Open Veterinary Journal, (2021), Vol. 11(4): 603–612
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)
Original Research
DOI: 10.5455/OVJ.2021.v11.i4.10

Submitted: 06/06/2021 Accepted: 18/10/2021 Published: 06/11/2021

Branham sign in dogs undergoing interventional patent ductus arteriosus occlusion or surgical ligation: A retrospective study

Filipe L. Madruga[1*], Yolanda Martinez Pereira[2], Ambra Panti[3], Ian Handel[2] and Geoff Culshaw[2]

[1]*Small Animal Teaching Hospital, University of Liverpool, Leahurst Campus, Chester High Road, Neston, Wirral, CH64 7TE, UK*
[2]*The Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush Campus, Roslin, EH25 9RG, UK*
[3]*Veterinary Specialists Scotland, Department of Veterinary Anaesthesia and Analgesia, 1 Deer Park Road, Livingston, EH54 8AG, UK*

Abstract

Background: The Branham sign is a baroreceptor response that follows patent ductus arteriosus (PDA) closure. Although described in dogs following both interventional and surgical ductal closure, a direct comparison of the Branham sign elicited by these two techniques has not been made.

Aim: Since closure with an Amplatz canine ductal occluder (ACDO) occurs over 10 minutes and surgical ligation (SL) is more rapid, we hypothesized that the Branham sign following occlusion of a PDA with an ACDO would be less severe than following SL.

Methods: Clinical records of dogs diagnosed with left-to-right shunting PDA between 2008 and 2018 were retrospectively reviewed. Of 139 dogs undergoing PDA occlusion, only 41 dogs (ACDO $n = 32$, SL $n = 9$) were included after applying exclusion criteria. Heart rate (HR) and blood pressure (BP) from occlusion time (T_0) until 30 minutes post occlusion (T_{30}) were recorded. Signalment and anesthetic protocol were also recorded. The influence of age and weight on the hemodynamic variations was assessed. Hemodynamic variables and calculations were compared between and within groups using a repeated measures general linear model, and *post hoc* tests were applied if significance was identified.

Results: A mild Branham sign was present in both groups, and hemodynamic changes were not significantly different between groups. In both groups, there was a significant decrease in HR (11 bpm, 5.3–16.3; $p < 0.001$) (10.4%, 5.4–15.5; $p < 0.001$) and increase in diastolic BP (9.5 mmHg, 3–16; $p = 0.002$) (23.5%, 7.1–39.9; $p = 0.002$), but systolic BP did not change significantly ($p = 0.824$). Age and weight did not influence Branham sign.

Conclusion: The Branham sign in dogs is mild in both groups, lasts for at least 30 minutes, and is independent of the method of PDA closure.

Keywords: ACDO, Branham sign, Dog, Ligation, PDA.

Introduction

Patent ductus arteriosus (PDA) is a vascular connection between the ascending aorta and the pulmonary trunk that abnormally persists after birth. It is a common congenital heart abnormality in dogs and leads to left-sided congestive heart failure at a young age (Buchanan, 2001).

Management options for PDA include surgical ligation (SL) via left fourth intercostal thoracotomy and transvascular occlusion. Surgical techniques include standard ligation, Jackson-Henderson technique, or hemostatic clips. Transvascular occlusion is by embolization coils, Amplatzer vascular plug 2 or, most frequently, Amplatz canine duct occluder (ACDO) (Ranganathan *et al.*, 2018; Scansen, 2018; Wagner, 2019). The overall rate of successful occlusion is reported to be similar between methods, 95% for SL and 94% for ACDO (Blossom *et al.*, 2010), but the less invasive nature of transvascular occlusion and the lower incidence of morbidity (7.1% *vs.* up to 28% with SL) (Ranganathan *et al.*, 2018), mean that transvascular methods are frequently undertaken.

Rapid closure of a PDA leads to profound and abrupt alterations to cardiac and vascular hemodynamics. These include an acute increase in mean blood pressure (BP) from volume overload in the presence of a closed ductus, which in turn stimulates the baroreceptors, leading to a reflex bradycardia (Wattanasirichaigoon and Pomposelli, 1997; Velez-Roa *et al.*, 2004). This cardiovascular response is known as the Branham or Nicoladoni sign (Wattanasirichaigoon and Pomposelli, 1997). These events can be tracked closely by direct BP measurement and heart rate (HR) monitoring, and can be severe enough to require medical intervention (Pascoe, 2016).

Recent publications have demonstrated the Branham sign in dogs following transvascular occlusion

***Corresponding Author:** Filipe L. Madruga. Small Animal Teaching Hospital, University of Liverpool. Leahurst Campus, Chester High Road, Neston, Wirral, CH64 7TE, UK. Tel: +44 (0)151 795 6100. Email: *f.lalanda-madruga@liverpool.ac.uk*

(De Monte *et al.*, 2017; Parisi *et al.*, 2020) but a direct comparison of BP and HR changes between surgical and non-surgical methods has not been made. Since closure of the ductus with a device takes several minutes longer than by SL (Stanley *et al.*, 2003; Porciello *et al.*, 2014), we hypothesized that the Branham sign following ACDO is less severe than following SL. This is of clinical relevance as a milder Branham sign would mean a reduced likelihood of clinical intervention following use of an ACDO, namely the use of muscarinic anticholinergics, though its use is usually unnecessary, unless bradycardia becomes hemodynamically significant (Robinson and Borgeat, 2016). It could also provide additional support for the use of newer generation transvascular devices in dogs for whom, thus far, surgery has been the only option, such as very small dogs.

Material and Methods

Computerized records of dogs referred to our institution between January 2008 and January 2018 were reviewed. Dogs diagnosed with left-to-right shunting PDA were identified.

Inclusion criteria were, closure of PDA with an ACDO (Infiniti Medical, Palo Alto, California) or by SL, complete general anesthesia record, recording of occlusion time, and HR/BP data available up to 30 minutes post occlusion. Exclusion criteria were absence of occlusion time identification (T_0) and administration of an anticholinergic, opioid or positive inotrope <20 minutes prior to occlusion, or <30 minutes after occlusion, a change in the rate of administration of an infusion between those time points and monitoring of BP by non-invasive methods and use of anticoagulants (other than heparin saline for equipment flushing).

Collected data included age, sex, weight, breed, PDA occlusion technique, perioperative anesthetic drugs, type of ventilation (spontaneous or mechanical), artery cannulated, and end tidal carbon dioxide ($ETCO_2$), anesthetic agents and body temperature at T_0. HR (beats per minute, bpm) and BP (systolic and diastolic BP, mmHg) were collected at 5-minute intervals after T_0 to 30 minutes post occlusion (T_{30}). The percentage (%) of variation in HR and BP from T_0, rate of change compared to previous time point (mmHg/minute) and rate of % change (%/minute) compared to previous time point were all calculated (Table 1).

All interventional and surgical procedures were undertaken by a European College of Veterinary Internal Medicine (ECVIM) or European College of Veterinary Surgery/ Royal College of Veterinary Surgeons (ECVS/ RCVS) Diplomate or supervised enrolled resident, and anesthesia was performed by a supervised European College of Veterinary Anaesthesia and Analgesia (ECVAA)-enrolled resident, or ECVAA Diplomate. HR was monitored with a three-lead electrocardiogram. BP was monitored with an arterial cannula placed in a peripheral artery (metatarsal or auricular), through a multiparametric monitor (Datex Ohmeda S/5 Monitor ®, General Electric Healthcare, Chalfont St Giles, United Kingdom). The transducer used in monitoring invasive BP was zeroed to atmospheric pressure prior to its use and positioned at the level of the right atrium.

Statistical analysis

Continuous variables and residuals from multiple comparison tests were tested for normality (Shapiro-Wilk test). Single comparisons (age and weight) were made between ACDO and SL groups with paired *t*-test for parametric data or Mann–Whitney *U* tests for nonparametric data. Gender differences were determined with Fisher's exact test.

Hemodynamic variables and calculations were compared between and within groups using a repeated measures general linear model with procedure type (ACDO or SL) and time-point post occlusion (T_0–T_{30}) as fixed factors, patient case number as a random factor nested within procedure type, and age and weight as co-variates. Interaction between procedure type and time-points was also assessed. Where significance was identified, Dunnett's (compared to T_0) or Tukey's (compared to previous time point) *post hoc* tests were applied as appropriate.

Due to the retrospective nature of this study and the limitations inherent to a retrospective power calculation (Zhang *et al.*, 2019), a prospective two-sample *t*-test power calculation was favored. We predicted that the maximum reduction in HR in SL dogs would be 10 beats/minute more than in ACDO dogs, suggesting that sample sizes of 6 dogs per group would achieve 80% power.

For all tests, significance was set at $p < 0.05$. Results are expressed as mean ± standard deviation for parametric data or median ± range for nonparametric data.

Ethical approval

Table 1. Hemodynamic parameters calculated for HR and BP variation, including units. T_{x-5} represents the value of HR or BP of a specific time point. T_0 represents the value of HR or BP at occlusion time. represents the value of HR or BP of the previous time point. Rate of change T_x represents the calculated rate of change of HR or BP for a specific time point.

Parameter	Formula	units
% change	T_x/T_0	%
Rate of change	$[T_x–T_{(x–5)}]/5$	mmHg or bpm/minute
Rate of % change	[Rate of change at $T_x/T_{(x–5)}$] × 100	%/minute

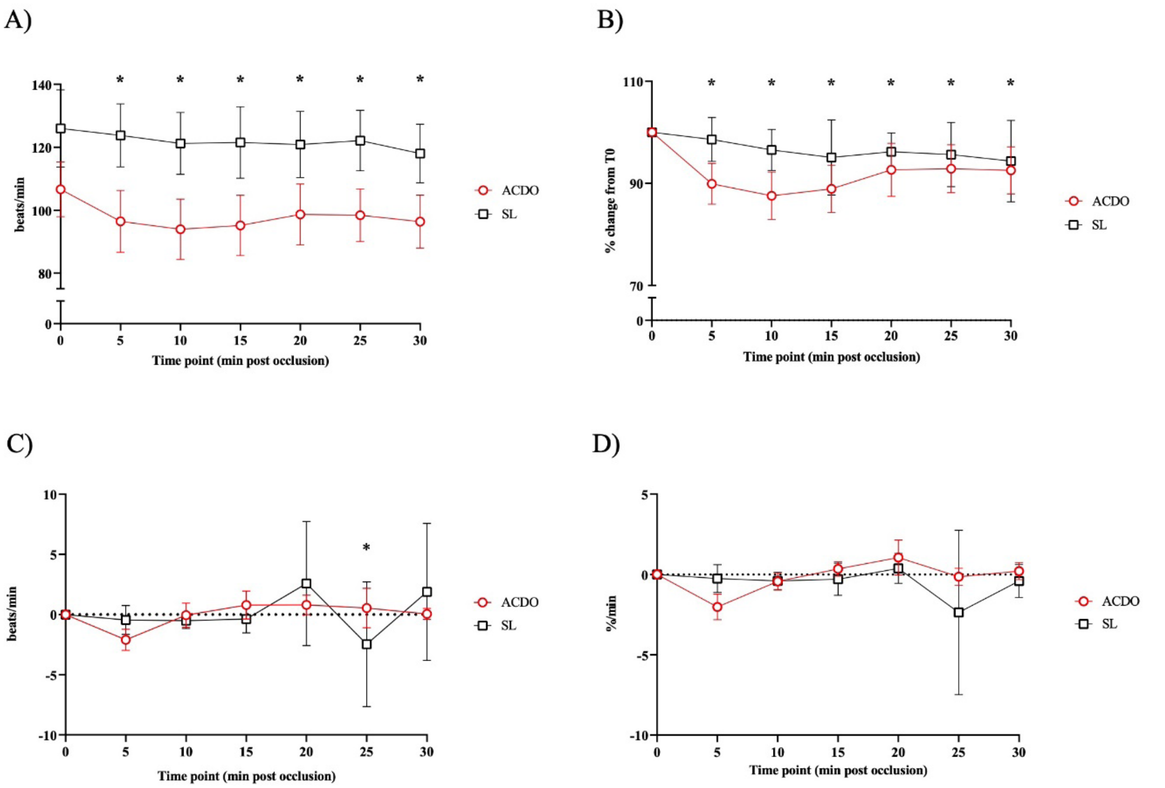

Fig. 1. Changes in HR of dogs undergoing PDA closure with SL or ACDO: (A): variation from T_0; (B): percentage of change from T_0; (C): rate of change; (D): rate of percentage of change.
ACDO–Amplatz canine duct occluder group; min–minutes; SL–Surgical ligation group.
Asterisks (*) indicate significance ($p < 0.05$) to T_0 (graphs A and B), or to previous time point (graphs C and D) in both groups combined.

This project was approved by a local veterinary ethical review committee (VERC reference 25.21).

Results

Of the 139 dogs undergoing PDA occlusion, only 41 dogs (ACDO $n = 32$, SL $n = 9$; Table 2) were included.

The median age of all the dogs was 6 months (range 2–84), with a median weight of 10.5 kg (range 3.2–43.5). Dogs in the ACDO group were older (median 8 months, range 2–84) than dogs in the SL group (median 2 months, range 2–11) ($p = 0.001$), and heavier (median 11.2 kg, range 3.65–43.45) than SL dogs (median 5.3 kg, range 3.2–27) ($p = 0.001$).

Most dogs were female (21/32 ACDO, 7/9 SL) in both groups ($p = 0.48$).

Various breeds were represented, but the German Shepherd Dog (GSD) was the most common breed in both groups (9/32 ACDO, 3/9 SL; Table 2).

Pethidine was the most used opioid in premedication in both groups (31/32 ACDO, 6/9 SL), whilst acepromazine was the most used sedative (12/32 ACDO, 2/9 SL). Propofol was the induction agent of choice (22/32 ACDO, 7/9 SL), and sevoflurane was favored to maintain anesthesia (20/32 ACDO, 6/9 SL). For intraoperative analgesia, the commonest opioid administered to ACDO dogs was methadone ($n = 11/32$), whereas fentanyl (5–10 mg/kg/minute, mcg kg^{-1} $minute^{-1}$) was preferred for SL ($n = 5/9$). Other opioids that were used are listed in Table 2. Adjunctive analgesia was provided by continuous infusion of lidocaine (10–40 mcg kg^{-1} $minute^{-1}$) in 6/32 ACDO dogs, whereas a continuous infusion of ketamine (5–10 mcg kg^{-1} $minute^{-1}$) fulfilled this role in 3/9 SL dogs.

Invasive BP monitoring was mainly via dorsal metatarsal artery (17/32 ACDO dogs, 5/9 SL dogs), with the auricular artery being the second most used site (5/32 ACDO dogs, none in SL dogs).

Only 7/35 ACDO dogs were mechanically ventilated compared to all the SL dogs.

There was no difference in mean body temperature between groups at T_0 (37.4°C ± 0.8°C; $p = 0.619$). Similarly, T_0 values of mean end tidal of isoflurane (ACDO 1.56% ± 0.27%, SL 1.6% ± 0.16%; $p = 0.984$), mean end tidal of sevoflurane (ACDO 2.44% ± 0.33%, SL 2.5% ± 0.52%; $p = 0.206$), and median $ETCO_2$ (ACDO 47 mmHg, 39–67, SL 54 mmHg, 35–81; $p = 0.133$) were also not significantly different between groups.

Table 2. Population description ($n = 41$).

Case	Breed	Gender	Age (months)	Weight (kg)	Opioid	Sedative	Induction	Co-Induction	Inhalant	Analgesia 1	Analgesia 2
ACDO 1	GSD	F	36	29.4	Pethidine	Acepromazine	Propofol		Isoflurane	Morphine	Fentanyl bolus
ACDO 2	English Springer Spaniel	F	4	8.6	Pethidine	Acepromazine	Propofol		Isoflurane	Buprenorphine	
ACDO 3	Weimaraner	M	48	33.8	Pethidine		Propofol		Isoflurane	Methadone	Fentanyl bolus
ACDO 4	Collie Cross	NF	72	16.8	Pethidine	Acepromazine	Propofol	Fentanyl	Isoflurane	Methadone	
ACDO 5	GSD	F	60	33.1	Pethidine	Midazolam	Propofol	Midazolam	Isoflurane	Buprenorphine	
ACDO 6	GSD	M	5	10.7	Pethidine	Acepromazine	Propofol		Sevoflurane	Pethidine	
ACDO 7	Labradoodle	F	4.5	10.9	Pethidine	Acepromazine	Alfaxalone		Sevoflurane		
ACDO 8	Newfoundland	F	54	43.45	Pethidine	Midazolam	Propofol	Fentanyl	Sevoflurane		
ACDO 9	Cocker Spaniel	M	5	8.8	Pethidine		Propofol	Midazolam	Sevoflurane	Buprenorphine	
ACDO 10	Cocker Spaniel	F	6	7.4	Pethidine		Propofol	Midazolam	Sevoflurane	Buprenorphine	
ACDO 11	Corgi	M	10	13.85	Pethidine		Propofol		Sevoflurane	Buprenorphine	
ACDO 12	GSD	F	48	28.6	Pethidine		Propofol		Sevoflurane	Methadone	
ACDO 13	Border Collie	F	9	10.5	Pethidine		Propofol		Sevoflurane	Methadone	
ACDO 14	Newfoundland	F	5	31.8	Pethidine		Propofol		Sevoflurane	Methadone	
ACDO 15	Cavalier King Charles Spaniel	F	7	6.5	Pethidine		Propofol		Sevoflurane	Fentanyl infusion	Lidocaine infusion
ACDO 16	Labradoodle	M	3	11.25	Pethidine		Propofol		Isoflurane	Methadone	
ACDO 17	GSD	M	2	11.65	Pethidine		propofol		Sevoflurane	Methadone	
ACDO 18	Cockerpoo	F	5	3.65	Pethidine	Acepromazine	Alfaxalone	Midazolam	Sevoflurane	Methadone	
ACDO 19	Border Collie	M	3	6.2	Pethidine		Ketamine	Midazolam	Sevoflurane	Alfentanil infusion	Lidocaine infusion
ACDO 20	GSD	NF	24	32	Pethidine		Propofol	Midazolam	Sevoflurane	Fentanyl infusion	
ACDO 21	Border Collie	NF	8	14.5	Pethidine	Acepromazine	Propofol	Midazolam	Sevoflurane	Methadone	
ACDO 22	GSD	F	60	15	Pethidine	Acepromazine	Propofol	Midazolam	Sevoflurane	Pethidine	Methadone
ACDO 23	Cocker Spaniel	F	4	4.9	Pethidine		Propofol	Midazolam	Sevoflurane	Lidocaine infusion	
ACDO 24	Border Collie	F	10	10.25	Pethidine		Alfaxalone	Midazolam + Ketamine	Isoflurane	Pethidine	Fentanyl bolus

(Continue)

ACDO 25	Flat Coated Retriever	F	3	6.9	Pethidine		Alfaxalone	Midazolam	Isoflurane	Methadone	Lidocaine infusion
ACDO 26	GSD	M	43	36.15	Pethidine	Acepromazine	Alfaxalone	Midazolam	Sevoflurane	Fentanyl infusion	Lidocaine infusion
ACDO 27	Cross Breed	NF	84	8	Pethidine	Acepromazine	Alfaxalone	Midazolam	Isoflurane	Fentanyl infusion	
ACDO 28	Terrier Cross	F	30	11.2	Pethidine		Alfaxalone	Midazolam	Sevoflurane	Fentanyl infusion	Lidocaine infusion
ACDO 29	GSD	F	8	29.3	Pethidine	Acepromazine	Alfaxalone	Midazolam	Sevoflurane	Fentanyl infusion	Lidocaine infusion
ACDO 30	Cockerpoo	M	4	3.95	Pethidine		Propofol	Midazolam	Isoflurane	Pethidine	
ACDO 31	Doberman Pinscher	M	8	30.1	Buprenorphine	Acepromazine	Alfaxalone	Midazolam	Isoflurane	Buprenorphine	
ACDO 32	Cavalier King Charles Spaniel	M	12	9.95	Pethidine		Propofol		Isoflurane	Methadone	
SL 1	Cocker Spaniel	F	2	3.15	Pethidine		Propofol		Isoflurane	Methadone	
SL 2	West Highland White Terrier	M	4	5.3	Pethidine		Alfaxalone		Sevoflurane	Pethidine	Morphine bolus Fentanyl infusion
SL 3	GSD	F	2	10	Pethidine		Alfaxalone		Sevoflurane	Morphine	
SL 4	Shetland Sheepdog	F	3	3.25	Methadone	Acepromazine	Propofol	Midazolam	Sevoflurane	Fentanyl infusion	Ketamine infusion
SL 5	Border Collie	F	2	5.38	Pethidine		Propofol	Midazolam	Sevoflurane	Pethidine	Methadone
SL 6	GSD	F	2	5.5	Methadone		Propofol	Midazolam	Sevoflurane	Fentanyl infusion	
SL 7	Cocker Spaniel	M	2	3.75	Pethidine		Propofol		Sevoflurane	Fentanyl infusion	Ketamine infusion
SL 8	GSD	F	11	27	Pethidine	Acepromazine	Propofol	Midazolam	Isoflurane	Fentanyl infusion	Ketamine bolus
SL 9	Cross Breed	F	4	3.4	Methadone		Propofol	Midazolam	Isoflurane	Methadone	Ketamine infusion

ACDO–Amplatz canine duct occluder; F–female; GSD–German shepherd dog; M–Male; NF–Neutered female; NM–Neutered male; SL–Surgical ligation.

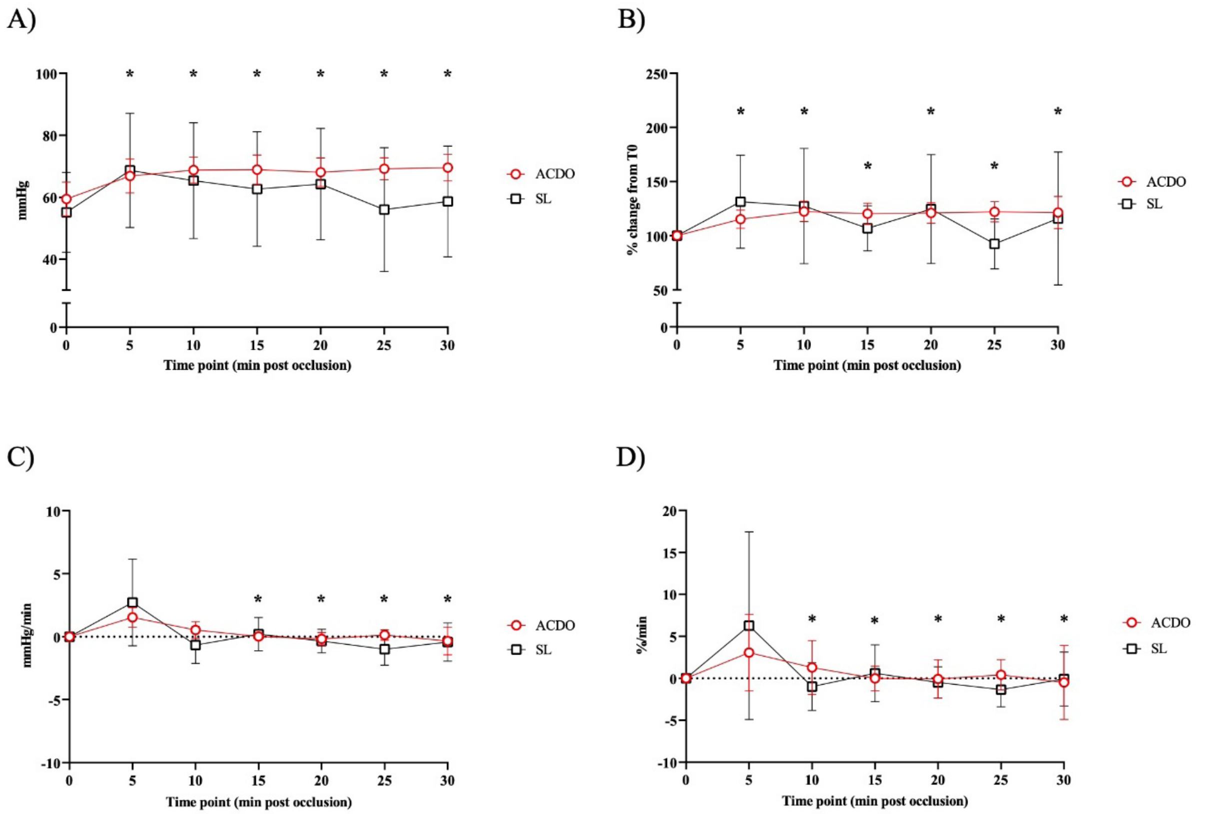

Fig. 2. Changes in diastolic BP of dogs undergoing PDA closure with SL or ACDO: (A): variation from T_0; (B): percentage of change from T_0; (C): rate of change; (D): rate of percentage of change.
ACDO–Amplatz canine duct occluder group; min–minutes; SL–Surgical ligation group.
Asterisks (*) indicate significance ($p < 0.05$) to T_0 (graphs A and B), or to previous time point (graphs C and D) in both groups combined.

Hemodynamic changes

A Branham sign was observed in both groups and, between T_0 and T_{30}, no differences in HR ($p = 0.140$), systolic ($p = 0.184$) or diastolic ($p = 0.568$) BP could be identified between the two groups. As the hemodynamic changes were not significantly different between group ACDO and SL, results are presented for both groups simultaneously and not separately.

HR decreased by 11 bpm (5.3–16.3) by T_{10}, a reduction of 10.4% (5.4–15.5) from T_0, at a rate of 1 bpm (0–3) or 1.2%/minute (0–2.5) ($p < 0.001$) (Fig. 1A–D). From T_{10}, HR increased by 3 bpm (0–5; $p = 0.004$) (2.5%/minute, 0–4.3; $p = 0.002$) until T_{20}, but never reached its initial value (Fig. 1A-D).

By contrast, diastolic BP increased by 9.5 mmHg (3–16) by T_{10}, an increment of 23.5% (7.1–39.9) from baseline, at a rate of 1.5 mmHg/minute (0–3.4) or 3%/minute (0.9–7.6) ($p = 0.002$) (Fig. 2A–D). From T_{15}, diastolic blood pressure (DBP) started to decrease at a rate of 2 mmHg/minute (0–4; $p = 0.009$) or 3.7%/minute (0.9–6.7; $p = 0.009$) until T_{25}, although a very mild increase (4%, 0–8; $p = 0.04$), was noted at T_{30}.

Mild fluctuations in systolic BP after T_0 were not significant ($p = 0.155$) (Fig. 3A–D).

Influence of age and weight on the cardiovascular changes between groups

HR at all time points in both groups combined was not independent of age ($p = 0.040$), but all measures of HR changes were age independent (Table 3). Weight was not associated with any of the hemodynamic changes observed (Table 3).

Discussion

This study illustrates the changes in BP that initiate the Branham sign following PDA occlusion in dogs. It compares the magnitude of the response between surgical and ACDO methods. Our results show that both methods elicit a similarly mild Branham sign that is maximal 10 minutes after ductal occlusion and lasts for at least a further 20 minutes. However, we could not exclude a longer duration as the analyzed period was limited to 30 minutes. It is linked to changes in mean BP that occur as soon as the ductus is occluded and is adequate to prevent an increase in systolic BP but not diastolic BP. It is also independent of age and weight.

Previous studies have described the cardiovascular changes observed following PDA ligation in dogs (Gozalo-Marcilla *et al.*, 2012; Selmic *et al.*, 2013), but in

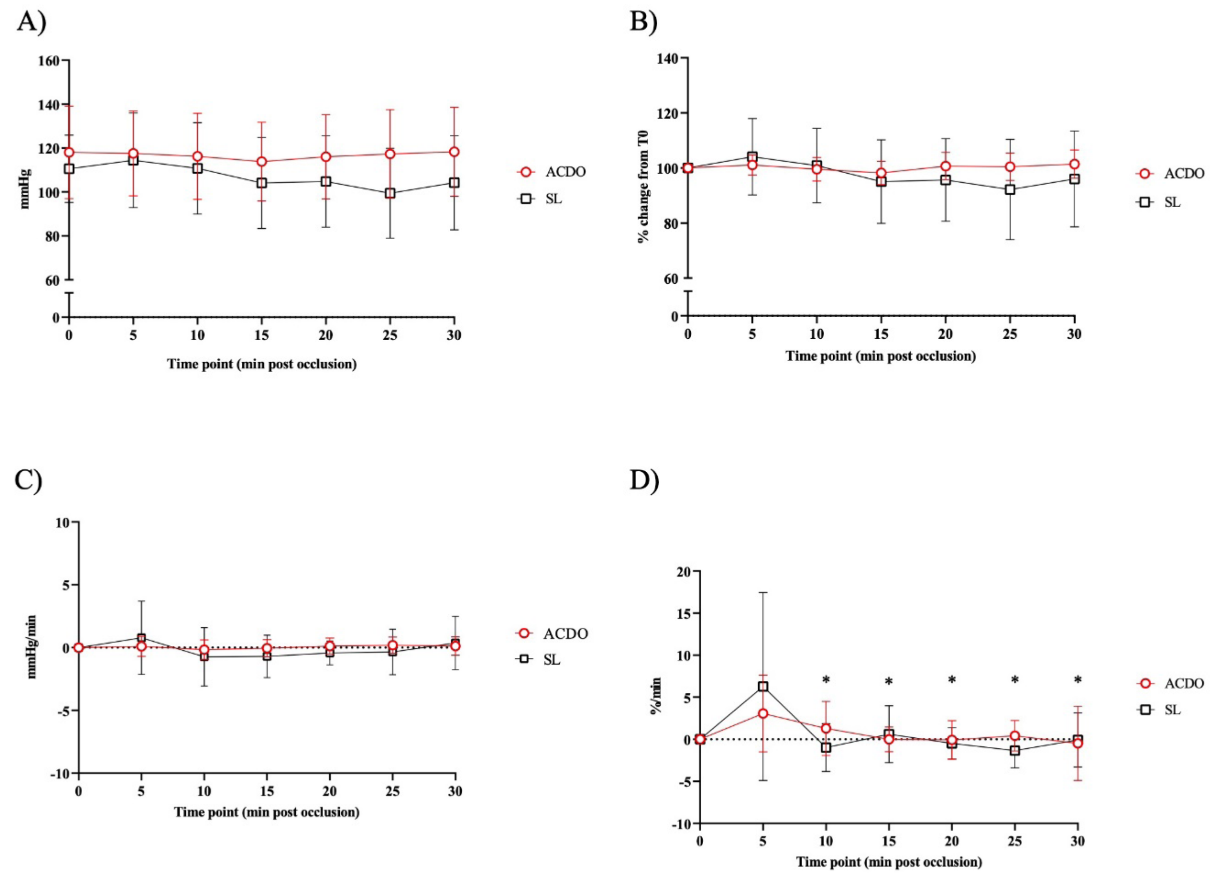

Fig. 3. Changes in systolic BP of dogs undergoing PDA closure with SL or ACDO: (A): variation from T_0; (B): percentage of change from T_0; (C): rate of change; (D): rate of percentage of change.
ACDO–Amplatz canine duct occluder group; min–minutes; SL–Surgical ligation group.
Asterisks (*) indicate significance ($p < 0.05$) to T_0 (graphs A and B), or to previous time point (graphs C and D) in both groups combined.

the two most recent, De Monte *et al.* (2017) identified a significant decrease in HR and increase in DBP similarly to our results, and Parisi *et al.* (2020) only identified a significant increase in DBP. Our study differs in three important ways. First, we included only animals with direct intra-arterial BP measurements, which is the gold-standard for continuous arterial BP measurement and allows quick detection of sudden changes in BP (MacFarlane *et al.*, 2010; Bartels *et al.*, 2016). Although BP readings do vary according to the artery within which BP is being measured (Acierno *et al.*, 2015; da Cunha *et al.*, 2017), this variation is small compared to the well-recognized measurement discrepancies with indirect methods (Seliskar *et al.*, 2013). We believe that our intra-arterial data accurately reflect the systolic and diastolic hemodynamic consequences of PDA occlusion. Second, our data includes measurements up to 30 minutes after PDA occlusion, which is longer than those obtained by Parisi *et al*. (2020). This is important because regulation of BP is dependent on plasma volume as well as sympathetic tone, and profound changes in effective plasma volume occur after ductal occlusion (Epstein *et al.*, 1953). Extending the study window by a period relevant to both methods of ductal occlusion has demonstrated that the Branham sign is maintained for this duration. Furthermore, our data suggest that the reduction in plasma volume required to permit restoration of HR to pre-occlusion levels without a consequent increase in systolic BP has not been achieved by 30 minutes. Characterization of the modification of compensatory renal mechanisms involving renin-angiotensin-aldosterone system and pressure natriuresis would require accurate measurement and collection of urine, which was beyond the remit of this study, though it would be unlikely to observe such changes during the proposed timeframe for this study. Third, our study makes a direct comparison between surgical and non-surgical methods and, contrary to our hypothesis, we were unable to demonstrate different cardiovascular consequences between the groups. We had predicted a greater Branham sign in the surgical dogs, as a consequence of a more rapid occlusion, but this was not apparent, despite adopting several mathematical determinants of magnitude or rate of

Table 3. *p* values for age and weight for both measured and calculated cardiovascular parameters, with significance set at $p < 0.05$.

Factor	Cardiovascular parameter	*p* value
Age	HR	0.040
	DBP	0.777
	SBP	0.170
	% HR	0.320
	% DBP	0.755
	% SBP	0.991
	Rate of change HR	0.887
	Rate of change DBP	0.483
	Rate of change SBP	0.460
	Rate of % change HR	0.955
	Rate of % change DBP	0.652
	Rate of % change SBP	0.847
Weight	HR	0.065
	DBP	0.467
	SBP	0.563
	% HR	0.784
	% DBP	0.563
	% SBP	0.235
	Rate of change HR	0.954
	Rate of change DBP	0.670
	Rate of change SBP	0.517
	Rate of % change HR	0.810
	Rate of % change DBP	0.4
	Rate of % change SBP	0.642

DBP–Diastolic blood pressure; HR–Heart rate; SBP–Systolic blood pressure.

change of HR and diastolic BP. We considered whether this might be a consequence of a particular anesthetic protocol, particularly one incorporating more potent opioids that could have at least partially attenuated the cardiovascular changes that typically follow occlusion of a PDA (Szilagyi, 1987; Shanazari *et al.*, 2011). The range of opioids used tend to decrease HR and BP to a different degree (KuKanich and Wiese, 2015), and although no cardiovascular differences were found between groups, their contribution, although likely to be minimal, cannot be completely ruled out. Similarly, ketamine increases HR and BP (Haskins *et al.*, 1985) but usually only when used at higher doses than those used in our study (Franco *et al.*, 2018), and lidocaine exerts minimal cardiovascular effects (Ortega and Cruz, 2011; Moran-Munoz *et al.*, 2017). Still, the contribution of these adjunctive analgesics to the hemodynamic changes observed cannot be completely excluded.

We also examined $ETCO_2$, temperature and the end tidal of inhalational agents at the time of closure, but these were not different between groups. We conclude that the use of different anesthetic protocols, particularly, the variation in analgesia employed, does not fully explain the mild nature of the Branham sign observed in the SL dogs.

There are several alternative explanations for the similarity in Branham sign between the two groups. One possibility is that soft tissue surgeons, mindful of a potential Branham sign, have adapted their technique to ligate PDAs gradually over several minutes (Broaddus and Tillson, 2010). This approach has been adopted at our institution and could mimic the gradual closure achieved with an ACDO. Greater nociception from thoracotomy could increase the sympathetic drive in SL dogs and mitigate the Branham sign. Furthermore, we normally select larger ACDOs, with a waist to minimal ductal diameter of at or near to 2:1, rather than 1.5:1 (data not included), and a width of device at least 2 mm wider than the ampulla. This might tend to occlude ductal flow more rapidly, thus mimicking the cardiovascular effects of SL.

Age and weight are commonly cited as potential cofounding variables in observational studies (Norgaard *et al.*, 2017). These two factors are relevant to our study because weight influences circulating blood volume and therefore hemodynamic changes, whilst age is associated with autonomic maturation, particularly of the baroreceptor reflex (Hageman *et al.*, 1986). In our institution, dogs <5 kg have been more likely to undergo SL because their femoral arteries are often not large enough to accommodate the delivery system required for ACDO deployment. However, we were unable to demonstrate an influence of age or weight on the magnitude of the Branham sign. This is of clinical relevance because new generation devices such as the Amplatzer vascular plug 2 (Wagner, 2019) and ductal occluder (Hulsman *et al.*, 2021) can be deployed either through smaller delivery systems or venous routes, paving the way to interventional closure in an age and weight of dogs previously more likely to undergo SL. Where interventional closure is possible, it is usually adopted because SL carries a higher rate of major complications such as ductal rupture and hemorrhage (Goodrich *et al.*, 2007; Meijer and Beijerink, 2012).

Since a Branham sign is a useful real-time guide to the interventionalist that occlusion of the ductus has occurred, and age and weight do not appear to modify it, we conclude that the Branham sign also is likely to be a useful monitoring tool in smaller and younger dogs undergoing interventional ductal occlusion.

The retrospective nature of this study is its major limitation. Consequently, anesthetic protocols were non-standardized although an influence on the magnitude of the Branham sign could not be identified.

Additionally, despite statistically similar doses of inhalational anesthetic agents at the time of occlusion, the depth of anesthesia could have been different between patients. The smaller number of dogs in the SL group could mean that our study was underpowered to demonstrate differences between ACDO and SL dogs. For simplicity, power analysis was based on a two-sample *t*-test of maximum reduction in HR. The use of multiple comparison tests requires larger numbers of animals to maintain power. However, on observing the trends in the data sets, if a type II error exists, it would appear to be more likely that it masks a greater Branham sign in the ACDO dogs than the SL dogs. This is still consistent with our conclusion that the ACDO method of ductal occlusion does not elicit a lesser Branham sign than the current SL technique.

Conclusion

In conclusion, our study demonstrates that a mild Branham sign is common in dogs undergoing surgical and ACDO ductal ligation and the hemodynamic changes that elicit it can be tracked over at least 30 minutes by intra-arterial BP monitoring. The magnitude of the Branham sign is not dependent on the method of ductal closure or the age or weight of the dog.

Conflict of interest

The authors declare that there is no conflict of interests.

Authors' contributions

Filipe Madruga–Data collection, manuscript writing, statistical analysis. Yolanda Martinez Pereira–Original manuscript idea, manuscript revision. Ambra Panti–Critical manuscript revision. Ian Handel–Statistical analysis, manuscript revision. Geoff Culshaw–Critical manuscript revision, statistical analysis.

References

Acierno, M.J., Domingues, M.E., Ramos, S.J., Shelby, A.M. and da Cunha, A.F. 2015. Comparison of directly measured arterial blood pressure at various anatomic locations in anesthetized dogs. Am. J. Vet. Res. 76, 266–271.

Bartels, K., Esper, S.A. and Thiele, R.H. 2016. Blood pressure monitoring for the anesthesiologist: a practical review. Anesth. Analg. 122, 1866–1879.

Blossom, J.E., Bright, J.M. and Griffiths, L.G. 2010. Transvenous occlusion of patent ductus arteriosus in 56 consecutive dogs. J. Vet. Cardiol. 12, 75–84.

Broaddus, K. and Tillson, M. 2010. Patent ductus arteriosus in dogs. Compend. Contin. Educ. Vet. 32, E3.

Buchanan, J.W. 2001. Patent ductus arteriousus morphology, pathogenesis, types and treatment. J. Vet. Cardiol. 3, 7–16.

da Cunha, A.F., Ramos, S.J., Domingues, M., Shelby, A., Beaufrere, H., Stout, R. and Acierno, M.J. 2017. Validation of noninvasive blood pressure equipment: which peripheral artery is best for comparison studies in dogs? Vet. Anaesth. Analg. 44, 1068–1075.

De Monte, V., Staffieri, F., Caivano, D., Nannarone, S., Birettoni, F., Porciello, F., Di Meo, A. and Bufalari, A. 2017. Heart rate and blood pressure variations after transvascular patent ductus arteriosus occlusion in dogs. Res. Vet. Sci. 113, 73–78.

Epstein, F.H., Shadle, O.W., Ferguson, T.B. and McDowell, M.E. 1953. Cardiac output and intracardiac pressures in patients with arteriovenous fistulas. J. Clin. Invest. 32, 543–547.

Franco, L.G., Wilges, C.H.M., Junior, D.P., Cerejo, S.A., Nishimura, L.T. and Bittar, I.P. 2018. Effects of ketamine constant rate infusions on cardiac biomarkers and cardiac function in dogs. Vet. Anaesth. Analg. 45, 250–259.

Goodrich, K.R., Kyles, A.E., Kass, P.H. and Campbell, F. 2007. Retrospective comparison of surgical ligation and transarterial catheter occlusion for treatment of patent ductus arteriosus in two hundred and four dogs (1993-2003). Vet. Surg. 36, 43–49.

Gozalo-Marcilla, M., Seymour, C.J., Schauvliege, S., Bosmans, T. and Gasthuys, F. 2012. Anesthetic management for the correction of a patent ductus arteriosus by means of either surgical ligation or transarterial occlusion in dogs. Vlaams. Diergeneeskundig. Tijdschrift. 81, 17–21.

Hageman, G.R., Neely, B.H. and Urthaler, F. 1986. Cardiac autonomic efferent activity during baroreflex in puppies and adult dogs. Am. J. Physiol. 251, H443–H447.

Haskins, S.C., Farver, T.B. and Patz, J.D. 1985. Ketamine in dogs. Am. J. Vet. Res. 46, 1855–1860.

Hulsman, A.H., Breur, J. and Szatmari, V. 2021. Low profile vascular plug for transarterial occlusion of patent ductus arteriosus in small dogs. J. Vet. Intern. Med. 35, 98–106.

KuKanich, B. and Wiese, A.J. 2015. Opioids. In Veterinary anesthesia and analgesia, Eds., Grimm, K.A., Lamont, L.A., Tranquilli, W.J., Greene, S.A. and Robertson, S.A. 5th ed. Ames, Iowa: Wiley Blackwell, pp: 207–226.

MacFarlane, P.D., Grint, N. and Dugdale, A. 2010. Comparison of invasive and non-invasive blood pressure monitoring during clinical anaesthesia in dogs. Vet. Res. Commun. 34, 217–227.

Meijer, M. and Beijerink, N.J. 2012. Patent ductus arteriosus in the dog: a retrospective study of clinical presentation, diagnostics and comparison of interventional techniques in 102 dogs (2003-2011). Tijdschr. Diergeneeskd. 137, 376–383.

Moran-Munoz, R., Valverde, A., Ibancovichi, J.A., Acevedo-Arcique, C.M., Recillas-Morales, S., Sanchez-Aparicio, P., Osorio-Avalos, J. and Chavez-Monteagudo, J.R. 2017. Cardiovascular effects of constant rate infusions of lidocaine, lidocaine and dexmedetomidine, and dexmedetomidine in dogs anesthetized at equipotent doses of sevoflurane. Can. Vet. J. 58, 729–734.

Norgaard, M., Ehrenstein, V. and Vandenbroucke, J.P. 2017. Confounding in observational studies based on large health care databases: problems and potential solutions - a primer for the clinician. Clin. Epidemiol. 9, 185–193.

Ortega, M. and Cruz, I. 2011. Evaluation of a constant rate infusion of lidocaine for balanced anesthesia in dogs undergoing surgery. Can. Vet. J. 52, 856–860.

Parisi, C., Phillips, V., Ferreira, J., Linney, C. and Mair, A. 2020. Anaesthetic management and complications of transvascular patent ductus arteriosus occlusion in dogs. Vet. Anaesth. Analg. 47, 581–587.

Pascoe, P.J. 2016. Intrathoracic surgery and interventions. In BSAVA Manual of canine and feline anaesthesia and analgesia. Eds., Duke-Novakovski, T., Vries, M.d. and Seymour, C. 3rd ed. Quedgeley, Gloucester: British Small Animal Veterinary Association.

Porciello, F., Caivano, D., Giorgi, M.E., Knafelz, P., Rishniw, M., Moise, N.S., Bufalari, A., Fruganti, A. and Birettoni, F. 2014. Transesophageal echocardiography as the sole guidance for occlusion of patent ductus arteriosus using a canine ductal occluder in dogs. J. Vet. Intern. Med. 28, 1504–1512.

Ranganathan, B., LeBlanc, N.L., Scollan, K.F., Townsend, K.L., Agarwal, D. and Milovancev, M. 2018. Comparison of major complication and survival rates between surgical ligation and use of a canine ductal occluder device for treatment of dogs with left-to-right shunting patent ductus arteriosus. J. Am. Vet. Med. Assoc. 253, 1046–1052.

Robinson, R. and Borgeat, K. 2016. Cardiovascular disease. In BSAVA Manual of canine and feline anaesthesia and analgesia. Eds., Duke-Novakovski, T., Vries, M.d. and Seymour, C. 3rd ed. Quedgeley, Gloucester: British Small Animal Veterinary Association, pp: 283–313.

Scansen, B.A. 2018. Cardiac interventions in small animals: areas of uncertainty. Vet. Clin. North Am. Small Anim. Pract. 48, 797–817.

Seliskar, A., Zrimsek, P., Sredensek, J. and Petric, A.D. 2013. Comparison of high definition oscillometric and doppler ultrasound devices with invasive blood pressure in anaesthetized dogs. Vet. Anaesth. Analg. 40, 21–27.

Selmic, L.E., Nelson, D.A., Saunders, A.B., Hobson, H.P. and Saunders, W.B. 2013. An intrapericardial technique for PDA ligation: surgical description and clinical outcome in 35 dogs. J. Am. Anim. Hosp. Assoc. 49, 31–40.

Shanazari, A.A., Aslani, Z., Ramshini, E. and Alaei, H. 2011. Acute and chronic effects of morphine on cardiovascular system and the baroreflexes sensitivity during severe increase in blood pressure in rats. ARYA. Atheroscler. 7, 111–117.

Stanley, B.J., Luis-Fuentes, V. and Darke, P.G. 2003. Comparison of the incidence of residual shunting between two surgical techniques used for ligation of patent ductus arteriosus in the dog. Vet. Surg. 32, 231–237.

Szilagyi, J.E. 1987. Opioid modulation of baroreceptor reflex sensitivity in dogs. Am. J. Physiol. 252, H733–H737.

Velez-Roa, S., Neubauer, J., Wissing, M., Porta, A., Somers, V.K., Unger, P. and van de Borne, P. 2004. Acute arterio-venous fistula occlusion decreases sympathetic activity and improves baroreflex control in kidney transplanted patients. Nephrol. Dial. Transplant. 19, 1606–1612.

Wagner, T. 2019. Plugging the gap between ACDOs and coils: experience with the amplatz vascular plug-2. In Proceedings of the autumn meeting of the veterinary cardiovascular society.

Wattanasirichaigoon, S. and Pomposelli, F.B., Jr. 1997. Branham's sign is an exaggerated Bezold-Jarisch reflex of arteriovenous fistula. J. Vasc. Surg. 26, 171–172.

Zhang, Y., Hedo, R., Rivera, A., Rull, R., Richardson, S. and Tu, X.M. 2019. *Post hoc* power analysis: is it an informative and meaningful analysis? Gen. Psychiatr. 32, e100069.