DVM, DSVs
Department of Surgery and Radiology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
E-mail: mmfard@ut.ac.ir

hypnosis, sedation, analgesia and muscle relaxation,[8] as well as, allow smooth induction and recovery from anaesthesia.[1] Moreover, α_2-adrenoceptor agonist drugs intensely cause cardiovascular dysfunctions such as bradycardia and hypertension followed by hypotension, decreased myocardial contractility and perfusion and arrhythmia.[9,10] The duration and intensity of these effects depend on the type of α_2-adrenoceptor agonist that is used and also its dose and route of administration.[1]

Echocardiography as an available imaging tool for equine and small animals, is a non-invasive ancillary tool for the heart assessment to evaluate its morphologic changes, abnormal wall thickness, chamber size and valvular appearance and function.[11,12] It is also a straightforward method for cardiac assessment in ruminants such as bovine[13,14] while rarely is used practically for camelids, thus camelids' cardiac diseases are mostly detected at slaughterhouses or incidentally discovered at postmortem examinations.[15] Recently, ultrasound machines have validated programs assist to calculate cardiac indices consisting CO. Echocardiography would complement clinical assessment of hemodynamic state by controlling of CO in animals.[16] Actually CO is the best beneficial parameter to investigate cardiac function.[17] Accordingly, transthoracic echocardiography (TTE) may indicate an appropriate and noninvasive mechanism for evaluating CO in camels. Information on echocardiographic changes following IV injection of xylazine and medetomidine is limited and to date, no study was done on camels in this field. This study was designed for preliminary investigation of the echocardiographic findings in one-humped camel under different sedative doses of xylazine and medetomidine.

Materials and Methods

Animals. Twenty immature one-humped male camels (6 - 8 months of age) weighting 140 - 160 kg were selected for the study. All camels were owned by the Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman and were kept in a large pen, having free access to hay and water and also supplemented with concentrate. The study was approved by Animal Care and Use Committee in University of Tehran (No. IR7508054/6/24). Prior to the study, camels were checked to be healthy by clinical and hematological evaluations. All trials were conducted in the morning and the ambient temperature was variable between 25.00 - 27.00 ˚C.

Drugs. Animals were placed randomly into four groups of five animals. Medetomidine hydrochloride (10.00 μg kg^{-1} as group ML, 20.00 μg kg^{-1} as group MH; Jurox, New South Wales, Australia) and xylazine hydrochloride (0.20 mg kg^{-1} as group XL, 0.40 mg kg^{-1} as group XH; Alfasan, Woerden, Netherlands) were injected into left jugular vein.

Echocardiography protocol. In order to verify heart health, before the study, all of the animals were checked up by echocardiographic examination, based on the real time B-mode and M-mode echocardiography. Also color flow and pulsed wave doppler imaging were taken to check up probable pulmonic, mitral, tricuspid and aortic valves regurgitation or turbulent jets. Then the echocardiographic examinations were performed in four steps of before injection (T-base), 3 (T3), 60 (T60) and 120 (T120) min after drug injections. All echocardiographic examinations were done on the camels with sternal recumbency. In order to attain good contact between the transducer and intercostal space, the right fore limb was shift cranially to the same side. The procedure was done through the thoracic wall, using a multi-frequency phased-array transducer (1.00 – 5.00 MHz), connected to a portable ultrasound equipment (MicroMaxx; Sono Site, Washington, USA). Maximum depth of 160 mm was set to gain images. During echocardiographic examinations, concurrent single-lead electrocardiogram, base-apex method, which was integrated in the ultrasound machine was recorded. In order to procure standardized planes and correct measurements, echocardiographic procedure was executed using intracardiac guidelines to adjust the transducer place according to the previously published methods in camelids and cattle.[13,18-20] Right parasternal short axis plane (RPSSAx) M-mode echocardiography at papillary muscles level (mushroom appearance) was used to determine measurements of the right ventricular parietal wall thickness (RVPW), right ventricular internal diameter (RVID), interventricular septal thickness (IVS), left ventricular internal diameter (LVID) and left ventricular parietal wall thickness (LVPW) in both diastolic and systolic phases. A M-mode echocardiography from the right parasternal caudal short axis plane (RPSSAx) at mitral valve level (fish mouth appearance) was applied for measurement of the minimal distance between the anterior leaflet of mitral valve in early diastole (E point) and interventricular septum (abbreviated as EPSS) and the velocity of mitral valve closure (E-F slope), the line from E point to the partial closure of the mitral valve leaflet in mid diastole (F point).[19] Furthermore, M-mode echocardiography from the right parasternal short axis plane (RPSSAx) at the level of aortic valve (AoV) was used for evaluating systolic time intervals, pre ejection period (PEP), left ventricular ejection time (LVET), PEP+LVET (QAVC) and PEP/LVET indices. Also, at this plane, B-mode images were obtained to measure left atrium diameter (LA), aortic valve diameter (Ao) and the ratio of the left atrium diameter to the aortic diameter (LA/Ao). The calculated parameters and their particular method are listed in Table 1, including the fractional shortening of left ventricle (FS%), the left ventricular ejection fraction (EF%), left ventricular mass (LVmass), ejection rate (ER), mean circumferential fiber

shortening velocity (MeanVcf), the left ventricular volume in systole and diastole (LVVes and LVVed) were calculated based on Teichholz method, the stroke volume (SV) and finally cardiac output (CO).

Table 1. The cardiovascular parameters and their corresponding formula.

Parameters	Formula
CO	SV × HR
EF%	(LVVd – LVVs / LVVd) ×100
ER	LVVd – LVVs / LVVd × LVET
FS%	[(LVIDd-LVIDs) / LVIDd] ×100
LVmass	1.04 × (LVIDd + IVSd + LVPWd)^3-LVIDd^3 - 13.60
LVVed	7(LVIDd^3) / (2.40 + LVIDd)
LVVes	7(LVIDs^3) / (2.40 + LVIDs)
MeanVcf	(LVIDd - LVIDs)/(LVIDd × LVET)
QAVC	PEP + LVET
SV	LVVed - LVVes

CO: Cardiac output; EF%: Ejection fraction percentage; ER: Ejection rate; FS%: Fractional shortening percentage; LVmass: Left ventricular mass; LVVed: Left ventricle volume end diastole; LVVes: Left ventricle volume end systole; meanVcf: Mean circumferential fiber shortening velocity; QAVC: Pre ejection period (PEP) + Left ventricular ejection time (LVET); and SV: Stroke volume.

Beginning of the QRS complex was determined as the time point of end-diastole and the end of the T-wave was set for end-systole for quantitative data measuring. Also for all M-mode indices, the leading-edge technique and for B-mode indices, the inner-edge technique were used for measurements.[19] Three cardiac cycles were measured and the mean value for each index was gained. During examination time, images were saved on a memory card and evaluated afterward.

Statistical analysis. Data analysis were performed using SPSS Software program (version 24.0; IBM Corp, Armonk, USA). A repeated measure analysis of variance (ANOVA) followed by the Bonferroni test was used within and among groups to compare parametric data. Mean values and standard error for each assessed variable at each time point were calculated to determine the main effect of dose and time. Differences between means at $p \leq 0.05$ were considered significant.

Results

Table 2 indicates parameters that were derived from M-mode planes and Table 3 shows significant difference among groups in calculated parameters, as well as, LA, Ao, LA/Ao and HR indices. Significant change in left ventricular dimensions (gain of LVID and reduce of LVPW and IVS) and consequently change in LVVed, LVVes, LV Mass, FS%, EF% and SV were detected for the first time 3 min after drug injection in ML, MH and XH groups and after 60 min in XL group ($p \leq 0.05$).

Changes in these parameters were meaningful even until 120 min after injection in MH group ($p \leq 0.05$). Significant decreases were observed in SV and HR parameters 3 min after drug administrations in ML, MH and XH groups that led to significant decrease in CO ($p \leq 0.05$). Although SV was not changed 3 min after 0.20 mg kg^{-1} xylazine (XL group), but reduction of HR index caused significant decrease in CO in this group as well ($p \leq 0.05$). Similar to other parameters, increase in EPSS distance and decrease in E-F slope were significant compared to T-base after 3 min in ML, MH and XH groups ($p \leq 0.05$) (Fig. 1). Decrease in E-F slope was meaningful until 120 min in these groups ($p \leq 0.05$) but only in MH group, EPSS was statistically significant until 120 min ($p \leq 0.05$). In addition to all of the above mentioned parameters, changes in systolic time intervals, especially increase in PEP/LVET and decrease in LVET and QAVC indices were seen 3 min after drug administration in MH, ML and XH groups that was significant compared to T-base ($p \leq 0.05$) and remained significant until 120 min ($p \leq 0.05$).

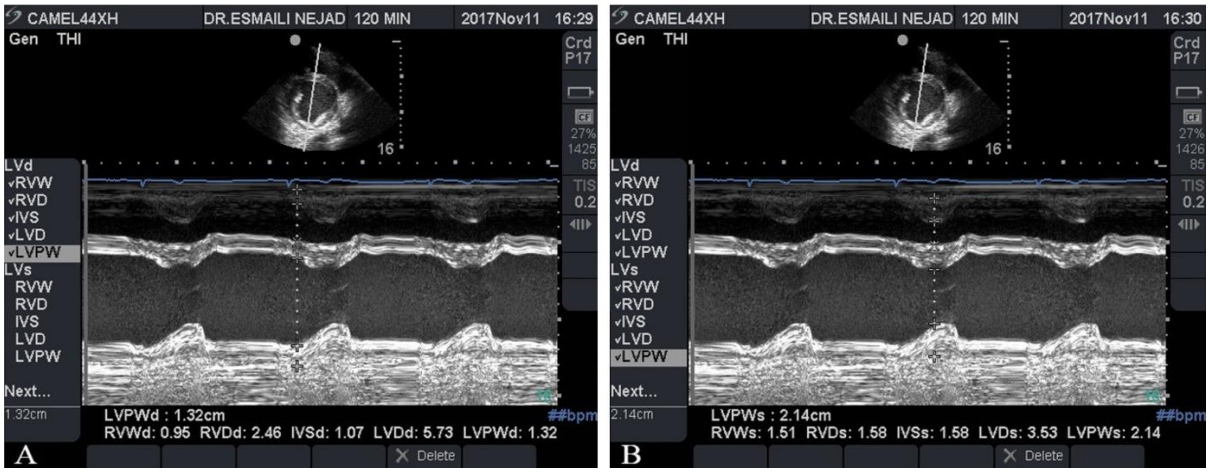

Fig. 1. M-mode echocardiography of *Camelus dromedarious*. Right parasternal short axis (RPSSAx) view at the level of mushroom appearance. Multi-frequency (1.00 - 5.00 MHz) phased-array transducer. Left and right ventricular studies (A: diastolic and B: systolic phases), after 120 min of intravenous injection of xylazine (0.40 mg kg^{-1}).

Table 2. Mean ± SE of M-mode echocardiographic parameters during, 3, 60 and 120 min after administering two different doses of medetomidine and xylazine.

Indices		ML				MH				XL				XH			
		T-base	3	60	120	T-base	3	60	120	T-base	3	60	120	T-base	3	60	120
Diastole	RVPW (cm)	1.03 ± 0.02^{a}	0.92 ± 0.03^{b*}	0.96 ± 0.02^{c}	1.01 ± 0.02^{a}	1.01 ± 0.02^{a}	0.83 ± 0.03^{b*}	0.94 ± 0.02^{c}	0.96 ± 0.02^{c}	1.04 ± 0.02^{a}	1.03 ± 0.03^{a§}	0.93 ± 0.02^{b}	1.04 ± 0.02^{a}	1.03 ± 0.02^{a}	0.83 ± 0.03^{b*}	0.92 ± 0.02^{c}	0.99 ± 0.02^{d}
	RVID (cm)	1.74 ± 0.03^{a}	2.11 ± 0.02^{b*}	1.87 ± 0.02^{c*}	1.87 ± 0.03^{d*}	1.77 ± 0.03^{a}	2.91 ± 0.02^{b§}	2.46 ± 0.02^{c§}	2.28 ± 0.03^{d§}	1.72 ± 0.03^{a}	1.76 ± 0.02$^{a¥}$	2.01 ± 0.02$^{b¥}$	1.75 ± 0.03$^{a¥}$	1.87 ± 0.03^{a}	2.16 ± 0.02^{b*}	1.97 ± 0.02$^{c¥}$	1.89 ± 0.03^{a*}
	IVS (cm)	1.33 ± 0.00^{a}	1.22 ± 0.012^{b*}	1.25 ± 0.01^{b*}	1.29 ± 0.014^{a*}	1.36 ± 0.00^{a}	0.99 ± 0.01^{b§}	1.12 ± 0.01$^{c€}$	1.23 ± 0.01^{d*}	1.33 ± 0.00^{a}	1.31 ± 0.01$^{a¥}$	1.22 ± 0.01^{b*}	1.31 ± 0.01$^{a¥}$	1.34 ± 0.00^{a}	1.07 ± 0.01$^{b€}$	1.13 ± 0.01$^{c€}$	1.22 ± 0.01^{d*}
	LVID (cm)	5.61 ± 0.02^{a}	5.98 ± 0.01^{b§}	5.84 ± 0.01$^{c¥}$	5.77 ± 0.01^{d*}	5.55 ± 0.02^{a}	6.18 ± 0.01^{b*}	5.90 ± 0.01^{c*}	5.74 ± 0.01^{d*}	5.63 ± 0.02^{a}	5.65 ± 0.01$^{a¥}$	5.85 ± 0.01$^{b¥}$	5.64 ± 0.01$^{a¥}$	5.58 ± 0.02^{a}	5.96 ± 0.01^{b§}	5.83 ± 0.01$^{c¥}$	5.75 ± 0.01^{d*}
	LVPW (cm)	1.27 ± 0.01^{a}	0.99 ± 0.03^{b*}	1.10 ± 0.02^{c*}	1.20 ± 0.02^{d}	1.29 ± 0.01^{a}	0.92 ± 0.03^{b*}	1.08 ± 0.02^{c}	1.18 ± 0.02^{d}	1.27 ± 0.01^{a}	1.25 ± 0.03$^{a¥}$	1.00 ± 0.02$^{b¥}$	1.25 ± 0.02^{a}	1.29 ± 0.01^{a}	1.01 ± 0.03^{b*}	1.09 ± 0.02^{c}	1.16 ± 0.02^{d}
Systole	RVPW (cm)	1.72 ± 0.02^{a}	1.60 ± 0.01^{b*}	1.65 ± 0.19^{c}	1.70 ± 0.21^{d}	1.71 ± 0.02^{a}	1.54 ± 0.01^{b*}	1.62 ± 0.01^{c}	1.64 ± 0.02^{d}	1.70 ± 0.02^{a}	1.68 ± 0.01$^{b¥}$	1.59 ± 0.01^{c}	1.68 ± 0.02^{b}	1.68 ± 0.02^{a}	1.56 ± 0.01^{b*}	1.61 ± 0.01^{c}	1.65 ± 0.02^{d}
	RVID (cm)	1.29 ± 0.01^{a}	1.99 ± 0.01^{b*}	1.57 ± 0.01^{c*}	1.34 ± 0.01^{a*}	1.30 ± 0.01^{a}	2.26 ± 0.01^{b§}	1.77 ± 0.01^{c§}	1.73 ± 0.01^{d§}	1.30 ± 0.01^{a}	1.32 ± 0.01$^{a¥}$	1.83 ± 0.01$^{b¥}$	1.31 ± 0.01^{a*}	1.31 ± 0.01^{a}	2.07 ± 0.01$^{b€}$	1.72 ± 0.01$^{c€}$	1.43 ± 0.01$^{d€}$
	IVS (cm)	2.26 ± 0.01^{a}	1.87 ± 0.01^{b*}	2.02 ± 0.02^{c*}	2.17 ± 0.01^{d}	2.22 ± 0.01^{a}	1.83 ± 0.01^{b*}	1.90 ± 0.02^{b§}	2.01 ± 0.01^{c}	2.27 ± 0.01^{a}	2.26 ± 0.01$^{a¥}$	2.01 ± 0.02^{b*}	2.25 ± 0.01^{a}	2.27 ± 0.01^{a}	1.59 ± 0.01^{b§}	1.85 ± 0.02^{c§}	2.11 ± 0.01^{d}
	LVID (cm)	3.46 ± 0.03^{a}	4.48 ± 0.02^{b*}	4.13 ± 0.02^{c*}	3.90 ± 0.02^{d*}	3.40 ± 0.03^{a}	5.00 ± 0.02^{b§}	4.53 ± 0.02^{c§}	3.92 ± 0.02^{d*}	3.51 ± 0.03^{a}	3.53 ± 0.02$^{a¥}$	4.00 ± 0.02$^{b¥}$	3.53 ± 0.029$^{a¥}$	3.44 ± 0.03^{a}	4.44 ± 0.02^{b*}	4.07 ± 0.02^{c*}	3.85 ± 0.02^{d*}
	LVPW (cm)	1.97 ± 0.02^{a}	1.60 ± 0.01^{b*}	1.81 ± 0.01^{c*}	1.93 ± 0.01^{a*}	2.01 ± 0.02^{a}	1.48 ± 0.01^{b§}	1.58 ± 0.01^{c§}	1.74 ± 0.01^{d§}	1.98 ± 0.02^{a}	1.96 ± 0.01$^{a¥}$	1.70 ± 0.01$^{b¥}$	1.96 ± 0.01$^{a¥}$	2.03 ± 0.02^{a}	1.63 ± 0.01^{b*}	1.75 ± 0.01^{c*}	1.90 ± 0.01^{d*}
EPSS (cm)		0.96 ± 0.02^{a}	1.18 ± 0.02^{b*}	1.09 ± 0.02^{c}	1.02 ± 0.03^{a*}	0.94 ± 0.02^{a}	1.22 ± 0.02^{b*}	1.13 ± 0.02^{c}	1.11 ± 0.03^{c*}	0.94 ± 0.02^{a}	0.94 ± 0.02$^{a¥}$	1.08 ± 0.02^{b}	0.94 ± 0.03$^{a¥}$	0.88 ± 0.02^{a}	1.14 ± 0.02^{b*}	1.04 ± 0.02^{c}	0.94 ± 0.03$^{a¥}$
E-F Slope (cm sec^{-1})		19.68 ± 0.31^{a}	15.38 ± 0.18^{b*}	16.82 ± 0.14^{c*}	18.22 ± 0.18^{d*}	19.72 ± 0.31^{a}	13.54 ± 0.18^{b§}	14.66 ± 0.14^{c§}	15.94 ± 0.18^{d§}	19.7 ± 0.31^{a}	19.44 ± 0.18$^{a¥}$	17.26 ± 0.14^{b*}	19.58 ± 0.18$^{a¥}$	19.62 ± 0.31^{a}	15.62 ± 0.18^{b*}	16.36 ± 0.14^{c*}	17.22 ± 0.18$^{d€}$
PEP (sec)		0.08 ± 0.00	0.11 ± 0.00*	0.10 ± 0.00	0.09 ± 0.00	0.08 ± 0.00	0.11 ± 0.00*	0.10 ± 0.00	0.10 ± 0.00	0.08 ± 0.00	0.08 ± 0.00¥	0.10 ± 0.00	0.09 ± 0.00	0.09 ± 0.00	0.11 ± 0.00*	0.10 ± 0.00	0.1 ± 0.00
LVET (sec)		0.34 ± 0.00^{a}	0.28 ± 0.00^{b*}	0.30 ± 0.00^{c}	0.32 ± 0.00^{d}	0.35 ± 0.00^{a}	0.26 ± 0.00^{b§}	0.28 ± 0.00^{c§}	0.31 ± 0.00^{d§}	0.35 ± 0.00^{a}	0.33 ± 0.00$^{a¥}$	0.30 ± 0.00^{b}	0.34 ± 0.00$^{a¥}$	0.35 ± 0.00^{a}	0.29 ± 0.00^{b*}	0.30 ± 0.00^{b*}	0.33 ± 0.00$^{c¥}$
QAVC (sec)		0.43 ± 0.00^{a}	0.39 ± 0.00^{b*}	0.40 ± 0.00^{b}	0.42 ± 0.00^{c}	0.43 ± 0.00^{a}	0.37 ± 0.00^{b*}	0.39 ± 0.00^{c}	0.41 ± 0.00^{d§}	0.43 ± 0.00^{a}	0.42 ± 0.00$^{b¥}$	0.40 ± 0.00^{a}	0.43 ± 0.00$^{a¥}$	0.44 ± 0.00^{a}	0.39 ± 0.00^{b*}	0.41 ± 0.00^{b}	0.43 ± 0.00^{c}
PEP/LVET		0.24 ± 0.00^{a}	0.38 ± 0.00^{b*}	0.34 ± 0.00^{c*}	0.29 ± 0.00^{d}	0.24 ± 0.00^{a}	0.44 ± 0.00^{b§}	0.38 ± 0.00^{c§}	0.32 ± 0.00^{d§}	0.24 ± 0.00^{a}	0.24 ± 0.00$^{a¥}$	0.34 ± 0.00^{c*}	0.27 ± 0.00$^{d¥}$	0.25 ± 0.00^{a}	0.37 ± 0.00^{b*}	0.34 ± 0.00^{b*}	0.29 ± 0.00^{c}

ML: Medetomidine low dose, MH: Medetomidine high dose, XL: Xylazine low dose, and XH: Xylazine high dose.

RVPW: Right ventricular parietal wall; RVID: Right ventricular internal dimension; IVS: Interventricular septum; LVID-d: Left ventricular internal dimension; LVPW: Left ventricular parietal wall; EPPS: E-point to septal separation; E-F slope: The line from E point to F point of mitral valve; PEP: Pre ejection period; LVET: Left ventricular ejection time; QAVC: PEP+LVET. PEP/LVET: pre ejection period / Left ventricular ejection time.

^{abcd} Different letters indicate a significant difference between two study times within each group ($p \leq 0.05$).

$^{*§€¥}$ Different symbols indicate a significant difference between two study groups within the same time ($p \leq 0.05$).

Table 3. Mean ± SE of calculated parameters during, 3, 60 and 120 min after administering two different doses of medetomidine and xylazine.

Indices	ML				MH				XL				XH			
	T-base	3	60	120	T-base	3	60	120	T-base	3	60	120	T-base	3	60	120
LVVed (mL)	154.56 ± 1.56^{a}	178.80 ± 1.35^{b*}	169.78 ± 0.87^{c*}	165.12 ± 0.88^{d*}	150.72 ± 1.56^{a}	193.20 ± 1.35^{b§}	173.80 ± 0.87^{c§}	158.32 ± 0.88^{d§}	155.86 ± 1.56^{a}	157.02 ± 1.35$^{a¥}$	170.02 ± 0.87^{b*}	156.60 ± 0.88^{a§}	152.58 ± 1.56^{a}	177.82 ± 1.35^{b*}	168.96 ± 0.87^{c*}	163.28 ± 0.88^{d*}
LVVes (mL)	49.80 ± 1.26^{a}	91.90 ± 1.01^{b*}	75.72 ± 1.23^{c*}	66.10 ± 1.11^{d*}	47.58 ± 1.26^{a}	118.42 ± 1.01^{b§}	94.04 ± 1.23^{c§}	66.84 ± 1.11^{d*}	51.20 ± 1.26^{a}	51.94 ± 1.01$^{a¥}$	70.04 ± 1.23^{b*}	51.94 ± 1.11$^{a¥}$	49.02 ± 1.26^{a}	89.68 ± 1.01^{b*}	73.20 ± 1.23^{c*}	64.00 ± 1.11^{d*}
LVmass (g)	385.04 ± 3.62^{a}	344.44 ± 5.47^{b*}	357.76 ± 3.48^{b*}	377.1 ± 4.60^{a*}	390.34 ± 3.62^{a}	304.22 ± 5.47^{b§}	333.40 ± 3.48^{c§}	354.56 ± 4.60^{d§}	389.04 ± 3.62^{a}	383.88 ± 5.47$^{a¥}$	335.42 ± 3.48^{b§}	383.22 ± 4.60^{a*}	389.76 ± 3.62^{a}	316.94 ± 5.47^{b§}	339.58 ± 3.48^{c§}	363.42 ± 4.60^{d§}
FS (%)	38.80 ± 0.40^{a}	25.60 ± 0.23^{b*}	29.60 ± 0.45^{c*}	32.80 ± 0.66^{d*}	39.00 ± 0.40^{a}	19.60 ± 0.23^{b§}	23.60 ± 0.45^{c§}	31.00 ± 0.66^{d*}	38.20 ± 0.40^{a}	37.40 ± 0.23$^{a¥}$	31.40 ± 0.45^{b*}	37.40 ± 0.66$^{a¥}$	38.60 ± 0.40^{a}	26.20 ± 0.23^{b*}	30.40 ± 0.45^{c*}	34.60 ± 0.66$^{d¥}$
EF (%)	68.60 ± 0.50^{a}	48.60 ± 0.38^{b*}	55.60 ± 0.67^{c*}	60.60 ± 0.55^{d*}	69.00 ± 0.50^{a}	38.80 ± 0.38^{b§}	46.00 ± 0.67^{c§}	57.80 ± 0.55^{d§}	68.00 ± 0.50^{a}	67.00 ± 0.38$^{a¥}$	58.40 ± 0.67^{b*}	66.60 ± 0.55$^{a¥}$	68.20 ± 0.50^{a}	50.00 ± 0.38^{b*}	57.00 ± 0.67^{c*}	61.40 ± 0.55^{d*}
SV (mL)	104.76 ± 0.70^{a}	86.90 ± 0.87^{b*}	94.04 ± 1.07^{c*}	99.02 ± 0.89^{d*}	103.16 ± 0.70^{a}	74.78 ± 0.87^{b§}	79.76 ± 1.07^{c§}	91.46 ± 0.89^{d§}	104.68 ± 0.70^{a}	105.08 ± 0.87$^{a¥}$	99.98 ± 1.07$^{b¥}$	104.66 ± 0.89$^{a¥}$	103.58 ± 0.70^{a}	88.14 ± 0.87^{b*}	95.74 ± 1.07^{c*}	99.48 ± 0.89^{d*}
HR (bpm)	59.00 ± 1.23^{a}	38.40 ± 0.85^{b*}	43.40 ± 0.91^{c*}	50.00 ± 0.97^{d*}	58.60 ± 1.23^{a}	30.00 ± 0.85^{b§}	36.60 ± 0.91^{c§}	41.40 ± 0.97^{d§}	58.20 ± 1.23^{a}	45.00 ± 0.85$^{b¥}$	50.40 ± 0.91$^{c¥}$	58.00 ± 0.97$^{a¥}$	58.00 ± 1.23^{a}	39.6 ± 0.85^{b*}	44.40 ± 0.91^{c*}	50.60 ± 0.97^{d*}
CO (L min^{-1})	6.17 ± 0.11^{a}	3.33 ± 0.07^{b*}	4.08 ± 0.08^{c*}	4.95 ± 0.10^{d*}	6.04 ± 0.11^{a}	2.24 ± 0.07^{b§}	2.91 ± 0.08^{c§}	3.78 ± 0.10^{d§}	6.09 ± 0.11^{a}	4.68 ± 0.07$^{b¥}$	5.03 ± 0.08$^{c¥}$	6.07 ± 0.10$^{a¥}$	6.00 ± 0.11^{a}	3.48 ± 0.07^{b*}	4.24 ± 0.08^{c*}	5.03 ± 0.10^{d*}
ER	1.94 ± 0.02^{a}	1.71 ± 0.02^{b*}	1.82 ± 0.02^{c*}	1.84 ± 0.03^{c*}	1.93 ± 0.02^{a}	1.45 ± 0.02^{b§}	1.60 ± 0.02^{c§}	1.82 ± 0.03^{d*}	1.91 ± 0.02	1.98 ± 0.02$^{¥}$	1.94 ± 0.02$^{¥}$	1.94 ± 0.03$^{¥}$	1.89 ± 0.02^{a}	1.67 ± 0.02^{b*}	1.78 ± 0.02^{c*}	1.77 ± 0.03^{c*}
MeanVcf (circ sec^{-1})	1.09 ± 0.01^{a}	0.88 ± 0.02^{b*}	0.96 ± 0.02^{c*}	0.98 ± 0.02^{c*}	1.10 ± 0.01^{a}	0.74 ± 0.02^{b§}	0.82 ± 0.02^{c§}	0.98 ± 0.02^{d*}	1.07 ± 0.01	1.11 ± 0.02$^{a¥}$	1.04 ± 0.02^{b*}	1.09 ± 0.02$^{¥}$	1.07 ± 0.01^{a}	0.87 ± 0.02^{b*}	0.98 ± 0.02^{c*}	0.99 ± 0.02^{c*}
LA (cm)	4.92 ± 0.02^{a}	5.17 ± 0.02^{b*}	5.01 ± 0.02^{c*}	4.95 ± 0.02^{d}	4.89 ± 0.02^{a}	5.24 ± 0.02^{b*}	5.17 ± 0.02^{c§}	5.01 ± 0.02^{d}	4.90 ± 0.02^{a}	4.90 ± 0.02$^{a¥}$	5.01 ± 0.02^{b*}	4.91 ± 0.02$^{a¥}$	4.98 ± 0.02^{a}	5.15 ± 0.02^{b*}	5.01 ± 0.02^{c*}	5.03 ± 0.02^{d*}
Ao (cm)	4.23 ± 0.02	4.31 ± 0.02*	4.30 ± 0.03*	4.25 ± 0.02	4.17 ± 0.02^{a}	4.48 ± 0.02^{b§}	4.45 ± 0.03^{b§}	4.26 ± 0.02^{c}	4.20 ± 0.02	4.24 ± 0.02*	4.25 ± 0.03*	4.20 ± 0.02	4.21 ± 0.02^{a}	4.34 ± 0.02^{b*}	4.35 ± 0.03^{b*}	4.27 ± 0.02^{a}
LA/Ao	1.16 ± 0.00	1.17 ± 0.00	1.16 ± 0.00	1.16 ± 0.00	1.17 ± 0.00	1.17 ± 0.00	1.16 ± 0.00	1.17 ± 0.00	1.16 ± 0.00	1.16 ± 0.00	1.17 ± 0.00	1.16 ± 0.00	1.18 ± 0.00	1.18 ± 0.00	1.17 ± 0.00	1.17 ± 0.00

ML: Medetomidine low dose, MH: Medetomidine high dose, XL: Xylazine low dose, and XH: Xylazine high dose.

LVVed: Left ventricle volume end diastole; LVVes: Left ventricle volume end systole; LVmass: Left ventricular mass; FS%: Fractional shortening percentage; EF%: Ejection fraction percentage; SV: Stroke volume; HR: Heart rate; CO: Cardiac output; ER: Ejection rate; meanVcf: Mean circumferential fiber shortening (circ) velocity; LA: Left atrium diameter; Ao: Aortic valve diameter.

^{abcd} Different letters indicate a significant difference between two study times within each group ($p \leq 0.05$).

$^{*§¥}$ Different signs indicate a significant difference between two study groups within same time ($p \leq 0.05$).

Discussion

Overall, in the present study it was demonstrated that IV injections of xylazine and medetomidine at different sedative doses provided sedation with mild to moderate cardiovascular depression within two hours and were followed by good to excellent recovery in all treatments. Significant decrease of CO was observed in all test subjects, following IV administration of medetomidine and xylazine. Changes in echocardiographic parameters in group XL were significantly lower in intensity and shorter in duration than other groups. Actually, cardiac parameters were returned to normal state after 120 min of injection in this group, however, animals that received 20.00 μg kg^{-1} medetomidine, became deeply sedated and changes in most echocardiographic factors such as LVmass, FS%, EF% and SV were significant even until 120 min after injection ($p \leq 0.05$).

In one study, IV injection of combined tramadol-xylazine following premedication with 0.20 mg kg^{-1} xylazine was effective and safe for soft tissue surgery in camels.[21] Decrease in HR index subsequent to the sedation with xylazine and medetomidine is a typical effect of α_2-adrenoceptor agonist drugs due to sympathetic blockage and vagal stimulation.[22-24] In the present experiment, mean HR was remained stable during treatment in all groups and returned to baseline in XL group. As previously mentioned, significant reduction of SV and HR was noted, 3 min after drug administrations in ML, MH and XH groups that led to significant decrease in CO ($p \leq 0.05$). Although SV was not changed after 3 min in XL group, however, reduction of heart rate index caused significant decrease in CO in this group as well ($p \leq 0.05$). It means that even if contraction ability was not changed, bradycardia could reduce cardiac output solely.

Decrement of HR index correlates with decrement of norepinephrine release and subsequent binding of medetomidine to α_2-adrenoceptors.[24,25] On the other hand, decrease of CO in medetomidine groups of the present experiment was most likely due to the low HR.[7] In one study that was performed on ten adult female horses, authors concluded that compared to baseline values, cardiac output was significantly decreased 10, 20, and 40 min after administration of medetomidine (4.00 μg kg^{-1}; IV) and significantly increased 40 and 60 min after administration of xylazine (0.40 mg kg^{-1}; IV).[26] In another study, dexmedetomidine was injected to six experimental ponies at 3.50 μg kg^{-1}, IV. Anaesthesia was maintained with isoflurane (5 min later an infusion of dexmedetomidine) for 150 min, HR fell after dexmedetomidine injection and were reduced significantly ($p < 0.05$) at 5 min after injection, Cardiac index (CI) was reduced significantly for the first 20 min and SV for the first 5 min.[27] Also Bettschart-Wolfensberger *et al.* discovered that maintenance of anesthesia induced by medetomidine–propofol was appropriate for heavy horses in any surgical procedures.[28] They also noted that use of this anaesthetic combination, provided rapid and qualified sedation with adequate cardiovascular function, which made it unnecessary to use sympathomimetic drugs. The cardiopulmonary changes in the sheep were very similar to those in the ponies after the administration of medetomidine. After IV administration of 5.00, 10.00 and 20.00 μg kg^{-1} of medetomidine, significant decrease in HR and CO were seen. However, the decrease was not significantly dose dependent. SV was also decreased after the administration of the two higher doses of medetomidine in both ponies and sheep.[29] In our examination decrease in cardiac parameters such as HR, SV and CO were seen even in low dose groups and these changes were significantly dose dependent.

In M-mode echocardiography, LVmass by the Penn-cube method accurately quantitates and ascertain LV hypertrophy. In this method LVmass index was estimated by left ventricular internal dimension (LVID) and wall thickness (LVPW and IVS) at end-diastole.[30] There is no reference range for LVmass in camels like humans but in the present study significant reduction in LVmass was visible after drug injection (more prominent in MH and XH groups) and had negative correlation with LVIDd, LVVed and LVVes. Indeed, LVmass index was lower in patients with ischemic, eccentric dilatory, hypertensive cardiomyopathy or cardiomyopathies of other etiologies and could lead to cardiac failure.[31] Therefore, sedation with α_2-adrenoceptor agonist drugs could temporarily cause eccentric dilatory cardiomyopathy based on the present M-mode echocardiographic findings. Actually reduction of left ventricle wall thickness and increasement of left ventricle internal lumen significantly influenced other cardiac parameters in all groups at most times.

To the best knowledge of authors this was the first study, investigating the echocardiographic effects of the α_2-adrenoceptor agonists in camelids.

The PEP is a heart-dependent index of cardiac function affected by loading conditions and myocardial contractility.[32] Myocardial contractility is known to be inversely correlated to PEP and PEP/LVET parameters.[32] In echocardiographic study whenever PEP and PEP/LVET indices were became lower, cardiac systolic function was better and *vice versa*. Furthermore, increase in LVET index is along with high level of SV.[32] In the present examination although increase in PEP index was visible after drug injection, however, was not statically significant, while increase in PEP/LVET and decrease in LVET and QAVC parameters were seen 3 min after drug administration that was significant compared to the base line time in MH, ML and XH groups ($p \leq 0.05$) and remained significant until 120 min ($p \leq 0.05$). Thus, it is likely that myocardial contractility was reduced in the present study. Actually based on our results IV injection of α_2- adrenoceptor

agonist drugs temporarily affected cardiac systolic time intervals that had direct relationship with decrease in FS%, EF%, SV and consequently CO. These significant changes that was observed during sedation were consistent with depressed both systolic and diastolic functions. Many studies in the literature, has been performed concerning the effects of medetomidine on cardiac function in canine breeds. In one of them, Saponaro *et al*. reported that although medetomidine or acepromazine alone could provide an equivalent and acceptable sedation with a good recovery process, however, combination of medetomidine with acepromazine produced a significant reduction of HR and CO (more notable at time 15 min) as compared to acepromazine alone.[33]

In conclusion, this study documented that, all four protocols were eligible for sedation and premedication in healthy camels. Low and high doses of medetomidine and high dose of xylazine could be applicable protocols in *Camelus dromedarious* requiring sedation for clinical procedure such as rectal examination and sperm insemination and/or as premedication for general anaesthesia, while MH group may be used for surgical procedure. This is clinically important as it may expedite the onset of peak sedation, associated with longer duration of echocardiographic parameters reduction in dromedary camel. Moreover, they had lots of impact on the echocardiographic variables evaluated in present study. Indeed, results of current study demonstrated that IV injection of α_2-adrenoceptor agonist drugs produced a dose dependent and temporary change in cardiac output that was similar to dilatory cardiomyopathy and caused thinning of left and right free wall and intraventricular septum and increased left and right ventricular internal dimensions in both systolic and diastolic phases.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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