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RESEARCH ARTICLE

Evaluation of Cardiopulmonary Effects in Young and Adult Dogs Under Anesthesia Induced by Butorphanol-Midazolam-Propofol Versus Dexmedetomidine-Tiletamine-Zolazepam

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ABSTRACT

Since distinct physiological characteristics are exhibited by dogs of various ages, the effects on cardiopulmonary function, hepatic and renal metabolism, vary depending on the induction anesthesia protocol employed. Butorphanol-midazolam-propofol (BMP) and dexmedetomidine-tiletamine-zolazepam (DZ) are the most commonly adopted induction anesthesia protocols for canines. In this study, induction effects and cardiopulmonary impacts of BMP and DZ anesthesia protocols in young (Y) and adult (A) dogs were investigated. Twelve adult and twelve young dogs were allocated into four groups: DZ-A, BMP-A, DZ-Y, and BMP-Y. In DZ protocol, tiletamine-zolazepam and dexmedetomidine were injected intravenously. In BMP protocol, butorphanol, midazolam and propofol were used for anesthesia induction. Following tracheal intubation, the anesthesia was sustained using isoflurane. Post-intubation, non-invasive blood pressure (NIBP), heart rate (HR), peripheral hemoglobin oxygen saturation (SpO_2), respiratory rate (RR), end-tidal carbon dioxide ($ETCO_2$), and body temperature (BT) were monitored at 0 - 60 minutes. Time from induction to intubation, duration of anesthesia, time from sternal recumbency to standing, and induction, intubation, and recovery scores were also recorded. Results demonstrated that the DZ-A and DZ-Y groups exhibited significantly better induction, recovery, and intubation success rates compared to the BMP-A and BMP-Y groups, respectively. Additionally, NIBP and HR of the DZ-Y group were lower than those of the BMP-Y group. Other physiological parameters and indicators of liver and kidney function for the four treatment groups remained unaffected, with values were within normal ranges. In conclusion, both the BMP and DZ protocols are viable options for young dogs; however, the DZ protocol has a lesser impact on HR and NIBP. In adult dogs, the DZ protocols demonstrates superior efficacy for induction than BMP protocol.

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INTRODUCTION

Propofol is a widely used intravenous anesthetic for induction of anesthesia (Barbosa *et al.*, 2024). Co-administration of midazolam and butorphanol before propofol not only diminishes the required dosage of propofol but also enhances the induction quality and significantly mitigates the risk of adverse cardiopulmonary effects (Kojima *et al.*, 2002; Seo *et al.*, 2015). Zoletil® is a dissociative anesthetic with tiletamine and zolazepam in a 1:1 ratio. Its potential side effects include hypertension, tachycardia, increased cardiac output, and ataxia (Cullen and Reynoldson, 1997). Dexmedetomidine is a potent α2-adrenergic receptor agonist that promotes sedation and analgesia by reducing the activity of the sympathetic nervous system (Xu *et al.*, 2023). The sedative effect of dexmedetomidine is dose-dependent; while higher doses may enhance sedation, they are also linked to negative effects, including bradycardia and decreased cardiac output (Lewis *et al.*, 2022). In veterinary practice, the combination of tiletamine-zolazepam and dexmedetomidine is commonly used for induction of anesthesia in canines to minimize the risk of adverse reactions (Kucharski *et al.*, 2022).

Significant physiological differences exist between young and adult dogs, especially during anesthesia.

Compared to adults, young dogs are at higher risk of adverse effects during anesthesia, primarily due to limited cardiovascular compensatory capacity, increased tissue oxygen consumption, and a larger body surface area-to-weight ratio, all of which contribute to an increased risk of adverse reactions (Robinson and Borer-Weir, 2013). Furthermore, the sympathetic nervous system in young dogs is underdeveloped, leading to insufficient compensatory mechanisms for drug-induced bradycardia. Consequently, they are more susceptible to hypotension when administered α2-adrenergic receptor agonists and opioids. Additionally, the immature hepatic enzyme system in young dogs results in slower drug metabolism, increasing the likelihood of drug accumulation within the body (Grandy and Dunlop, 1991; Robinson and Borer-Weir, 2013). The butorphanol-midazolam-propofol (BMP) and dexmedetomidine-tiletamine-zolazepam (DZ) protocols represent two commonly employed drug combinations for inducing anesthesia in dogs (Sano *et al.*, 2003; Kusolphat *et al.*, 2022). However, the responsiveness to these protocols may vary between young and adult dogs, potentially affecting anesthetic outcomes.

Currently, the research focusing on the selection of anesthesia induction protocols for dogs across various age groups remains relatively scarce. We hypothesized that the two anesthesia induction protocols, namely BMP and DZ, are capable of providing stable induction effects with minimal side effects. In this study, BMP and DZ protocols were employed to anesthetize young and adult dogs. The effects of these two protocols on induction quality, cardiopulmonary function, and hepatic and renal function were evaluated in young and adult dogs separately.

MATERIALS AND METHODS

Management of experimental animals: Dogs expected candidates for this study were individually housed in sanitized kennels in the Animal Hospital of Northeast Agricultural University, Harbin, Heilongjiang, China, during the period from March 2020 to June 2021 and provided with ample drinking water and standardized diets. All procedures and operations in this study adhered strictly to the guidelines for the care and use of laboratory animals and were approved by the Laboratory Animal Ethics Committee of Northeast Agricultural University, Harbin, Heilongjiang, China. All the dogs were adopted after the experiment. Prior to drug administration, the dogs underwent American Society of Anesthesiologists (ASA) classification, complete blood count (CBC), and comprehensive physical examination. The exclusion criteria included: body condition scores (BCS) exceeding 7 or below 3, anemia defined as hematocrit (HCT) less than 24%, evident clinical signs of systemic diseases, or exposure to medications within 48 hours prior to the study. Ultimately, a total of 24 healthy mixed-breed dogs (comprising 12 young dogs and 12 adult dogs, with equal representation of males and females were enrolled in the study. The data about body weight and age in young and adult dogs are presented in Table 2 and Table 3, respectively. All the enrolled dogs had ASA classifications of Grade I.

Table 1: Explanation of simple descriptive score (SDS)

SDS	Description
1	Extremely excited, screaming, walking aimlessly, and ignoring commands.
2	Somewhat excited but calm quickly when soothed
3	Slight reactions, making soft sounds and swaying slightly without aimless walking.
4	Quiet and remain calm when soothed.

Table 2: The time and quality of anesthesia, body weight, and age in the DZ-Y and BMP-Y groups

Variables	BMP-Y	DZ-Y	P-value
The time from induction to intubation (minutes)	3.27±0.55	3.53±0.77	0.899
Time of duration (minutes)	64.17±3.19	81±6.78**	< 0.001
Time from sternal recumbency to standing (minutes)	4.05+0.61	7.12±0.88**	< 0.001
PPF usage (mg·kg^{-1})	2.50±0.55	0±0**	< 0.001
Induction quality (scale: 0 - 3)	1(0-2)	0(0-1)*	0.038
Ataxia (scale: 0 - 3)	0.5(0-3)	1(0-3)	> 0.05
Recovery quality (scale: 1- 3)	2(2-3)	3.5(2-4)*	0.043
Intubation score (1-4)	3(2-4)	4(3-4)*	0.025
Body weight (kg)	2.38±0.43	2.43±0.39	0.999
Age (months)	3.83±0.75	3.50±0.55	0.919

Values are presented as mean±SD or median (range: min - max). *Significant difference between treatment groups (P<0.05), **Significant difference between treatment groups (P<0.01).

Table 3: The time and quality of anesthesia, body weight, and age in the DZ-A and BMP-A groups

Variables	BMP-A	DZ-A	P-value
The time from induction to intubation (minutes)	4.65±0.58	3.83±0.75	0.181
Time of duration (minutes)	65.67±3.44	75.5±5.32*	0.012
Time from sternal recumbency to standing (minutes)	3.45±0.66	6.37±0.86**	<0.001
PPF usage (mg·kg^{-1})	4.00±0.89	0.17±0.41**	<0.001
Induction quality (scale: 0 - 3)	1.5 (1-2)	0(0-1)**	<0.001
Ataxia (scale: 0 - 3)	0.5(0-3)	1(0-2)	>0.05
Recovery quality (scale: 1- 3)	2(1-3)	3(2-4)*	0.018
Intubation score (1-4)	2.5(2-4)	4(3-4)*	0.035
Body weight (kg)	5.72±0.9	5.83±0.90	0.991
Age (year)	3.83±1.17	3.67±1.03	0.989

Values are presented as mean±SD or median (range: min - max). *Indicates a significant difference between treatment groups (P<0.05), **Indicates P<0.01.

Anesthesia protocol and grouping design: Before the experiment, adult dogs were fasted for 12 hours, while young dogs were fasted for 4 hours. During this period, all dogs had free access to water. Experimental dogs were randomly divided into four groups (n=6 per group). The four experimental groups were: Butorphanol-midazolam-propofol adult group (BMP-A), Butorphanol-midazolam-propofol young group (BMP-Y), Dexmedetomidine-tiletamine-zolazepam adult group (DZ-A), and dexmedetomidine-tiletamine-zolazepam young group (DZ-Y).

Prior to drug administration, it was ensured that the respiratory anesthesia machine and electrocardiogram monitor were functioning properly. After the dog was calm, a 24G intravenous catheter (B. Braun, Germany) was inserted into the cephalic vein of the forelimb. In the DZ group, 1.0mg·kg^{-1} tiletamine-zolazepam (Zoletil®), and 2.0μg·kg^{-1} dexmedetomidine were administered intravenously. In the BMP group, 0.2mg·kg^{-1} butorphanol and 0.2mg·kg^{-1} midazolam were administered intravenously, followed by propofol (1-4mg·kg^{-1}) to complete the induction. Once the dog exhibited no tension in the upper and lower jaws and the swallowing reflex

was weakened or absent, tracheal intubation was performed immediately (4.0-5.5mm tubes for juveniles; 7.0-8.5mm tubes for adults). In the DZ group, if tracheal intubation conditions remained unmet following drug administration, an intravenous supplementation of propofol at a dose of 0.5-4mg·kg^{-1} was administered. The actual final propofol (PPF) usage (mg/kg) used across the four treatment groups was subsequently recorded. The tracheal tube was secured, and the pediatric breathing circuit (semi-open mode, oxygen flow rate 1.0L/min) was connected. The anesthesia machine (RWD Life Science Co., Ltd.) and monitoring equipment were also connected. The volatilization tank was opened to deliver 1% isoflurane, which was maintained for 60 minutes. Afterward, the volatilization tank was closed, and 100% oxygen inhalation was initiated to allow the animal to awaken naturally. When the animal exhibited a swallowing reflex, the tracheal tube was removed, and dogs were placed back into their cage after full recovery.

Evaluation of anesthesia quality and time documentation: After drug administration, the following parameters were recorded separately for each dog: the time from induction to intubation, the duration from intubation to sternal recumbency (duration time), and the time from sternal recumbency to standing. A blind evaluation of the induction quality, intubation, ataxia, and recovery quality scores for each treatment group was conducted by three veterinarians.

The quality of induction and ataxia (Score 0-3) was assessed using the previously described scoring system (Reed *et al.*, 2019); where 0 indicated no ataxia, normal ambulation, and a smooth induction process; 1 denoted minimal ataxia with preserved ambulation and uncomplicated induction; 2 reflected mild ataxia, which made induction challenging; 3 signified pronounced ataxia or crawling during walking, or an unsatisfactory induction outcome. Recovery quality was evaluated based on the Simple descriptive score (SDS, Table 1), as descried previously (Jiménez *et al.*, 2012). Intubation score was recorded as 1-4 points; 1 point for vigorous laryngeal reflex during intubation with jaw closure and difficulty in proceeding; 2 points for diminished laryngeal reflex during intubation accompanied by mild tongue twitching; 3 points for subtle eyelid twitching observed during intubation; 4 points for absence of laryngeal reflex during intubation (Covey-Crump and Murison, 2008). Anesthesia scores were recorded by the methodologies outlined in previous studies (Diao *et al.*, 2017 , Reed *et al.*, 2019) at 0, 5, 10, 20, 30, 40, 50, and, 60 minutes post-intubation. The overall score was calculated by adding the individual ratings for posture, sedation, analgesia, skeletal muscle relaxation, and auditory response. Higher scores were associated with superior anesthetic quality. A perfect score of 16 signified excellent anesthesia, scores ranging from 11 to 15 reflected moderate anesthesia, and a score lower than 11 indicated mild anesthesia.

Monitoring of fundamental physiological parameters: Non-invasive blood pressure (NIBP) indicators included systolic blood pressure (SAP), mean arterial pressure (MAP), and diastolic blood pressure (DAP). Respiratory function indicators including respiratory rate (RR), peripheral blood oxygen saturation (SpO_2), end-tidal carbon dioxide partial pressure ($ETCO_2$), heart rate (HR) and body temperature (BT) were monitored at 0, 5, 10, 20, 30, 40, 50, and 60 minutes post-intubation using the iMEC 8 Vet multi-parameter monitor (Mindray, China). HR, SPO_2, $ETCO_2$, and BT were continuously monitored using electrocardiograph (ECG) crocodile clips (lead II), an arterial oxygen saturation probe, a sidestream capnography module for end-tidal carbon dioxide measurement, and an esophageal temperature probe. NIBP was assessed via oscillometry with a blood pressure cuff (Puppies, size 1, 3-6cm; adult dogs, size 3, 6-11cm) positioned posterior to the elbow joint of the right forelimb. Respiratory rate was determined manually using the parameter monitor.

Surveillance of adverse reaction: Following drug administration, the following adverse effects were closely monitored and documented: muscle tremors, reflux, cardiac arrest, hypoventilation, hypoxemia, bradycardia, and persistent hypotension (MAP <60mmHg for over 10 minutes). Fortunately, none of the dogs in each group showed such adverse effects.

Analysis of liver and kidney functions: Whole blood samples (3mL) were collected from the saphenous vein of the hind limb or the cephalic vein of the forelimb at three time points: prior to drug administration, 30 minutes post-induction, and 60 minutes post-induction. The samples were placed in heparin anticoagulant tubes, and centrifuged. Plasma was aspirated and analyzed using an automatic biochemical analyzer to measure the concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and creatinine (CRE).

Statistical analysis: The Shapiro-Wilk test was conducted on all data to assess their conformity to a normal distribution. Parametric variables were represented as mean ± standard deviation (SD), whereas non-parametric variables were described using the median (min - max).

Student's t-test was applied to compare the time from induction to intubation, duration time, time from extubation to sternal recumbency, time from sternal recumbency to standing, and PPF usage between the BMP-A and DZ-A groups, as well as between the BMP-Y and DZ-Y groups. The Kruskal-Wallis test followed by Dunn's multiple comparison test was performed to evaluate the differences in induction quality, intubation score, ataxia, recovery quality, and other relevant aspects among the treatment groups. The general linear mixed model (LMM) was applied to assess general physiological parameters (including SAP, MAP, DAP, HR, RR, SpO_2, $ETCO_2$, and BT), with time, treatment group, and their interaction included as fixed effects, while individual animals were treated as random effects. ANOVA analysis with Tukey's test was utilized for conducting pairwise comparisons of parameters (physiological parameters and blood biochemical index) among different treatments, whereas Dunnett's test was used for multiple comparisons of parameters (physiological parameters and blood biochemical index) at different time points within the

same treatment group relative to the baseline value (0 minutes). Anesthesia scores were evaluated via a generalized linear mixed model (GLMM), with a Poisson distribution and log link function assumed. Anesthesia scores among different treatment groups were compared using the Kruskal-Wallis test, and also to evaluate differences in behavioral scores at various time points within the same treatment group compared to the baseline (0 minutes). In all statistical analyses, $P<0.05$ was considered statistically significant.

RESULTS

Anesthesia time, induction, intubation and recovery quality in young groups: All 12 puppies successfully completed this part of the experiment and exhibited smooth recovery with no adverse reaction. Table 2 summarizes the time from induction to intubation, maintenance duration, induction quality, intubation score, recovery quality, degree of ataxia, PPF usage, body weight, and age across dogs of BMP-Y and DZ-Y groups. Statistically non-significant differences were found in the time from induction to intubation, ataxia, body weight age between young dogs of two anaesthesia groups. However, the DZ-Y group exhibited significantly better induction quality, recovery quality, and intubation scores compared to the BMP-Y group ($P<0.05$). Additionally, the DZ-Y group demonstrated a significantly longer duration of anesthesia and time from sternal recumbency to standing related to the BMP-Y group ($P<0.001$), while the BMP-Y group had a higher PPF usage than the DZ-Y group ($P<0.001$).

Anesthesia scores and general physiological indicators in young dogs: As illustrated in Fig. 1, the anesthesia scores of the young group showed statistically non-significant differences between the treatment groups, time points, or their interaction. Specifically, at 50 and 60 minutes, the DZ-Y group demonstrated significantly higher anesthesia scores in comparison to the BMP-Y group ($P<0.05$). Notably, within the BMP-Y group, the anesthesia score at 60 minutes was significantly reduced compared to that at 0 minutes ($P<0.05$).

The cardiopulmonary parameter monitoring results for the young group are presented in Fig. 2. The overall trend of arterial blood pressure in each treatment group gradually decreased over time without hypotension. In both treatment groups, NIBP (SAP, MAP, and DAP) exhibited significant changes over time ($P_{time}<0.001$), with marked decrease in SAP (Fig. 2A), MAP (Fig. 2B) and DAP (Fig. 2C) was observed in DZ-Y than BMP-Y group. Additionally, SAP, MAP, and DAP showed significant differences between the treatment groups ($P<0.001$). The interaction effects of time and treatment group on SAP and MAP were significant ($P<0.05$). However, no interaction effect was observed for DAP. In the DZ-Y group, SAP, MAP, and DAP were significantly lower than baseline values (0 minute) during the 20-60 min interval ($P<0.05$).

The BMP-Y group exhibited relatively minimal HR fluctuations and maintained a consistently higher HR compared to the DZ-Y group (Fig. 2D). Following an initial decrease, the HR gradually recovered, resulting in an average reduction of 10-15 beats/min relative to baseline in DZ-Y group. Mean HR value was higher in BMP-Y than DZ-Y group ($P<0.05$). However, time ($P_{time}=0.081$) and the interaction effects between time and treatment groups were statistically non-significant. Notably, the HR in the DZ-Y group was significantly lower at 30 and 40 minutes compared to baseline ($P<0.05$; Fig. 2D). For both the BMP-Y and DZ-Y groups, RR (Fig. 2E), $ETCO_2$ (Fig. 2F), SpO_2 (Fig. 2G), and body temperature (Fig. 2H) remained within normal ranges. Significant differences were observed in RR (Fig. 2E), $ETCO_2$ (Fig. 2F), and SpO_2 (Fig. 2G) among treatment groups ($P<0.05$), while no notable differences were noted for time or interaction effects. Body temperature decreased significantly over time ($P<0.001$; Fig. 2H), but no notable differences were observed between treatment groups or their interactions. Throughout the monitoring period, no adverse reactions such as hypoxia, bradycardia, or hypotension were observed in the young group.

Anesthesia time, induction, intubation and recovery quality in adult dogs: All 12 adult dogs successfully completed this part of the experiment and exhibited smooth recovery without any adverse reaction. Table 3 summarizes the time from induction to intubation, maintenance duration, induction quality, intubation score, recovery quality, degree of ataxia, and PPF usage across treatment groups. In the DZ-A and BMP-A groups, statistically non-significant variations were detected in body weight, age, time from induction to intubation, and ataxia. The DZ-A group showed significantly better induction quality, recovery quality, and intubation scores compared to the BMP-A group ($P<0.05$). Furthermore, the DZ-A group exhibited a significantly longer duration of

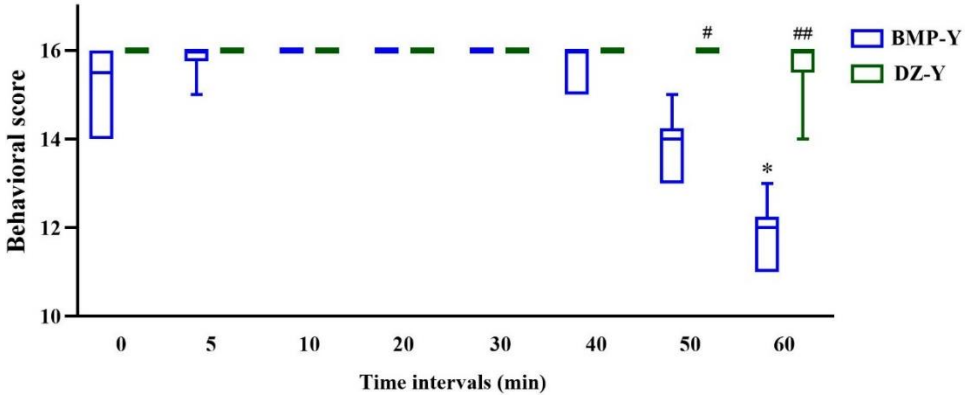

Fig. 1: The anesthesia scores of the combination of BMP or DZ young dogs. Data are presented as medians (min-max) (n=6). A significant difference compared to the baseline within the same group is indicated by *($P<0.05$). Significant differences between treatment groups are denoted by #($P<0.05$) and ##($P<0.01$).

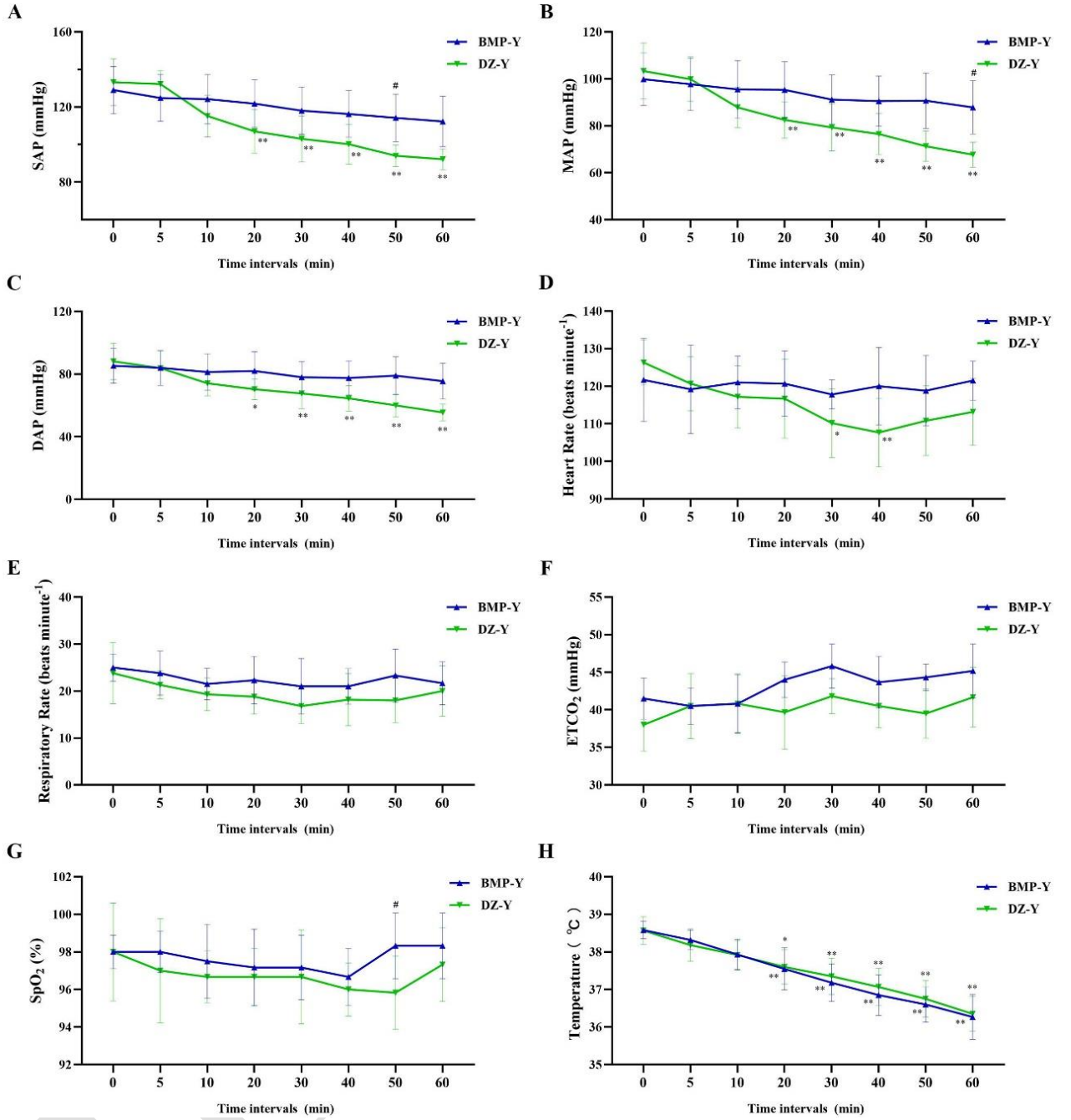

Fig. 2: Cardiopulmonary parameter of the combination of BMP or DZ young dogs. (A) SAP, (B) MAP, (C) DAP, (D) HR, (E) RR, and (F) $ETCO_2$ (G) SPO_2, and (H) BT. A significant difference compared to the baseline within the same group is indicated by *(P<0.05) and **(P<0.01). Significant differences between treatment groups are de-noted by #(P<0.05).

anesthesia and time from sternal recumbency to standing compared to the BMP-A group (P<0.05), while the BMP-A group had a higher PPF usage than the DZ-A group (P<0.001).

Anesthesia scoring and general physiological indicators in adult dogs: As shown in Fig. 3, the DZ-A group demonstrated markedly elevated anesthesia scores in comparison to the BMP-A group (P=0.045). In the BMP-A group, the anesthesia scores from 10 to 40 minutes were significantly higher compared to baseline value (P<0.05).

The physiological parameter monitoring results for the adult group are presented in Fig. 4. Statistically non-significant differences were observed in SAP (Fig. 4A), MAP (Fig.4B), and DAP (Fig. 4C) with respect to time, treatment group, or their interaction. All NIBP measurements stayed within the normal range and exhibited minimal fluctuations. Significant differences in HR were noted between treatment groups, with values for DZ-A being lower than those of BMP-A (P<0.05; Fig. 4D). However, no significant changes were observed over time or in the interaction between time and treatment groups.

RR, $ETCO_2$, SpO_2, and body temperature remained within the normal range in both the BMP-A and DZ-A groups. Marked variations in RR (Fig. 4E) and $ETCO_2$ (Fig. 4F) were detected across the treatment groups (P<0.05), but no difference was found with respect to time or the interaction between time and treatment groups.

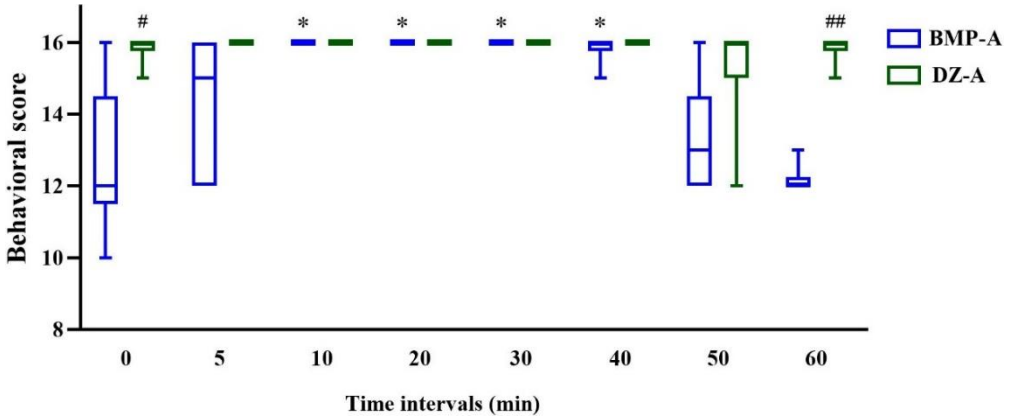

Fig. 3: The anesthesia scores of the combination of BMP or DZ adult dogs. A significant difference compared to the baseline within the same group is indicated by *(P<0.05). Significant differences between treatment groups are de-noted by #(P<0.05) and ##(P<0.01).

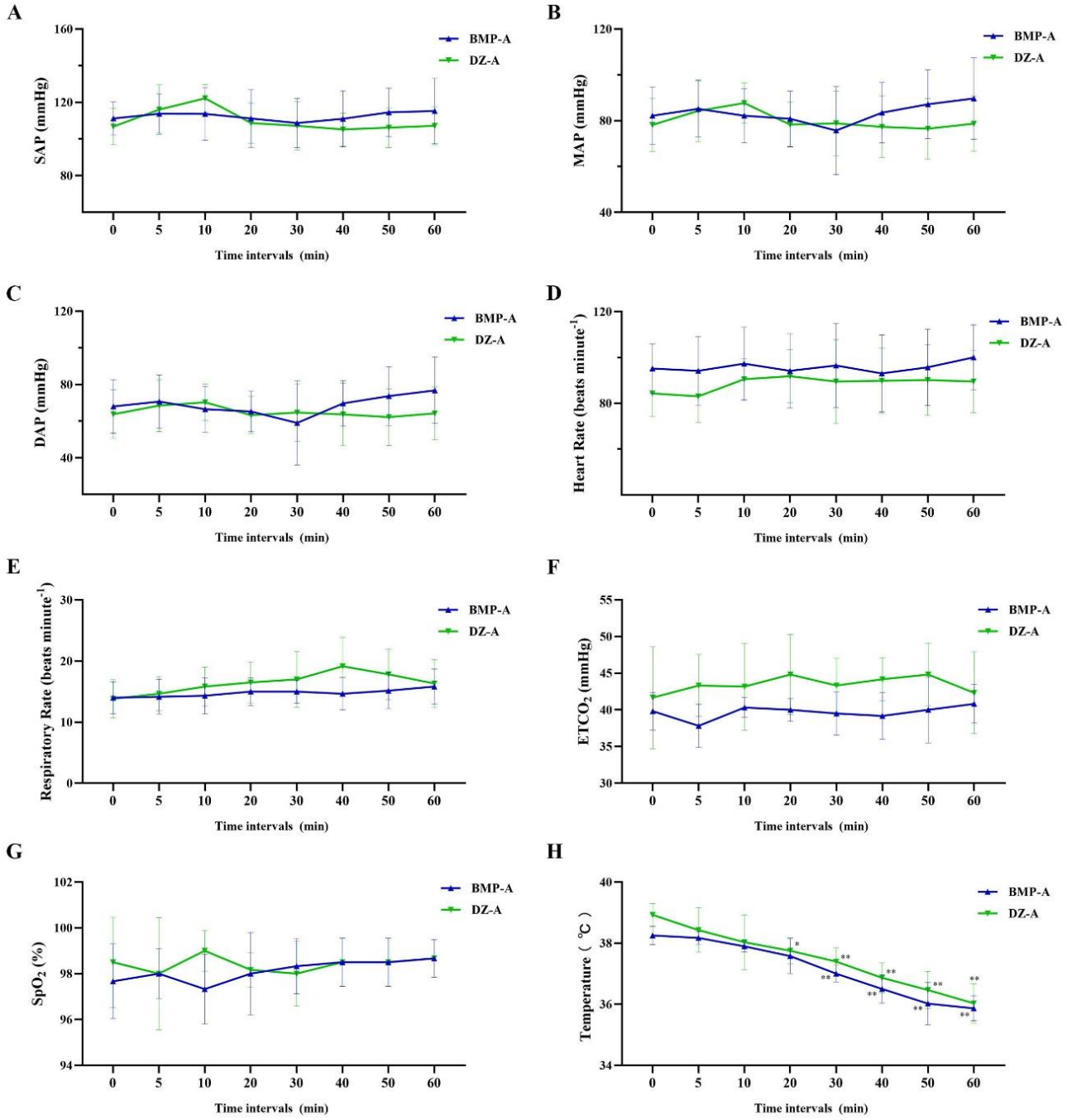

Fig. 4: Cardiopulmonary parameter of the combination of BMP or DZ adult dogs. (A) SAP, (B) MAP, (C) DAP, (D) HR, (E) RR, and (F) $ETCO_2$ (G) SPO_2, and (H) BT. A significant difference compared to the baseline within the same group is indicated by *(P<0.05) and **(P<0.01). Significant differences between treatment groups are de-noted by #(P<0.05) and ##(P<0.01).

There was no difference in the SpO_2 values between the two groups, over time, or in their interaction (Fig. 4G). Body temperature decreased significantly across different treatment groups and over time (Fig. 4H; $P<0.05$).

The impact of BMP and DZ combination on hepatic and renal functions in young and adult animals: As presented in Table 4, in the BMP-A, DZ-A, BMP-Y, and DZ-Y groups, the concentrations of ALT, AST, ALP, BUN, and CRE at 30 min and 60 min did not exhibit statistically significant differences compared with those before drug treatment (0 min). At each corresponding time point (0 min, 30 min, and 60 min), no statistically significant differences were observed in the levels of ALT, AST, ALP, BUN, and CRE between BMP-A and DZ-A groups or between BMP-Y and DZ-Y groups.

Table 4: Plasma indicators of liver and kidney functions in dogs of four groups at different time periods

Variables	Groups	0 min	30 min	60min
ALT	BMP-A	25.17±10.98	23.17±8.44	25.17±9.78
	DZ-A	25.17±8.45	20.00±8.66	24.67±8.42
	BMP-Y	11.50±3.89	10.83±4.17	12.67±3.67
	DZ-Y	15.17±3.19	13.00±2.53	14.83±2.93
AST	BMP-A	27.33±10.76	27.17±14.54	24.50±4.64
	DZ-A	28.83±13.98	24.50±7.48	28.67±11.13
	BMP-Y	26.00±8.02	23.33±8.31	28.33±5.43
	DZ-Y	25.00±5.06	23.50±6.80	26.50±7.09
ALP	BMP-A	31.67±12.03	25.33±7.84	31.00±10.26
	DZ-A	30.50±14.71	28.33±13.98	29.00±13.39
	BMP-Y	138.17±55.08	122.50±52.18	137.83±55.05
	DZ-Y	125.33±71.66	111.67±61.11	126.83±80.09
BUN	BMP-A	3.43±1.47	3.40±1.35	3.58±1.09
	DZ-A	3.80±1.15	3.50±1.20	3.43±1.32
	BMP-Y	2.80±1.14	2.92±1.17	2.95±1.13
	DZ-Y	2.73±1.65	2.77±1.55	2.98±1.06
CRE	BMP-A	49.48±8.62	46.07±7.92	49.18±8.11
	DZ-A	30.08±1.89	27.73±1.99	29.18±1.83
	BMP-Y	24.15±3.15	24.65±2.78	25.62±2.74
	DZ-Y	25.10±3.93	22.88±2.87	24.25±1.46

Values are presented as mean±SD. Statistically, differences in all parameters among four treatment groups and three time periods were non-significant.

DISCUSSION

In the present study, DZ and BMP protocols were applied to induce anesthesia in young and adult dogs, while isoflurane was used to maintain the anesthetic effects. The primary objective was to systematically assess the efficacy and safety of the two distinct induction methods in both young and adult dogs, thereby providing valuable reference data for veterinarians to optimize clinical decision-making regarding age-appropriate anesthesia induction protocols.

All dogs enrolled in the study successfully completed the procedures and exhibited no adverse reactions throughout the study period. Moderate anesthesia in dogs is characterized by an anesthesia total score exceeding 11 (Lu *et al.*, 2011; Diao *et al.*, 2017). We observed that in young dogs, the combination of DZ and BMP with isoflurane maintenance anesthesia provided moderate anesthesia effects, lasting approximately for 50 minutes and 60 minutes, respectively. In adult dogs, the same combinations resulted in moderate anesthesia effects lasting approximately for 55 minutes and 60 minutes, respectively. Overall, the use of the DZ protocol for induction of anesthesia yielded higher anesthesia scores and better results compared to BMP protocol. Conversely, the BMP protocol demonstrated a progressive reduction in anesthesia scores compared to the DZ protocol during the 40- to 60-minute time period.

Analysis of the anesthesia time for the two protocols demonstrated that, in both young and adult dogs, there was no difference in the time from induction-to-intubation between the BMP and DZ protocols. Nevertheless, regarding anesthesia duration and the time from sternal recumbency to standing, the DZ-A group exhibited significantly longer durations compared to the BMP-A group ($P<0.05$). A similar trend was seen for the two time periods (anesthesia duration and time from sternal recumbency to standing) for young dogs. In terms of induction and recovery quality, the DZ protocol outperformed the BMP procedure in both adult and young dogs. The intubation scores demonstrated that both adult and young dogs exhibited greater intubation difficulty with the BMP protocol compared to the DZ protocol. The PPF usage was significantly higher in BMP than DZ group in both young and adult dogs ($P<0.05$). The potential cause of this outcome could be attributed to the fact that dexmedetomidine exhibits a more potent sedative effect compared to midazolam (Jafarbeglou *et al.*, 2024; Lehmann *et al.*, 2025). Additionally, tiletamine-zolazepam, as a dissociative anesthetic, provides a longer duration of anesthesia, whereas butorphanol serves only as an analgesic with mild anesthetic properties (Krimins *et al.*, 2012). Consequently, the DZ protocol demonstrated a more effective induction effect than the BMP protocol, which required a higher dose of propofol to achieve adequate induction anesthesia.

Blood pressure (BP) serves as a critical indicator reflecting cardiac afterload, myocardial oxygen consumption and workload, as well as peripheral circulation in animals (da Cunha *et al.*, 2017; Mahadappa *et al.*, 2024). In adult dogs, both the DZ and BMP protocols exhibited minimal effects on NIBP (SAP, MAP, and DAP), with similar trends of change observed in both groups (all values remained within the normal range). During the early phase of anesthesia, the DZ-A group exhibited a transient increase in NIBP, likely attributable to the administration of dexmedetomidine (Alvaides *et al.*, 2008; Weerink *et al.*, 2017). Previous research in cats has indicated that the combination of dexmedetomidine and isoflurane induces an initial rise in mean arterial pressure, followed by compensatory reduction (Siao *et al.*, 2017). In young dogs, the BMP protocol had negligible effects on NIBP, whereas the DZ protocol resulted in a gradual decline in NIBP (with an average decrease of 25-30%), though all data remained within the normal range of 90-160mmHg for SAP, 50-100mmHg for DAP, and 60-100mmHg for MAP. Collectively, these findings suggest that the DZ protocol had a relatively higher influence on NIBP in young dogs than the BMP protocol.

HR reflects the frequency of cardiac contractions and is influenced by age, gender, and other physiological factors. Dexmedetomidine reduces heart rate through activation of presynaptic receptors at peripheral nerve endings, suppression of norepinephrine release, and inhibition of sympathetic nervous system activity in the central nervous system (Bhana *et al.*, 2000; Kang *et al.*, 2019). The extent of HR reduction correlates with age,

exhibiting a faster decrease in young dogs. Our findings indicate that the BMP protocol had minimal influence on HR in adult dogs, while the HR of the DZ-A group was notably lower than that of the BMP-A group, initially decreasing before gradually recovering. Equally, the BMP protocol had little effect on HR in young dogs, whereas the HR of the DZ-Y group initially decreased (by 10-20 beats per minute, 0-40 min) and subsequently increased (40- 60 min). All treatment groups maintained HR values within the normal range (60-160 beats min^{-1}). According to Kellihan *et al.* (2015), comprehensive evaluation suggests that the BMP protocol exerts a lesser impact on heart rate; however, caution should be exercised when using DZ in animals with cardiovascular diseases or undergoing cardiovascular screening.

The SpO_2, and RR, of the four treatment groups were consistently maintained within normal physiological ranges with minimal fluctuations (SpO_2: 94%-100%, RR: 15-30 beats minute $^{-1}$). For BT, a gradual decline was observed as the duration of anesthesia increased (Kim *et al.*, 2022). In this study, all four treatment groups exhibited a consistent downward trend in BT over time; however, the values remained consistently within the normal range (36-39°C), and no instances of hypothermia were recorded. In terms of ETCO2, the DZ-A group exhibited significantly higher levels compared to the BMP-A group. Notably, all values in the adult and young group were well-maintained within the normal range (35-55 mmHg). Based on these findings, it can be concluded that the DZ and BMP protocols exert relatively minor effects on SpO_2, $ETCO_2$, RR, and BT in both young and adult dogs.

The liver is a vital metabolic organ that plays a major role in the metabolism and excretion of various substances. ALT, AST, and ALP serve as critical indicators of hepatic function. ALT levels increase in the bloodstream upon hepatocellular damage, while AST concentrations reflect the overall health of the liver. ALP facilitates the transport of substances across cell membranes (Giannini *et al.*, 2005; Mousavi *et al.*, 2021; Mousavi *et al.*, 2022). The kidneys are essential for drug clearance. BUN and CRE levels are key markers for evaluating renal function, which may elevate in cases of renal impairment, potentially leading to toxic effects (Shi *et al.*, 2024). In this study, we observed that the liver (ALT, AST, ALP) and kidney (BUN, CRE) function indicators in the four groups showed non-significant variations related to baseline levels prior to and 30 and 60 minutes after drug administration. These findings suggest that neither the BMP nor the DZ induction protocols had a substantial effect on the hepatic and renal function indicators in adult and young dogs.

Conclusions: Overall, for young dogs, both the BMP and DZ induction protocols represent viable options. The BMP protocol has a lesser impact on HR and NIBP in puppies, whereas the DZ protocol eliminates the need for additional propofol treatment and is associated with better induction and recovery quality, as well as smoother intubation. For adult dogs, the DZ induction protocol exhibits excellent stability, delivers high-quality induction effects, and enhances the smoothness of tracheal intubation.

Authors' contributions: HB, RL, ZZ and SD contributed to the methodology, investigation, and data curation; HB and ZZ were responsible for project administration, conceptualization, supervision and funding acquisition; ZZ, HB, RG and TM conducted formal analysis and software validation; HB and ZZ prepared the original draft, while HB, SD, RG and ZZ carried out review and editing of the manuscript. All authors have reviewed and endorsed the final version of the manuscript.

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