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Surgery

Effect of administering dexmedetomidine with or without atropine on cardiac troponin I level in isoflurane-anesthetized dogs

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ABSTRACT. We aimed to determine whether dexmedetomidine administration with or without atropine increases cardiac troponin I (cTnI) level in healthy dogs. We hypothesized that 10 µg/kg dexmedetomidine + atropine increases the cTnI level, whereas 5 µg/kg dexmedetomidine + atropine does not. Eighteen healthy, pet dogs that underwent an orthopedic surgery or ovariohysterectomy were included in this study. The dogs were randomly assigned to atropine (0.02 mg/kg)–dexmedetomidine (10 µg/kg), saline–dexmedetomidine (10 µg/kg), and atropine (0.02 mg/kg)–dexmedetomidine (5 µg/kg) groups. Each dog was premedicated with atropine or saline intramuscularly (IM). After 10 min, they were IM injected with dexmedetomidine (10 or 5 µg/kg)–morphine (0.5 mg/kg)–midazolam (0.2 mg/kg). Following this, anesthesia was induced after 10 min with propofol and maintained with isoflurane in 100% oxygen. The median plasma cTnI level at 6, 12 and 24 hr after premedication was significantly higher than that at baseline. The cTnI level in the atropine–dexmedetomidine (10 µg/kg) group was significantly higher than that in the saline–dexmedetomidine (10 µg/kg) and atropine–dexmedetomidine (5 µg/kg) groups at 6 and 12 hr after premedication. The cTnI level returned to normal within 72 hr after premedication in all groups. The administration of atropine in combination with 10 µg/kg dexmedetomidine increased the cTnI level, indicating subclinical myocardial damage.

KEY WORDS: atropine, canine, cardiac troponin I, dexmedetomidine, myocardial injury

Dexmedetomidine, an α-2 adrenergic receptor agonist, is widely used in veterinary medicine because of its sedative, analgesic, and muscle relaxation properties [8, 16]. Initially, dexmedetomidine causes peripheral vasoconstriction, which results in temporary hypertension, bradycardia, and up to 50% reduction in cardiac output (phase 1). Thereafter, during phase 2, the sympatholytic effect of dexmedetomidine leads to the dilation of the peripheral vessels, while maintaining a lowered heart rate [2, 3, 26]. However, preemptive administration of anticholinergics to prevent bradycardia can cause cardiac arrhythmias, hypertension, and increased myocardial workload, as indicated by previous studies in the field of veterinary medicine [3, 12, 21, 24, 27]. The extreme hypertensive effect of dexmedetomidine in combination with atropine premedication or glycopyrrolate treatment has been reported in humans [25, 39]. Therefore, the use of such a combination is controversial.

Blood cardiac troponin I (cTnI) level is a highly specific and sensitive marker of myocardial injury, and it has been used to diagnose myocardial damage in humans, dogs, and cats [4, 23]. An imbalance between oxygen supply and demand can lead to perioperative myocardial injury [33, 41]. Perioperative myocardial injury is generally characterized by an increase in isolated troponin level after surgery without any signs or symptoms. Mortality at 30 days in patients undergoing noncardiac surgery with increased postoperative cTnI level is observed in at least 3% in humans, and this increased risk of mortality continues for at least 1 year [33]. To the best of our knowledge, only a few studies have evaluated the effects of dexmedetomidine administration along with atropine on the cTnI level in recent years. Hence, in this study, we aimed to determine whether 10 or 5 µg/kg dexmedetomidine along with atropine can increase the cTnI level in clinically healthy dogs. We hypothesized that atropine combined with dexmedetomidine 5 µg/kg would not increase the cTnI level and could maintain a higher heart rate than dexmedetomidine administration alone.

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MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee of National Chung Hsing University (IACUC No.107-038). Eighteen client-owned dogs were admitted to National Chung Hsing University Veterinary Teaching Hospital from July 2017 to February 2018 for ovariohysterectomy (OHE) or orthopedic surgery. Based on the American Society of Anesthesiologists' classification system, these dogs were classified as 1 or 2. The age range of the dogs was 6 months to 5 years. The preoperative electrocardiogram, lactate level, cTnI level, physical examination, complete blood count (CBC), and serum biochemical examination were performed for each dog to fulfil the study enrollment process. None of the dogs had a history, clinical sign, or physical examination findings that indicated a heart disease. A 3-day hospitalization was required for each dog for blood sample collection. Dogs with cardiac disease, renal disease [31], and sepsis were excluded.

Experimental protocol

The dogs were randomly assigned (randomization by lottery) to three groups at the time of premedication (n=6 per group): 0.02 mg/kg atropine (Atropine Sulfate; Tai Yu, Hsinchu, Taiwan) combined with 10 µg/kg dexmedetomidine (Dexdomitor®, Zoetis, Inc., Parsippany, NJ, USA) (group AD10), saline combined with 10 µg/kg dexmedetomidine (group SD10), and 0.02 mg/kg atropine combined with 5 µg/kg dexmedetomidine (group AD5). The anesthesiologist was unaware of group assignment until the premedication was administered.

Food and water were withheld for 6–8 hr and 2 hr, respectively. A 20 or 22 gauge IV cannula was aseptically placed in the cephalic vein. All dogs rested for 30 min for environmental acclimatization. The baseline heart rates and blood pressures were then measured before premedication (baseline, BL). We referred to Congdon *et al*. [12] to determine the doses of dexmedetomidine and atropine, and Ko *et al*. [21] to decide the timing of administration. Atropine (0.02 mg/kg) (group AD10 and AD5) or saline (0.02 ml/kg, the same volume as atropine) (group SD10) was injected intramuscularly (IM). After 10 min, dexmedetomidine 10 µg/kg (group AD10 or SD10) or 5 µg/kg (group AD5) combined with 0.5 mg/kg morphine (both groups; Morphine HCl, Food and Drug Administration, Taipei, Taiwan) and 0.2 mg/kg midazolam (both groups; Dormicum®, Roche, Kaiseraugst, Switzerland), all mixed in the same syringe, was administered IM as premedication. Anesthesia was induced 10 min later with propofol (Fresofol® 1%; Fresenius Kabi, Bad Homburg, Germany) injected intravenously (IV) titrated to effect to intubation (T0) and maintained with isoflurane (Terrell Isoflurane USP®; Piramal Critical Care Inc., Bethlehem, PA, USA) in 100% oxygen with the end-tidal isoflurane concentration between 1.2% and 1.5%. All dogs were ventilated via intermittent positive pressure ventilation in the pressure-control mode to maintain the end-tidal CO_2 level between 35–45 mmHg. The dogs were in lateral or dorsal recumbency based on the surgery. Noninvasive oscillometric blood pressure was measured in the uncatheterized forelimb above the carpus with Pettrust (Pettrust®; BioCare, Taoyuan, Taiwan). If the forelimb was amputated, the oscillometer was placed in the tarsal region. A 22 or 24 gauge IV cannula was aseptically placed in the dorsal pedal artery for invasive blood pressure measurement. During anesthesia, electrocardiographic patterns, end-tidal CO_2, end-tidal isoflurane, tidal volume, heart rate (HR), systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP), esophageal temperature (E-PRESTN and E-CAIOv modules; GE Healthcare, Helsinki, Finland), and pulse oxymetry (Radical-7®; Masimo Corp., Irvine, CA, USA) were monitored continuously and recorded every 5 min. Lactated Ringer's solution (Liquor Lactated Ringer's; Chi Sheng Chemical Corp., Hsinchu, Taiwan) was administered at 5 ml/kg/hr after intubation to the end of surgery. Morphine (0.36 mg/kg/hr), lidocaine (1 mg/kg/hr; Xylocaine®; Cenexi Inc., Fontenay-sous-Bois, France), and ketamine (0.6 mg/kg/hr; Imalgene®; Merial Inc., Lyon Cedex, France) (MLK) constant-rate infusion was given for analgesia in each procedure. If the respiratory rate, HR, and mean blood pressure were ≥20% of the baseline values, the dogs were presumed to be experiencing nociception and rescue analgesia with fentanyl (3 µg/kg, Fentanyl; UBI Pharma Inc., Hsinchu, Taiwan) was administered IV. If hypotension (mean blood pressure <60 mmHg) occurred, IV bolus of Lactated Ringer's solution 3 ml/kg was administered within 5 min, which was repeated if hypotension persisted. A forced-air warming system (Bair Hugger Model 750; 3M Health Care, Saint Paul, MN, USA) was used to keep the dogs warm during the surgery. The dogs were administered 0.2 mg/kg meloxicam (Achefree®; Swiss Pharm Co., Ltd., Tainan, Taiwan) once subcutaneously (SC) after surgery, followed by 0.1 mg/kg SC once a day. Postoperative pain scores following the Glasgow Composite Measure Pain Scale were assigned by the same person. If the postoperative pain score was >6/24 or 5/20 for non-ambulatory dogs, morphine (0.5 mg/kg) was administered IM as rescue analgesia. In orthopedic surgery, MLK constant-rate infusion was administered as postoperative analgesia.

Cardiac troponin I and lactate

cTnI level was measured using the Abbott i-STAT portable clinical analyzer (i-STAT handheld; Abbott, Ontario, Canada), with a test cartridge, following a two-site ELISA method. The lower limit for detection of cTnI was 0.02 ng/ml. The range of plasma cTnI level in dogs was <0.03–0.07 ng/ml [38]. A cTnI level ≤0.07 ng/ml was considered as the normal level in this study. Lactate was measured using a point-of-care device (StatStrip Xpress® Lactate Hospital Meter; Nova Biomedical, Waltham, MA, USA). The normal range for dogs is <2 mmol/l [6]. Whole blood (0.1 ml) was collected from the cephalic or lateral saphenous vein immediately to determine the cTnI and lactate levels at baseline, and 6, 12, 24, 48, and 72 hr after premedication (after dexmedetomidine/morphine/midazolam injection).

Rate pressure product (RPP)

The product of HR and SBP (i.e., RPP) is a useful predictor of myocardial oxygen demand [18, 42]. Thus, we utilized this

method to estimate myocardial oxygen consumption every 5 min and calculated the RPP from these values. The normal range of RPP was below 12,000 mmHg × beats/min in humans [29]. In veterinary medicine, the normal range of RPP has not been established. We defined the normal range of RPP as 9,200–18,500 mmHg ×beats/min, based on previous studies [12, 20].

Statistical analysis

Continuous data are shown as descriptive statistics, median, and interquartile range (IQR) for each group. Age, weight, propofol dose, fentanyl dose for rescue analgesia in surgery, anesthesia time, rescue times in surgery, and hemodynamic variables were compare among the three groups using Kruskal–Wallis test at baseline (before atropine, BL), induction (T0), and 10 (T10), 20 (T20), 30 (T30), 45 (T45), and 60 (T60) min after induction. Post hoc contrast analyses were conducted using Steel's test for pairwise comparisons when significant group differences were observed. The cTnI and lactate levels were analyzed using the same test to compare the three groups at baseline and 6, 12, 24, 48, and 72 hr after dexmedetomidine/morphine/midazolam administration. The relationship between ECG arrhythmia combined with or without atropine was tested using Fisher's exact test. The relationship between the type of surgery (OHE or orthopedic), arrhythmia, anesthesia time (>255 min [43]), and cTnI level (>0.07 ng/ml or not) was tested using Fisher's exact test. Associations between hemodynamic variables were tested using linear regression analyses. In this study, two statistical software were applied for data analysis, including the use of MedCalc version 2.1.4.0 (MedCalc Software®, Mariakerke, Belgium) for regression analysis and Fisher's exact test, and SAS version 9.4 (SAS institute Inc., Cary, NC, USA) for Kruskal Wallis test and post hoc analysis by Steel's method. Results with a *P*-value of <0.05 were considered statistically significant.

RESULTS

Eighteen dogs, 2 males and 16 females, were included in this study. The breeds included mix breed (n=15), poodle (n=1), Shiba (n=1), and Belgian Shepherd (n=1). Thirteen dogs undergoing OHE surgery and six dogs undergoing orthopedic surgery (one dog femoral head osteotomy + OHE) were included in this study. One dog (femoral fracture open reduction) in the AD10 group, three (femoral head osteotomy, 2 dogs; forelimb amputation, 1 dog) in the AD5 group, and two (femoral fracture open reduction and forelimb amputation) in the SD10 group underwent orthopedic surgery. Demographic data are summarized in Table 1. There was no significant difference in age, weight, fentanyl dose for rescue analgesia in surgery, and anesthesia time among the three groups. Anesthesia time in only two dogs (285 and 320 min) was more than 250 min in the SD10 group, but their cTnI levels were normal. Propofol dose was significantly higher in the AD5 group than that in the SD10 group (*P*=0.0079). No dog was administered the rescue drug after the surgery.

Invasive arterial blood pressure was measured in 4/6, 4/6, and 3/6 dogs in the AD10, SD10, and AD5 groups, respectively. Arterial line placement could not be performed in seven dogs because of vasoconstriction. We measured the blood pressure in all groups using a non-invasive method and compared the values. The HR, SBP, MBP, DBP, and RPP values are summarized in Table 2. Overall, only two dogs developed hypotension in the AD5 group and both were administered an IV bolus of 3 ml/kg LR solution once. The cTnI level in these two dogs was <0.06 ng/ml at all time points.

There was no significant difference in the HR among the three groups at baseline (*P*=0.7267). In the SD group, the HR at T0, T45 and T60 was significantly lower than that at baseline (*P*=0.0074, *P*=0.0142, *P*=0.0346, respectively). In the AD10 group, the HR only was lower than that at baseline at T45 (*P*=0.0498). There was no significant difference in the HR at each observed time point among the three groups (Table 2).

No significant difference was observed in the SBP, MBP, and DBP values among the three groups at baseline (*P*=0.9598, *P*=0.9320, *P*=0.8488, respectively). In the AD10 group, the SBP at T10, T45 and T60 was significantly lower than that at baseline (*P*=0.0317, *P*=0.0158, *P*=0.0288, respectively). There were significant differences in the SBP values from T10, T30 to T60 in the SD10 group (*P*=0.00143, *P*=0.0418, *P*=0.0023, *P*=0.0023, respectively) and T10 to T60 in the AD5 group (*P*=0.0037, *P*=0.0020, *P*=0.0018, *P*=0.0033, *P*=0.0020, respectively) compared with the baseline values. There were significant differences in MBP values from T45 to T60 in the SD10 group (*P*=0.0018, *P*=0.0037, respectively) and T10 to T60 in the AD5 group (*P*=0.0347, *P*=0.0066, *P*=0.0018, *P*=0.0158, *P*=0.0033, respectively) compared with the baseline values. There were differences at T10, T20 and T30 in

Table 1. Characteristics of the three groups (median, interquartile range)

	AD10 (n=6)	SD10 (n=6)	AD5 (n=6)	*P* value
Sex (M/F)	0/6	1/5	1/5	
Age (month)	18 (12–24)	30 (24–36)	24 (24–36)	0.4423
Weight (kg)	9.3 (7.2–10.9)	11.3 (9.4–17.5)	9.55 (8–12.4)	0.5195
Propofol dose (mg/kg)	1 (1–2)[a]	0 (0–1)	2 (1.8–2)[b]	0.0079[a-b]
Fentany dose for rescue analgesia (µg/kg)	1.5 (0–6)	0 (0–12)	1.5 (0–6)	1.0000
Anesthesia time (min)	80 (60–150)	150 (80–320)	152.5 (80–200)	0.0909

M, male; F, female; AD, atropine-dexmedetomidine; SD, saline-dexmedetomidine; Group AD10, dexmedetomidine 10 µg/kg, intramuscularly (IM) combined with atropine (0.02 mg/kg, IM); group SD10, dexmedetomidine (10 µg/kg, IM); group AD5, dexmedetomidine (5 µg/kg, IM) combined with atropine (0.02 mg/kg, IM); *: Significant differences from baseline (BL) (*P*<0.05). Different letters indicate statistically significant differences. a–b: *P*<0.05.

Table 2. Median (interquartile range) of heart rate, systolic blood pressure, mean blood pressure, diastolic blood pressure and rate pressure product at various time points in three groups

	Group	BL	T0	T10	T20	T30	T45	T60
HR (beats/min)	AD10	117.5 (96–137)	122.5 (89–142)	127 (117–150)	120 (99–138)	100 (84–114)	96.5 (90–105)*	98 (89–98)
	SD10	113 (112–142)	76 (63–97)*	84 (73–94)	88.5 (60–96)	91 (74–95)	91.5 (79–95)*	84.5 (74–106)*
	AD5	116.5 (112–140)	116 (73–135)	109.5 (93–122)	120.5 (96–122)	108 (100–112)	94 (81–111)	91.5 (84–105)
SBP (mmHg)	AD10	149.5 (144–155)	143 (130–155)	129.5 (122–138)*	136.5 (112–150)	128 (119–147)	130 (119–138)*	130 (126–141)*
	SD10	150.5 (136–163)	138 (116–159)	129 (113–138)*	129.5 (117–142)	122 (115–138)*	111.5 (111–113)*	117 (114–120)*
	AD5	152 (144–159)	133.5 (126–156)	114.5 (110–118)*	108 (106–116)*	104.5 (102–110)*	107 (93–118)*	97.5 (84–112)*
MBP (mmHg)	AD10	108 (102–129)	117 (108–135)	100 (94–107)	104.5 (95–109)	102 (89–120)	101 (79–106)	106.5 (80–108)
	SD10	111 (102–123)	113.5 (96–126)	92.5 (75–106)	88.5 (78–103)	84.5 (81–95)	86 (83–89)*	83.5 (81–92)*
	AD5	114.5 (110–125)	105.5 (102–134)	91.5 (81–96)*	83.5 (78–87)*	80.5 (79–88)*	80.5 (72–98)*	75.5 (62–86)*
DBP (mmHg)	AD10	86 (75–113)	103.5 (82–117)	83.5 (76–92)	91 (84–97)	91 (85–103)	86.5 (79–96)	93 (76–94)
	SD10	84.5 (80–99)	98.5 (82–106)	73 (60–84)	68 (64–86)	69.5 (60–81)	72 (61–76)	70 (61–76)
	AD5	93 (85–102)	89.5 (85–119)	76.5 (60–81)	67.5 (57–70)	63.5 (58–64)*	64.5 (58–75)	61 (50–72)*
RPP (mmHg × beats/min)	AD10	16,768 (14,880–19,728)	17,321 (12,240–21,390)	16,073 (14,602–18,788)[a]	15,471 (14,541–17,802)	12,723 (12,054–14,098)*	12,682.5 (11,448–13,110)*	12,742.5 (10,486–14,210)*
	SD10	19,015 (15,120–22,720)	11,479 (7,308–11,834)*	10,624 (10,439–11,375)*[,b]	10,442.5 (9,204–13,632)*	11,397 (10,465–12,220)*	10,267.5 (8,927–11,009)*	9,926 (8,584–11,310)*
	AD5	17,544 (15,820–20,440)	15,034.5 (9,344–19,311)	11,696 (11,102–12,650)*	12,085 (10,208–13,420)*	10,875 (9,990–12,320)*	9,133.5 (8,505–12,099)*	8,787.5 (8,134–9,072)*

HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; RPP, rate pressure product. *: Significant differences from baseline (BL) (P<0.05). Different letters indicate statistically significant differences. a–b: P<0.05. The value without letter means no significant difference.

the SD10 group (P=0.0596, P=0.0596, P=0.0547, respectively) compared with the baselines values. The difference is very close to the significant level statistically by post hoc analysis of Steel's method. DBP was significantly lower in the AD5 group at T30, and T60 than at baseline (P=0.0115, P=0.0143) (Table 2).

There was no significant difference in the HR, SBP, MBP, and DBP values among the three groups (Table 2).

The cTnI and lactate levels in all three groups are summarized in Table 3. There was no significant difference in the cTnI level after OHE and orthopedic surgery (>0.07 ng/ml) (P=1.0000). Furthermore, there was no significant difference in the fentanyl for rescue analgesia during OHE (median, interquartile range: 0, 0–6) and orthopedic surgery (3, 0–9) (P=0.3026). Abnormal ECG recordings such as those indicative of 1–2 degree atrioventricular blocks were found for 3/6, 3/6, and 2/6 dogs in the AD10, SD10 and AD5 groups, respectively. No significant difference was found in ECG arrhythmia after atropine administration or increased cTnI level (>0.07 ng/ml) (both P=1.0000). Anesthesia time (>255 min) showed no significant difference with the cTnI level (>0.07 ng/ml) among the 18 dogs.

There was no significant difference in the cTnI level among the three groups at baseline (P=0.9791). The plasma cTnI level increased in the AD10 (6/6), AD5 (1/6), and SD10 (3/6) groups compared with that at baseline 12 hr after premedication. In three dogs in the AD10 group, the cTnI level reached as high as 0.1–0.25 ng/ml at 6–48 hr after premedication. The plasma cTnI level at 6, 12 and 24 hr in the AD10 group was significantly higher than that at baseline (P=0.0482, P=0.0022, P=0.0229, respectively). There was no significant difference in the plasma cTnI level in the SD10 and AD5 groups compared with the baseline values at any time point. The cTnI level returned to the normal levels within 72 hr after premedication in all groups. The plasma cTnI level in the AD10 group was significantly higher than that in the SD10 group at 6 and 12 hr after premedication (P=0.0389, P=0.0170, respectively). And the plasma cTnI level in the AD10 group was significantly higher than that in the AD5 group at 12 hr after premedication (P=0.0491) (Table 3).

There was no significant difference in the lactate level at baseline and all time points among the three groups (Table 3).

There was no significant difference in RPP among the three groups at baseline (P=0.6119). There were significant differences in the RPP values from T30 toT60 in the AD10 group (P=0.0038, P=0.0038, P=0.0094, respectively) and T10 to T60 in the AD5 group (P=0.0038, P=0.0094, P=0.0023, P=0.0060, P=0.0060, respectively) compared with the baseline values. The RPP substantially declined from T0 until T60 in the SD10 group (P=0.0018, P=0.0023, P=0.0030, P=0.0023, P=0.0018, P=0.0023, respectively). There were

Table 3. Median (interquartile range) of cardiac troponin I (cTnI) and lactate levels at various time points in the three groups

	BL	6 hr	12 hr	24 hr	48 hr	72 hr
cTnI						
AD10	0.02 (0.01–0.02)	0.07 (0.02–0.12)*,a	0.06 (0.03–0.10)*,a	0.04 (0.03–0.07)*	0.03 (0.02–0.03)	0.02 (0.01–0.03)
SD10	0.02 (0.00–0.02)	0.01 (0.00–0.01)b	0.01 (0.01–0.02)b	0.03 (0.01–0.04)	0.01 (0.01–0.02)	0.02 (0.01–0.02)
AD5	0.01 (0.01–0.02)	0.01 (0.00–0.02)	0.02 (0.01–0.02)b	0.02 (0.01–0.03)	0.02 (0.01–0.02)	0.02 (0.01–0.03)
Lactate						
AD10	1.0 (1.0–2.2)	1.1 (0.5–1.5)	1.4 (1.2–1.7)	1.5 (1.2–1.6)	1.4 (1.0–1.7)	1.3 (1.2–1.8)
SD10	1.6 (1.5–1.7)	1.5 (1.2–1.7)	1.5 (1.3–2.0)	1.4 (0.7–1.6)	1.0 (1.0–1.9)	1.2 (0.9–1.5)
AD5	1.5 (1.1–1.6)	2.2 (1.7–3.1)	0.9 (0.8–1.5)	1.2 (1.0–1.4)	1.4 (1.2–1.5)	1.1 (1.0–1.1)

BL, baseline; 6 hr, 6 hr after premedication; 12 hr, 12 hr after premedication; 24 hr, 24 hr after premedication; 48 hr, 48 hr after premedication; 72 hr, 72 hr after premedication; *: Significant differences from baseline (BL) (P<0.05). Different letters indicate statistically significant differences. a–b: P<0.05. The value without letter means no significant difference.

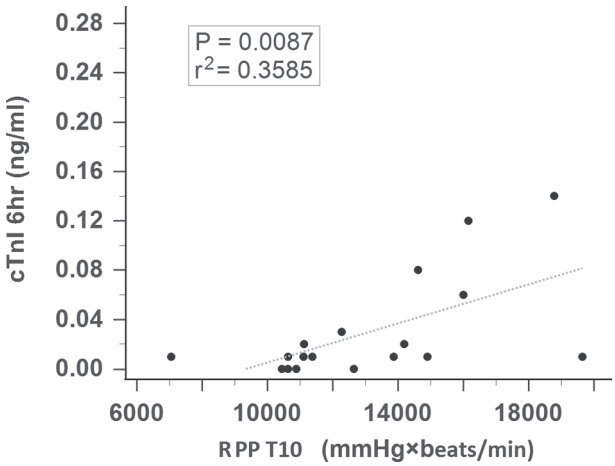

Fig. 1. Scatterplot and linear regression of the cardiac troponin I (cTnI) level and rate pressure product (RPP) recorded for 18 dogs. cTnI 6 hr and RPP T10 positively correlated.

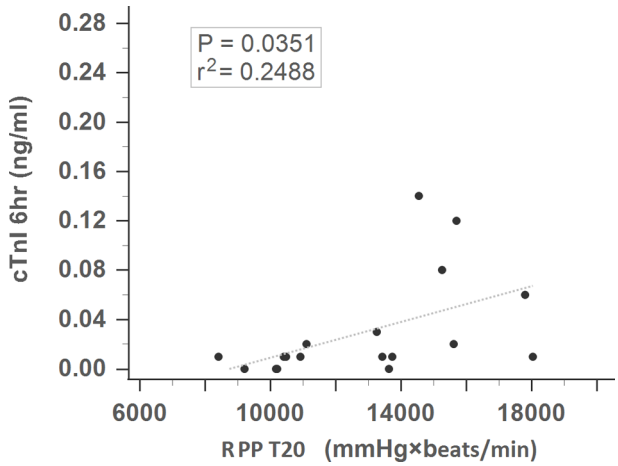

Fig. 2. Scatterplot and linear regression of the cardiac troponin I (cTnI) level and rate pressure product (RPP) recorded for 18 dogs. cTnI 6 hr and RPP T20 positively correlated.

significant differences in RPP between the AD10 and SD10 groups at T10 (P=0.0206) (Table 2). There were differences between the AD10 and SD10 groups at T20 (P=0.0509) and between the AD10 and AD5 groups at T10 (P=0.0509). The difference is very close to the significant level statistically by post hoc analysis of Steel's method.

A significant positive correlation between the cTnI level at 6 hr and RPP T10 (R^2=0.3585; P=0.0087) and RPP T20 (R^2=0.2488; P=0.0351) was observed (Figs. 1 and 2). Additionally, a significant positive correlation between the cTnI level at 12 hr and RPP T10 (R^2=0.3657; P=0.0078) was observed (Fig. 3). No significant correlations were detected between the cTnI level and HR, SBP, DBP and MBP.

DISCUSSION

On the basis of the results of this study, the IM administration of 0.02 mg/kg atropine along with 10 µg/kg dexmedetomidine can increase the plasma cTnI level, which was not observed with 5 µg/kg dexmedetomidine administration in combination with atropine. The cTnI level returned to normal levels within 72 hr.

In our study, the cTnI level increased from 6 to 24 hr after premedication, and peaked at 12 hr in the AD10 group, consistent

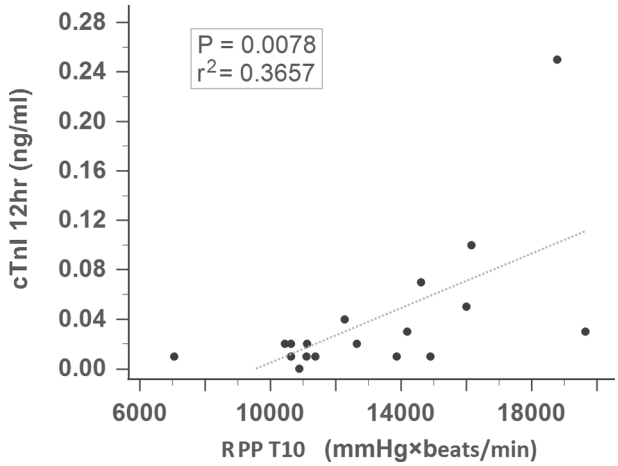

Fig. 3. Scatterplot and linear regression of the cardiac troponin I (cTnI) level and rate pressure product (RPP) recorded for 18 dogs. cTnI 12 hr and RPP T10 positively correlated.

with the results of previous studies [1, 37, 43]; however, a clear threshold of myocardial damage has not been established in dogs. The cTnI level has been reported to mildly increase (<1 ng/ml) in primary cardiac disease and rarely increased to above 1–2 ng/ml [23] in severe congestive heart failure. According to a previous study [23], increased cTnI levels are commonly observed in critically ill dogs and cats with secondary myocardial injury (mild: <1 ng/ml, common: >10 ng/ml). For example, increased cTnI level was detected in dogs with gastric dilatation–volvulus syndrome (2.05–24.9 ng/ml) [35] and pyometra (0.3–0.9 ng/ml) [17]. In this study, the highest increase in the cTnI level was in the range of 0.1–0.25 ng/ml at 6–24 hr after premedication in the AD10 group, suggesting that minor myocardial damage had occurred. In addition, a minor increase in the serum cTnI (<1.3 ng/ml) level may occur without histological evidence of myocardial cell injury [7]. The cTnI level returned to the normal range 72 hr after premedication in all dogs.

Increased RPP in the AD10 group may be the primary factor to cause an increase in the cTnI level. The association between the cTnI level and RPP has been corroborated by statistical analyses. Dexmedetomidine 10 µg/kg in combination with atropine increased the HR and blood pressure, resulting in increased cTnI level. A previous study [12] reported that when dexmedetomidine (10 µg/kg)–atropine (0.02 mg/kg) was administered IM, a peak RPP of 29,500 ± 1,390 mmHg beats/min was reached 30 min after injection. These trends are consistent with the outcome of the AD10 group in our study. RPP was higher in the group that received dexmedetomidine with atropine, which increased myocardial oxygen consumption. The peripheral vasoconstrictive effect is predominant after administering a high dose of α2-adrenoceptor agonists [32], such as 10 µg/kg dexmedetomidine, and anesthetization with isoflurane or propofol [22]. Therefore, the myocardial oxygen consumption in the AD10 group was higher than that in the AD5 group. The increase in the HR increases myocardial oxygen demand and impairs diastolic filling time. HR-induced increase in the cardiac output and initial peripheral vasoconstriction by dexmedetomidine results in this hypertensive effect [39]. The imbalance in myocardial oxygen supply and demand can result in myocardial injury. The severity and duration of myocardial injury may cause reversible or irreversible myocardial ischemia [41]. Perioperative myocardial injury is generally common, silent, asymptomatic, and strongly associated with mortality [33], and it can only be detected by routine troponin monitoring in humans [33]. However, the mortality risk due to subclinical myocardial injury in dogs is currently unknown. Therefore, it seems prudent to avoid RPP increase during surgery.

The finding that the baseline HR and blood pressure were high indicated that all dogs were nervous and not acclimated to the induction room; their sympathetic tone was elevated. Surgical stress and direct tissue injury can cause pain, which resulted in increased HR, high blood pressure, increased oxygen consumption, myocardial ischemia, and endocrine response [10]. In our study, the dogs underwent various surgical procedures and experienced different degrees of nociception. Lidocaine and ketamine are widely used in combination with morphine for multimodal analgesia in dogs. All groups received MLK by constant rate infusion to provide pain relief and to avoid these effects. Additionally, opioids such as morphine are known to relieve pain and exhibit cardioprotective effects. These cardioprotective effects occur via the primary δ-opioid receptor immediately after drug administration and reappear 24–48 hr after treatment [36]. Lidocaine infusion increases mitochondrial membrane stability and protects the myocardium from ischemic damage [34]. In addition, lidocaine is commonly used to prevent ventricular arrhythmias [11]. Franco *et al.* [13] reported that a ketamine infusion rate of 20 µg/kg/min would not change the cTnI level, HR, MAP, ejection fraction, and cardiac index in dogs. All dogs received MLK by constant rate infusion with a ketamine infusion rate of 10 µg/kg/min in this study. This rate was lower than that in a previous study [13]. It is supposed that the ketamine infusion rate used in our study would not increase the cTnI level. In general, morphine, lidocaine, and ketamine did not affect the cTnI level in this study.

To the best of our knowledge, the factors related to increased cTnI level are still not clear. Arrhythmia could be one of the possible causes of myocardial injury in critical noncardiac diseases [23]. Previous studies reported that higher serum cTnI levels were significantly associated with moderate and severe ECG abnormalities (frequent ventricular premature contraction or supraventricular premature contraction (>15/min), couplets, triplets, polymorphic ventricular premature contraction, ventricular tachycardia, and ventricular flutter or fibrillation) in dogs with gastric dilatation–volvulus syndrome [5, 35]. Arrhythmias were observed in all groups in our study, including first and second degree atrioventricular blocks. The first and second degree atrioventricular blocks are somewhat mild ECG abnormalities as reported previously [5, 35]. Thus, these abnormal ECG observations in our study were not severe enough to cause changes in the cTnI level.

In addition, increased cTnI levels have been shown to be related to the age of the dogs even without appreciable cardiac disease [30]. Older dogs (>8 years) are more likely to present with increased plasma cTnI level than young dogs [9]. However, in this study, dogs under 5 years of age were enrolled to exclude age-related variables. Meanwhile, a longer operation time (255 min) and the development of hypotension during anesthesia increased the cTnI level to 0.15 ng/ml in a previous study [43]. These observations were not consistent with our results. The anesthesia time was longer in 2 dogs (285 and 320 min) in the SD10 group, but their cTnI levels did not increase. The increase in the cTn1 level did not correlate with longer operation time in this study and neither did the two dogs with hypotension exhibit increased cTnI level in our study.

This study had some limitations in addition to those mentioned above. First, a small sample size and the use of nonparametric statistics may have contributed to type II error, leading to overlooking of significant differences among the groups. Second, blood pressure was not measured through an invasive procedure via an arterial line in all the dogs. Using a noninvasive blood pressure measurement device might have underestimated the SBP during hypertension [14], and thereby underestimating the RPP. We did not record vital signs immediately after the administration of atropine and other premedication. The interval between baseline and induction was approximately 20 min. After this period, the hemodynamic effects of dexmedetomidine might have progressed to stage 2 (i.e., central hypotensive effect), in which the vascular tone returns to the normal level or is slightly vasodilated and the heart rate remains low because of the suppression of the sympathetic tone [28, 32]. Furthermore, the vasodilatory effect of propofol [15] and the negative inotropy (decreases cardiac output) caused by isoflurane may have contributed to the lower blood pressure

[19, 40]. Invasive blood pressure measurement may be a better way to determine RPP more accurately. However, we still evaluated the trend in blood pressure and RPP in this manner. Third, despite different degrees of postoperative pain, dogs undergoing OHE and orthopedic surgery were still enrolled. More profound analgesia (MLK CRI) was administered after orthopedic surgery to prevent tachycardia induced by nociception. Finally, an SD5 group (dexmedetomidine 5 µg/kg) was not included in this study. However, after the pilot study, we found no increase in the cTnI level in the SD5 group. This supposition combined with the observation that 10 µg/kg dexmedetomidine alone does not increase the cTnI level indicates that the lack of an SD5 group would not affect the interpretation of the results.

In conclusion, our findings demonstrate that atropine administration does not increase the cTnI level and prevent bradycardia induced by 5 µg/kg dexmedetomidine. The administration of atropine in combination with 10 µg/kg dexmedetomidine increases the cTnI level, indicating subclinical myocardial damage.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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