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Esophageal Doppler-derived indices and arterial load variables provide useful hemodynamic information during assessment of fluid responsiveness in anesthetized dogs undergoing acute changes in blood volume

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OBJECTIVE
To investigate the relationship between invasively measured stroke volume (SV) and (1) esophageal Doppler-derived indices such as stroke distance (StrokeD), flow time corrected (FTc), stroke distance variation (SDV), and peak velocity variation (PVV); and (2) arterial load (AL) variables during evaluation of fluid responsiveness (FR) in anesthetized dogs undergoing sudden hemodynamic shifts in blood volume.

ANIMALS
6 healthy male dogs.

PROCEDURES
Dogs were anesthetized with isoflurane, ventilated mechanically, and instrumented to undergo sequential, nonrandomized experimental stages. The dogs transitioned from normovolemia (NORMO-BL) to hypovolemia (30% blood loss; HYPO-30), followed by autologous blood transfusion, and then to hypervolemia (colloid bolus). During each stage, SV was quantified using pulmonary artery thermodilution and its relationship with StrokeD, FTc, SDV, and PVV; and AL variables such as effective arterial elastance (Ea), dynamic arterial elastance (Ea_{dyn}), and total arterial compliance (C_a) were established.

RESULTS
As SV decreased significantly during HYPO-30 compared to NORMO-BL, there was a significant ($P < .001$) decrease in StrokeD, FTc, and C_a, with simultaneous increases in SDV, PVV, Ea, and Ea_{dyn}. Upon restoration of blood volume, these values stabilized closer to NORMO-BL. A significant ($P < .001$) correlation was observed between SV and StrokeD, FTc, Ea, Ea_{dyn}, and C_a.

CLINICAL RELEVANCE
Minimally invasive StrokeD, FTc, SDV, and PVV act as SV surrogates and help assess FR during different blood volume stages in healthy dogs. During hypovolemia-induced hypotension, Ea, Ea_{dyn}, and C_a may be able to guide therapeutic decisions favoring improvement in blood pressure and SV.

Fluid resuscitation is a fundamental component for restoring circulatory function in critically ill patients, and its ultimate goal is improving cardiac output (CO) and tissue oxygen delivery. However, the requirement of fluids must be determined based on frequent assessments of each patient's volume status to prevent hypoperfusion or fluid overload.[1] Goal-directed fluid therapy (GDFT) uses intensive monitoring of physiologic parameters and their prespecified values to guide hemodynamic stabilization. The response to GDFT is based on the Frank-Starling cardiac curve, and fluid responsiveness (FR) is the ability to synchronize CO and stroke volume (SV) with venous return.[2–5] An increase in CO or SV by >10% to 15% after volume expansion indicates FR, whereas a minimal difference in these parameters after a fluid challenge is demonstrative of fluid nonresponsiveness (FNR).[1]

In human patients undergoing GDFT, recording CO or SV by a gold standard method such as pulmonary artery thermodilution (PATD) may not always be practical because of its invasiveness,[6]

required expertise, and necessary equipment and cost. Doppler-derived indices such as stroke distance (StrokeD) and flow time corrected (FTc) can be determined with minimally invasive esophageal Doppler monitor (EDM) for optimizing SV in anesthetized and critically ill human patients.[7–9] In healthy and endotoxemic dogs, EDM is useful for monitoring hemodynamics under general anesthesia.[10–15] More recently, an EDM veterinary monitoring system has been introduced that also records other Doppler dynamic variables, such as peak velocity variation (PVV) and stroke distance variation (SDV) that are influenced by the cardiorespiratory interaction occurring with mechanical ventilation, largely resulting from applied tidal volume (VT) and airway pressures.[14] Like the other dynamic indices validated in dogs to distinguish between FR and FNR,[16] PVV and SDV may prove useful in guiding GDFT; however, these parameters have not been studied extensively in humans and animals.

Evaluation of FR can be challenging in individuals with depressed vascular tone, because they may not exhibit an increase in arterial blood pressure (ABP) despite augmentation of CO after fluid expansion.[17] In such scenarios, aggressive fluid therapy administered to achieve a target ABP may cause fluid overload. To determine whether a fluid challenge will improve ABP, it is necessary to examine preload dependency along with the arterial load (AL).[18] The AL can be reflective of cardiac afterload and represents net extracardiac forces that must be overcame by the ventricles during ejection. The effective arterial elastance (Ea) characterizes AL from the left ventricular pressure-volume data. The dynamic arterial elastance (Ea_{dyn}) is recommended for the functional assessment of AL and depicts the interaction between ABP and SV during a respiratory cycle.[18,19] The predictive ability of Ea_{dyn} in generating an ABP response to fluid expansion has been demonstrated in critically ill human patients.[20–24] Apart from experimental studies in rabbits[25,26] and pigs,[27] there is no literature available regarding the utility of Ea, Ea_{dyn}, or total arterial compliance (C_a) in veterinary medicine.

The objective of our study was: (1) to evaluate the relationship of StrokeD, FTc, PVV, SDV, Ea, Ea_{dyn}, and C_a in comparison with SV measured by the gold standard PATD; and (2) to investigate the relationship between AL variables and ABP during induction and correction of hypovolemia in anesthetized dogs. We hypothesized that (1) StrokeD, FTc, PVV, and SDV will track closely those hemodynamic changes occurring with different blood volume states and will be affected by variations in SV, and (2) AL variables will correlate with changes in ABP and SV in this experimental canine model.

Materials and Methods

Study animals

Virginia Tech University-Institutional Animal Care and Use Committee (protocol No. 20-235) approved the experimental procedures for this study. Six sexually intact male Beagles (age, 10 to 14 months; mean ± SD weight, 8.9 ± 0.3 kg) were included in this prospective, crossover, nonrandomized experimental study. A physical examination, CBC, and serum chemistry panel were performed to deem them healthy. Dogs were kept in a controlled-temperature environment and completed 2 weeks of acclimatization prior to the experiment.

Anesthetic induction and monitoring of standard parameters, pulse pressure variation and stroke volume variation

The dogs were fasted for 12 hours and had *ad libitum* water access before the day of the experiment. On the study day, for each dog, a 20-gauge, 3-cm IV catheter (SurFlash; Terumo Medical) was placed aseptically into a cephalic vein, and oxygen was supplemented (4 L/min) for 5 minutes using a fitted face mask connected to a small-animal rebreathing system. Intravenous propofol (Propoflo; Zoetis Inc) was titrated to effect to induce general anesthesia until orotracheal intubation was possible. The dog was then placed in dorsal recumbency and the endotracheal tube was connected to the rebreathing system attached to a ventilator integrated anesthesia machine (Aestiva 5/7900; GE-Datex Ohmeda). Anesthetic maintenance was achieved with isoflurane (Fluriso; VetOne) in oxygen (1 to 2 L/min) at a target end-tidal concentration of isoflurane between 1.6% to 1.8% as measured continuously by an infrared gas analyzer included in a multiparameter monitor (S/5; GE-Datex Ohmeda). Using the same monitor, a lead II ECG, heart rate (HR), esophageal temperature, oxygen saturation, end-tidal carbon dioxide concentration ($PETCO_2$), and spirometry were recorded. A forced-air warming device (Bair Hugger; 3M Medical) and circulating water blanket (Maxitherm; Jorgensen Labs) were in place to maintain the animal's body temperature between 36.7 and 38 °C throughout the experiment.

An IV rocuronium (Rocuronium Bromide; Almaject) bolus (0.4 mg/kg) followed by a constant-rate infusion of 0.4 mg/kg/h was administered to induce neuromuscular blockade. A supramaximal train-of-4 electrical stimulus (Stimpod 450X; Xavant Technology) of the common peroneal nerve was used to monitor the efficacy of the blockade. The dogs were ventilated mechanically using a volume-controlled mode with VT set at 12 mL/kg and a respiratory rate of 10 to 18 breaths/min to target the arterial partial pressure of carbon dioxide between 35 and 45 mm Hg, as measured by periodic arterial blood gas analysis. A 22-gauge, 2.5-cm catheter (SurFlo; Terumo Medical) was inserted aseptically into the dorsal pedal artery for monitoring invasive systolic, diastolic, and mean arterial pressure (MAP). A fluid-filled pressure transducer system (Deltran II; Utah Medical Products Inc) was attached to another multiparametric monitor (Carescape B850; GE HealthCare) and was leveled and zeroed at the level of the manubrium of the sternum (approx at the right atrium). This monitor also displayed the pulse pressure variation (PPV) and stroke volume variation (SVV) continuously using the E-PiCCO module based on pulse contour calculations. The PPV[28] and SVV[29] were calculated automatically by the monitor using the following formulas and

were recorded simultaneously at each time point as an average during 1 minute:

$$PPV\ (\%) = \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min})/2} \times 100$$

and

$$SVV\ (\%) = \frac{SV_{max} - SV_{min}}{(SV_{max} + SV_{min})/2} \times 100,$$

where PP_{max} and PP_{min} are the maximum and minimum pulse pressure, respectively; and SV_{max} and SV_{min} are the maximum and minimum stroke volume, respectively, over one respiratory cycle.

Instrumentation for CO monitoring by PATD and calculation of SV

A 5-Fr, 13-cm double-lumen catheter (MILA International Inc) was inserted aseptically into the left jugular vein and was used for withdrawing a fixed volume of blood during induction of hypovolemia, and for transfusing blood and colloids during correction of hypovolemia. A 6-Fr, 8.5-cm hemostasis introducer (Fast-Cath; Abbott Cardiovascular) was inserted aseptically and secured into the right jugular vein, through which a 5-Fr, 75-cm thermistor-tipped Swan-Ganz catheter (132FS; Edwards Lifesciences Corp) was advanced until its distal tip was located in the pulmonary artery. Correct placement was confirmed by observing characteristic pressure waveforms and pressure values upon connection with the monitor (Carescape B850; GE HealthCare) using pressure transducers (Deltran II, Utah Medical Products Inc). For each PATD-CO reading taken at the end of exhalation, a 3-mL bolus of chilled (2 to 5 °C) 0.9% sodium chloride solution was injected over < 3 seconds into the proximal port of the Swan-Ganz catheter. The appropriate computation constant was inserted in the monitor based on catheter model, quantity, and temperature of the injectate. The CO recorded equaled the mean of 3 consecutive measurements within 10% variation. The PATD-CO data were always collected after noting invasive ABP. Injections were done manually—and always by the same operator—to reduce bias, and at least 3 minutes were allowed between each injection. Calculation of SV was performed with the following formula at each time point:

$$SV\ (mL/beat) = \frac{CO\ measured\ by\ PATD}{HR}.$$

Instrumentation for EDM, velocity-time waveform, and recording of Doppler-derived indices and dynamic variables

The EDM veterinary monitoring system (CardioQ-EDMV+; Deltex Medical UK) attached to a 4.02-MHz continuous Doppler ultrasound emitting probe (K9P; Deltex Medical UK) was used to determine Doppler-derived indices and dynamic variables. A 120-cm-long probe was lubricated using aqueous gel and inserted into the oral cavity, then pushed gently into the esophagus **(Figure 1)**. The probe shaft contained 6 depth markers that were used to guide the insertion depth and facilitated correct probe placement. Advancement of the probe continued until the probe tip was in the region of the fifth to sixth thoracic vertebra, paralleling the aortic blood flow. At this point, the piezoelectric crystals present on the angled tip of the probe are oriented toward the descending thoracic aorta. Because of the density difference between the RBCs in the bloodstream and the

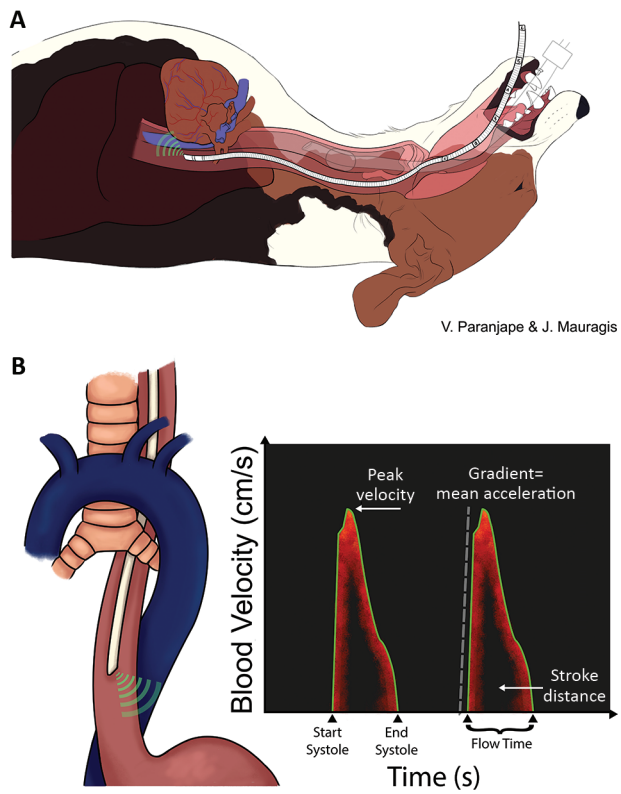

Figure 1—A—Graphical representation of a correctly positioned continuous esophageal Doppler ultrasound emitting probe (4.02-MHz; K9P-Deltex Medical UK) in an anesthetized dog. The probe is placed in the midthoracic region of the esophagus (at the level of the T5 to T6 vertebrae) and the posteriorly faced tip parallels the descending aortic blood flow. The probe shaft contains 6 depth markers that can be used to guide the insertion depth and facilitate accurate probe placement. This depiction displays the standard method of esophageal Doppler probe placement performed in all 6 study dogs. B—Schematic illustration of an optimal, real-time velocity-time waveform obtained by spectral analysis of the Doppler shift and depicting the descending aortic blood velocity paralleling the probe tip. Graphs for Doppler flow profiles from the esophagus include blood velocity shown on the *y*-axis (measured in centimeters per second) and time (measured in seconds) along *x*-axis. The green outline of each Doppler signal is detected automatically. The area of the triangle characterizes the stroke distance, triangle peak coincides with maximal peak velocity measured during systole, and the triangle base indicates the systolic flow time. The upslope of the graph (dashed gray line) is the mean acceleration of blood.

surrounding plasma, an "acoustic impedance mirror" is created to reflect the ultrasound emitted from the probe, which was held stationary at the site. The shift in the frequency of the reflected ultrasound waves returning from the mobile RBCs is converted into a real-time beat-to-beat waveform of blood velocity against time.[30–32] The probe was maneuvered by the operator to adjust the depth, and subtle rotational movements were made until the characteristic triangular waveform was visualized, coinciding with a distinct Doppler "whip crack" sound associated with peak blood flow from the descending thoracic aorta. Correct positioning and optimal flow signal were confirmed upon obtaining a consistent, clear, and sharp aortic waveform with the highest peak velocity, accompanied by a maximal pitch sound. The amount of amplification applied to the signal (gain) was also monitored closely to prevent a poor-quality signal.

The real-time velocity-time waveform (Figure 1) is obtained by spectral analysis of the Doppler shift and represents aortic blood velocity paralleling the probe tip. The triangle characterizes the systolic portion, the triangle peak coincides with maximal aortic velocity (peak velocity [PV]; in centimeters per second) measured during systole, and the triangle base indicates the systolic ejection time or flow time.[30–32] Flow time is defined as the time duration of the aortic flow during systole. However, because flow time is HR dependent, the EDM corrects this value automatically by a modification of Bazett's equation (flow time divided by the square root of the cycle time), displaying the flow time corrected to 1 cardiac cycle per second (FTc; measured in milliseconds). The upslope of the graph is the mean acceleration of blood measured in meters per seconds squared and the downslope depicts the deceleration of aortic flow during late systole.[30–32] The area under the systolic portion of the curve equals StrokeD, defined as the distance (in centimeters) traveled by the blood ejected by the left ventricle in the direction of the aorta during systole. The EDM calculates minute distance automatically by multiplying the StrokeD by the HR, and this variable denotes the volume during systole that travels across the aorta in 1 minute (measured in centimeters per minute).[30–32] The Doppler dynamic variables PVV and SDV were also calculated continuously and automatically by the EDM over each respiratory cycle.

To ensure the reliability of EDM data, the HR from this monitor was cross-matched with the pulse rate from the pulse-oximetry and arterial waveforms, and the HR from the ECG before every recording of Doppler-derived indices. Before data collection at each time point, at least 3 minutes were allowed after obtaining a consistent, highest quality signal and waveform; EDM data were noted before PATD-CO readings; for each variable, the average value over the 1-minute cycle was accounted; and 3 researchers were assigned to collect specific measurements and were blinded to the data obtained by others.

Assessment of AL variables

For evaluating AL and characterizing the arterial system, the systemic vascular resistance (SVR), C_a, and Ea were calculated using hemodynamic data from the Swan-Ganz catheter, invasive ABP, and CO monitor. The Ea, which is a change in pressure per change in volume, considers the steady and pulsatile elements of AL and is an integrative index of afterload. The C_a reflects only the pulsatile component of AL and is a major determinant of the cardiac workload. The functional assessment of AL was performed by calculating Ea_{dyn}, which displays a relationship between the cyclic variations in pulse pressure and SV induced by positive-pressure ventilation.[18,19] The formulas for all these indices were based on previous literature[18,19,22–27] and are as follows:

$$\text{SVR (dyn}\cdot\text{s/cm}^5) = \frac{(\text{MAP} - \text{Central venous pressure}) \text{ X } 80}{\text{CO}},$$

$$C_a \text{ (mL/mm Hg)} = \frac{\text{SV}}{\text{Arterial pulse pressure}},$$

$$\text{Ea (mm Hg/mL)} = \frac{0.9 \text{ X Systolic arterial pressure}}{\text{SV}},$$

and

$$Ea_{dyn} = \frac{\text{PPV}}{\text{SVV}}.$$

Experimental changes in blood volume

When instrumentation was completed, each dog went through sequential nonrandomized blood volume stages **(Figure 2)**. Baseline data were collected during normovolemia (stage 1: NORMO-BL). After this, hypovolemia was induced by blood withdrawal from the left jugular catheter over 20 minutes until 30% of the estimated total circulating blood volume was depleted (stage 2: HYPO-30). The total blood volume for dogs was estimated as 90 mL/kg of body weight.[33] The blood that was withdrawn was stored in blood collection bags containing an anticoagulant. The next step involved autologous blood transfusion using the blood volume withdrawn during HYPO-30 (stage 3: NORMO-BT) via the left jugular catheter over 20 minutes using an infusion pump (Alaris Carefusion; BD). During the next stage, a 20-mL/kg bolus of 6% hydroxyethyl starch was infused in the left jugular vein over 20 minutes via the same infusion pump (stage 4: HYPER-HS). At least 10 minutes were allowed for hemodynamic stabilization after each stage was induced and before any data were recorded.

Anesthetic recovery

After obtaining the final data, rocuronium was discontinued, the jugular and arterial catheters were removed, and the dogs were transitioned to recovery. After the dogs were extubated, they were transferred to individual cages and monitored for their vital signs and catheter sites for 72 hours. Postprocedure pain assessments were performed and analgesics were administered as needed.

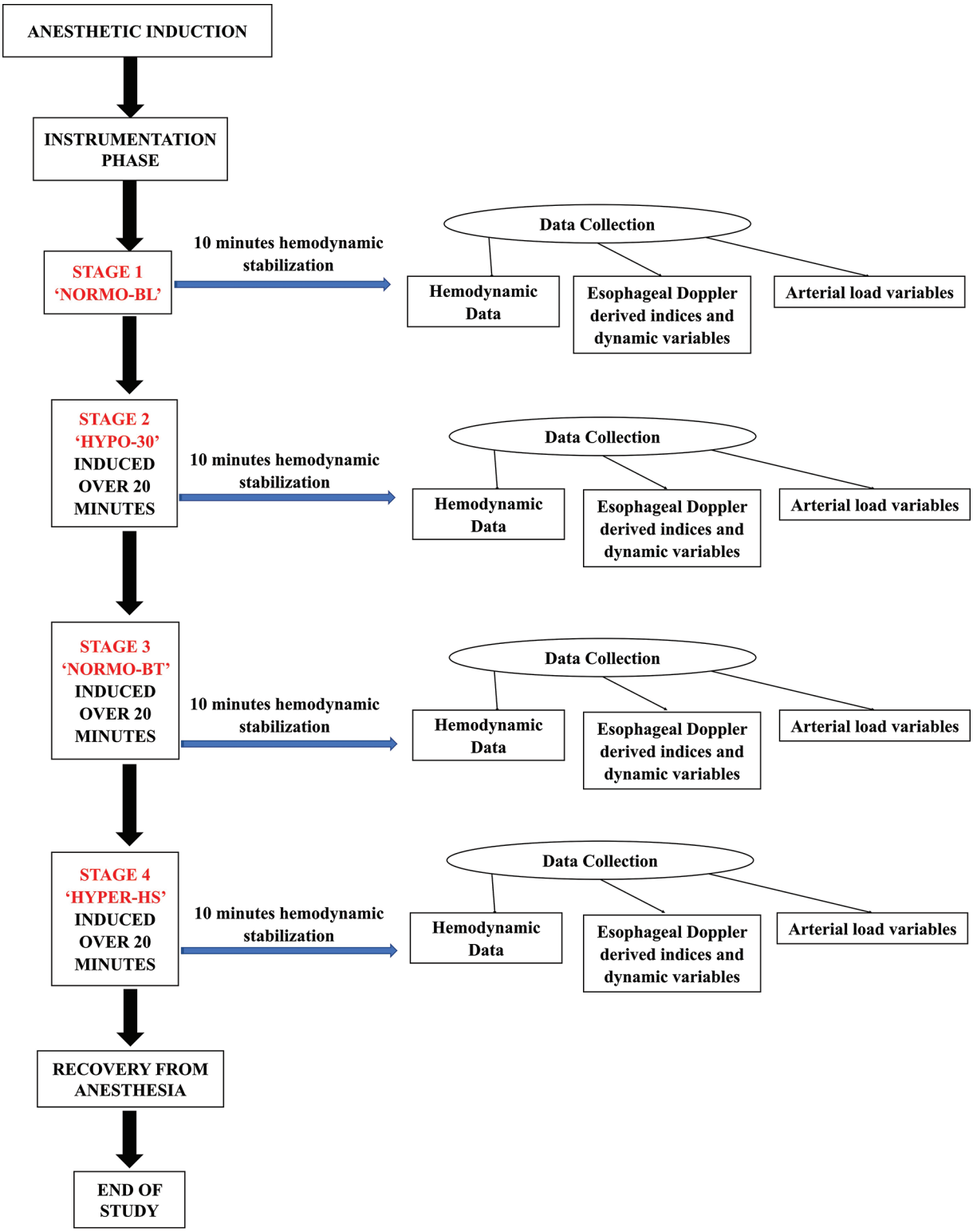

Figure 2—Time line of the data collection performed in 6 isoflurane-anesthetized dogs for collection of hemodynamic, esophageal Doppler monitor veterinary system (CardioQ-EDMV+; Deltex Medical UK) derived indices and dynamic variables, and arterial load variables. When instrumentation was completed, each dog went through sequential nonrandomized blood volume stages. First, baseline data were collected during normovolemia (stage 1: NORMO-BL). After this, hypovolemia was induced by blood withdrawal until 30% of the estimated total circulating blood volume was depleted (stage 2: HYPO-30). The next step involved autologous blood transfusion using the blood volume removed during HYPO-30 (stage 3: NORMO-BT), followed by a 20-mL/kg bolus of 6% hydroxyethyl starch infusion (stage 4: HYPER-HS). At least 10 minutes were allowed for hemodynamic stabilization after each stage was induced and before any data were recorded.

Statistical analysis

The normality of each physiologic variable used in this study for each stage (NORMO-BL, HYPO-30, NORMO-BT, and HYPER-HS) was assessed by the Shapiro-Wilk and D'Agostino-Pearson tests. All the physiologic variables were normally distributed and are therefore represented as mean ± SD. The correlation between SV and several variables (StrokeD, FTc, PVV, SDV, Ea, Ea_{dyn}, and C_a), and between MAP and Ea_{dyn} was evaluated using the least squares regression analysis. For comparing differences between each of the 4 experimental stages for all physiologic variables, a 1-way ANOVA for repeated measures was performed. To account for lack of sphericity in some cases, the Greenhouse and Geisser correction was applied to the analyses for cases where lack of sphericity was observed, followed by a post hoc Tukey adjustment for multiple pairwise comparisons. Last, a *t* test was conducted for pairwise comparisons. Values of $P < .05$ were considered significant for all analyses. All analyses were conducted using a commercial statistical software (SAS version 9.4; SAS Institute Inc).

Results

All dogs completed the study procedures successfully and recovered uneventfully. They were adopted out 3 weeks after the study ended into private homes. No missing data were reported.

Effect on SV and Doppler-derived indices and dynamic variables

The mean ± SD of the hemodynamic data and Doppler-derived parameters are reported **(Table 1)**. The SV values did not differ significantly among the dogs during NORMO-BL ($P = .781$). By depleting 30% of the circulating blood volume, all dogs exhibited a significant ($P = .013$) decrease in SV compared to NORMO-BL (17.1 ± 2.0 to 7.2 ± 0.2 mL). With hypovolemia commencing, there was a significant ($P < .001$) decrease in StrokeD (17.9 ± 0.7 to 10.7 ± 0.5 cm) and FTc (358 ± 14 to 315 ± 25 milliseconds), with a simultaneous significant increase in SDV (5.4 ± 0.8 to 14.5 ± 0.8%; $P = .033$) and PVV (3.1 ± 0.5 to 9.4 ± 0.5%; $P = .021$). After performing autologous blood transfusion (NORMO-BT), SV was seen to normalize; however, it was increased in comparison with NORMO-BL values. Similarly, StrokeD, FTc, SDV, and PVV values normalized during NORMO-BT. During HYPER-HS, SV was significantly ($P < .001$) greater than in NORMO-BL, HYPO-30, and NORMO-BT. The StrokeD and FTc were significantly increased during NORMO-BT; however, SDV ($P = .392$) and PVV ($P = .578$) did not differ between NORMO-BT and HYPER-HS. The changes in SV correlated significantly ($P < .001$) with StrokeD (r2 = 0.94), FTc ($r^2 = 0.82$), SDV ($r^2 = 0.89$), and PVV ($r^2 = 0.86$; **Figure 3**).

Table 1—Mean ± SD of hemodynamic, Doppler-derived indices and dynamic variables, and arterial load variables recorded in 6 healthy, mechanically ventilated, isoflurane anesthetized dogs undergoing 4 stages in a sequential order: baseline normovolemia (stage 1: NORMO-BL), 30% loss of circulating blood volume (stage 2: HYPO-30), autologous blood transfusion (stage 3: NORMO-BT), and 20-mL/kg colloid bolus (stage 4: HYPER-HS).

	Stage			
Variable	**NORMO-BL**	**HYPO-30**	**NORMO-BT**	**HYPER-HS**
Hemodynamic data				
SV (mL)	17.1 ± 2.0	7.2 ± 0.2[a]	19.9 ± 1.2[a,b]	23.2 ± 0.8[a,b,c]
PP (mm Hg)	59 ± 17	55 ± 19	70 ± 11[a,b]	74 ± 9[a,b]
MAP (mm Hg)	75 ± 8	50 ± 4[a]	81 ± 5[a,b]	89 ± 6[a,b,c]
PPV (%)	6.5 ± 2.2	18.0 ± 2.8[a]	7.4 ± 1.8[b]	5.3 ± 1.4[b]
SVV (%)	5.8 ± 1.9	13.0 ± 1.9[a]	6.7 ± 1.3[b]	5.7 ± 1.2[b]
Doppler-derived indices				
StrokeD (cm)	17.9 ± 0.7	10.7 ± 0.5[a]	19.5 ± 0.7[a,b]	25.1 ± 0.5[a,b,c]
MD (cm/min)	1,769 ± 121	1,525 ± 130[a]	2,392 ± 153[a,b]	3,277 ± 119[a,b,c]
PV (cm/s)	131 ± 3	96 ± 3[a]	131 ± 4[b]	137 ± 5[b]
MA (m/s^2)	13.1 ± 2.5	12.0 ± 2.4[a]	12.8 ± 2.5[b]	13.2 ± 2.7[b]
FTc (ms)	358 ± 14	315 ± 25[a]	344 ± 23[a,b]	362 ± 19[b,c]
Doppler dynamic variables				
SDV (%)	5.4 ± 0.8	14.5 ± 0.8[a]	6.6 ± 0.6[a,b]	4.3 ± 0.5[a,b,c]
PVV (%)	3.1 ± 0.5	9.4 ± 0.5[a]	4.8 ± 0.6[a,b]	2.2 ± 0.3[a,b,c]
Arterial load variables				
SVR (dynes · s/cm^5)	3,416 ± 470	3740 ± 270[a]	3,018 ± 332[a,b]	2,062 ± 129[a,b,c]
C_a (mL/mm Hg)	0.31 ± 0.1	0.15 ± 0.1[a]	0.25 ± 0.1[b]	0.32 ± 0.2[b,c]
Ea (mm Hg/mL)	6.2 ± 1.4	10.8 ± 1.7[a]	6.9 ± 0.9[b]	5.3 ± 0.4[a,b,c]
Ea_{dyn}	1.14 ± 0.3	1.39 ± 0.2[a]	1.10 ± 0.1[b]	0.93 ± 0.1[a,b,c]

[a]Significant difference ($P < .05$) from NORMO-BL. [b]Significant difference ($P < .05$) from HYPO-30. [c]Significant difference ($P < .05$) from NORMO-BT.

SV = Stroke volume. PP = Pulse pressure. MAP = Mean arterial pressure. PPV = Pulse pressure variation. SVV = Stroke volume variation. StrokeD = Stroke distance. MD = Minute distance. PV = Peak velocity. MA = Mean acceleration. FTc = Flow time corrected. SDV = Stroke distance variation. PVV = Peak velocity variation. SVR = Systemic vascular resistance. C_a = Total arterial compliance. Ea = Effective arterial elastance. Ea_{dyn} = Dynamic arterial elastance.

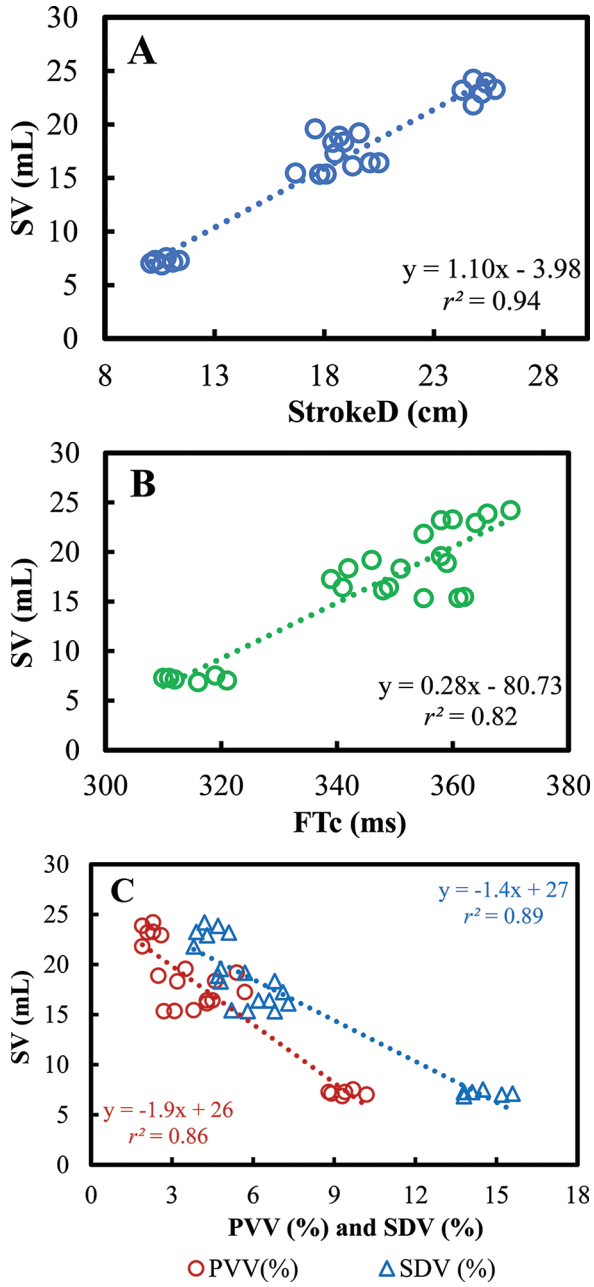

Figure 3—A—Scatterplot of stroke volume (SV) versus stroke distance (StrokeD) in 6 healthy, mechanically ventilated, isoflurane-anesthetized dogs subjected to acute changes in blood volume during experimental induction and correction of acute hemorrhagic shock. The dotted line represents the best-fit correlation. B—Scatterplot of SV versus flow time corrected (FTc) in 6 healthy, mechanically ventilated, isoflurane-anesthetized dogs subjected to acute changes in blood volume during experimental induction and correction of acute hemorrhagic shock. The dotted line represents the best-fit correlation. C—Scatterplot of SV versus peak velocity variation (PVV) and stroke distance variation (SDV) in 6 healthy, mechanically ventilated, isoflurane-anesthetized dogs subjected to acute changes in blood volume during experimental induction and correction of acute hemorrhagic shock. The red dotted line with red solid circles represents the best-fit correlation for PVV and the blue dotted line with blue solid triangles represents the best-fit correlation for PVV.

Effect on AL variables

The mean ± SD of the AL variables are summarized (Table 1). The C_a, Ea, and Ea_{dyn} values were similar (P = .362) in all dogs during NORMO-BL. After inducing HYPO-30, C_a decreased (P = .026; 0.31 ± 0.1 to 0.15 ± 0.1 mL/mm Hg), with corresponding significant increases seen in SVR (P = .035; 3,416 ± 470 to 3,740 ± 270 dynes · s/cm^5), Ea (P = .016; 6.2 ± 1.4 to 10.8 ± 1.7 mm Hg/mL), and Ea_{dyn} (P = .033; 1.14 ± 0.3 to 1.39 ± 0.2) values compared to NORMO-BL. Upon blood transfusion and colloid infusion, C_a was seen to increase significantly (P < .001) with a concurrent decrease in SVR, Ea, and Ea_{dyn}. The variations in SV and MAP during the 4 stages were followed closely by AL variables **(Figure 4)**. There was a significant (P < .001) correlation between SV and C_a (r^2 = 0.48), Ea (r^2 = 0.62), and Ea_{dyn} (r^2 = 0.59). Moreover, a

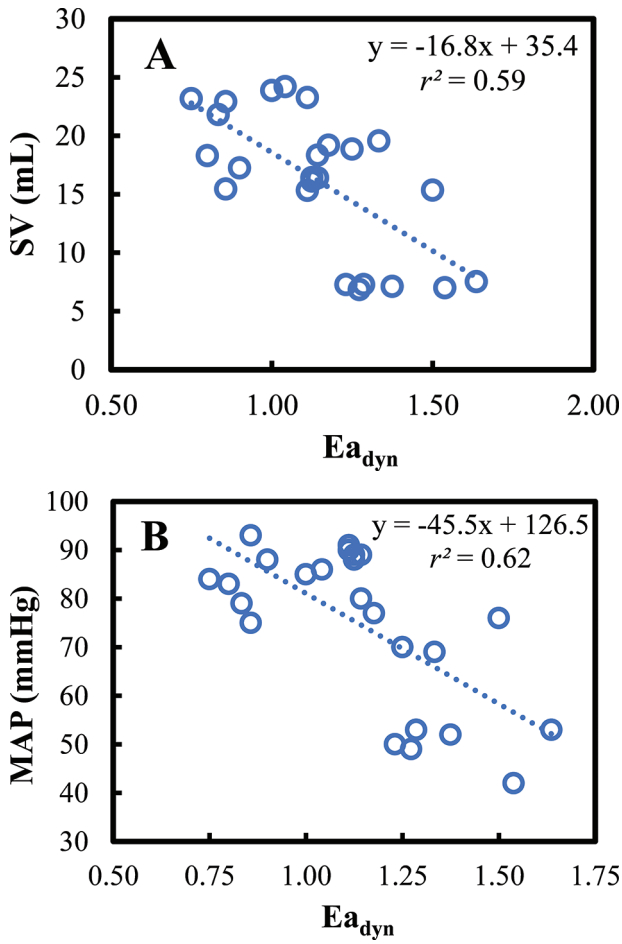

Figure 4—A—Scatterplot of stroke volume (SV) versus dynamic arterial elastance (Ea_{dyn}) in 6 healthy, mechanically ventilated, isoflurane-anesthetized dogs subjected to acute changes in blood volume during experimental induction and correction of acute hemorrhagic shock. The dotted line represents the best-fit correlation. B—Scatterplot of mean arterial pressure (MAP) versus Ea_{dyn} in 6 healthy, mechanically ventilated, isoflurane-anesthetized dogs subjected to acute changes in blood volume during experimental induction and correction of acute hemorrhagic shock. The dotted line represents the best-fit correlation.

significant (P = .039) inverse relationship was also observed between the MAP and Ea_{dyn} measurements (r^2 = 0.62), such that when MAP decreased significantly during HYPO-30, Ea_{dyn} was greater, and after normalization of MAP during NORMO-BT and HYPER-HS, Ea_{dyn} was less. Similarly, Ea and MAP also correlated significantly (P = .019) and displayed an inverse relationship. In contrast, C_a and MAP exhibited a significant (P = .025) direct relationship.

Discussion

In human patients, the GDFT algorithm using advanced hemodynamic monitoring has been shown successfully to reduce the risk of perioperative complications and improve postoperative patient outcomes.[2–5] In an effort to apply these findings and improve quality of patient care in veterinary medicine, specialists are investigating the use of minimally invasive methods such as the EDM as an alternative to PATD to evaluate FR and identify the patient's position on the Frank-Starling cardiac curve. To be adopted, the minimum requirement for this technique is to demonstrate safety and provide accurate information regarding the patient's hemodynamics. In our study, minimally invasive measurements of StrokeD, FTc, SDV, and PVV were able to track FR by detecting a reduction in SV during HYPO-30, followed by its increase during NORMO-BT and HYPER-HS. Even though FR is always described in context with the effect on CO or SV with volume expansion, patients can be fluid responders with or without exhibiting a concurrent increase in ABP.[18,19] Hence, AL was also assessed in our study. It was seen that C_a, Ea, and Ea_{dyn} correlated with SV significantly, and this observed relationship was able to guide how these variables may behave during acute hemorrhagic shock scenarios in which blood transfusion and colloid infusion is used.

The EDM allows estimations of preload, afterload, and contractility by evaluating the velocity-time waveform and Doppler-derived indices. During HYPO-30, the ventricular output reduced, subsequently decreasing the blood flow through the descending aorta and the area under the systolic portion of the curve. Corresponding to this hemodynamic change, a significant decrease in StrokeD, FTc, and PV was observed as the SV decreased. The StrokeD and FTc represent the degree of ventricular filling and hence can guide FR successfully.[7–9] These values were seen to stabilize during NORMO-BT and HYPER-HS as SV increased. The normal FTc values reported in healthy human subjects are 330 to 360 seconds,[30,31] whereas the range in our study dogs across all stages was 310 to 382 seconds, which was within the limits reported in another canine study.[10,34] We observed narrowing of FTc coinciding with increased afterload (i.e., increase in SVR) during HYPO-30. These two parameters are known to be inversely related.[30] During hypocontractile states or scenarios with high SVR, the waveform will appear dampened or narrowed with a reduced amplitude, indicating lower PV values,[30–32] as seen during hemorrhage in our study dogs. It is possible that compensatory reduction in the carotid sinus baroreceptor inhibition of sympathetic outflow during hypovolemia may have caused arteriolar vasoconstriction, further enhancing SVR and reducing PV measurements. The PV values returned closer to baseline when dogs reached NORMO-BL. Interpretation of individual Doppler-derived variables to assess hemodynamic status should be done cautiously, as changes in one variable can occur simultaneously with compensatory changes in the other variables as a result of ventriculoarterial coupling, which may confuse clinicians while analyzing specific effects on preload, afterload, and contractility.

In the face of mechanical ventilation, dynamic variables for assessing FR rely on the cardiopulmonary interactions induced by positive-pressure ventilation to assess preload dependency. The cutoff values in anesthetized dogs for discriminating fluid responders from nonresponders in a canine study were PPV > 13.8% and SVV > 14.7%.[35] Similar values were observed for both these parameters during HYPO-30. However, because of the lack of literature regarding Doppler dynamic variables such as SDV and PVV in humans and animals, no data were found to allow direct comparisons with our study findings. In canines, the cutoff values for aortic flow PVV and velocity-time integral percentage variation were > 9.4% and > 14.7%, respectively, as measured by transthoracic echocardiography.[36,37] In our study, when blood volume was depleted, a significant increment in SDV and PVV was noted in a manner similar to PPV and SVV, which then normalized during NORMO-BT. This trend indicated FR in all dogs that responded successfully to the autologous blood transfusion, leading to reduced respiratory variations in StrokeD and PV. Minimal changes in SDV and PVV during NORMO-BL and hypervolemia demonstrated FNR. The mean ± SD for SDV and PVV reported in our study dogs during hemorrhage was 14.5 ± 0.8% and 9.4 ± 0.5%, respectively. Overall SDV and PVV closely followed sudden hemodynamic variations across stages. However, because the physiologic basis of SDV and PVV is similar to other dynamic variables, they could be inaccurate with VT < 8 mL/kg, spontaneous breathing, positive end-expiratory pressure, cardiac arrhythmias, open-chest conditions, intra-abdominal hypertension, low respiratory system compliance, cor pulmonale, and altered vasculature tone.[1,28]

A corresponding EDM in humans (Cardio-Q ODM+; Deltex Medical UK) also displays continuous CO measurements by using a nomogram derived from age, height, and weight of the patient, and calibrating the descending aortic blood flow velocity against PATD-CO in humans.[30] When using this monitor in veterinary species, this information is vital to consider as the nomogram cannot be applied directly to animals because of interspecies variability. There are a few canine studies that report using the Cardio-Q ODM+ monitor to record hemodynamic variables in healthy or endotoxemic or cardiac patients.[10–13] Because the EDM measures blood flow velocity in a major, central vessel, its accuracy is preserved even with changes in the resistance,

impedance, and compliance of the arterial system.[30] Occasionally, signals from other vessels such as the pulmonary artery and coeliac axis may display arterial waveform patterns and incorrect readings. This can be prevented by paying close attention to the insertion depth and markers placed on the probe shaft. The Doppler probes for the EDM veterinary system are associated with a time limit for their use. When exceeded, the probe ceases to function and needs to be replaced. We needed an average of 2 to 5 minutes for probe placement during our study. Refocusing was required frequently and was performed at least 10 minutes before data collection. There may be other limitations to using the EDM in animals, such as (1) it can be performed with the animal only under deep sedation or general anesthesia; (2) it cannot be used in patients with coagulopathies or esophageal, pharyngeal, or laryngeal trauma or pathology; and (3) it should not be used in patients with thoracic aortic aneurysms, coarctation of the aorta, tissue necrosis, or infectious disease or during laser surgery.[30]

Organ perfusion is balanced by an adequate CO and perfusion pressure, and each component needs to be scrutinized separately.[18] In anesthetized animals, MAP ≥ 60 mm Hg is targeted to ensure optimum tissue perfusion and to prevent organ dysfunction. However, in hypotensive patients that are fluid responsive, it cannot be guaranteed that a targeted MAP will be achieved after administering a fluid challenge. Because the blood flow and ABP vary with each cycle, SVR cannot describe the AL solely because it represents resistance against a steady flow and is not comparable across the vascular tree.[18] Hence, newer variables such as Ea, Ea_{dyn}, and C_a have replaced the traditional SVR value. In a group of preload responders, fluid resuscitation triggered a decrease in Ea and SVR, and a simultaneous increase in C_a. However, there was no significant change in the AL parameters in preload nonresponders. Baseline Ea readings were also significantly higher in preload responders compared to nonrespond ers.[22,24,25] By studying the established hemodynamics of positive-pressure ventilation on left ventricular SV and arterial pressure, Ea_{dyn} allows the assessment of pressure responsiveness. The greater the value of Ea_{dyn}, the better the probability that a fluid bolus will augment the CO along with ABP resulting from optimum ventricular-arterial coupling and enhanced efficiency of the arterial-ventricular system. Conversely, if Ea_{dyn} is low, ABP will not respond even though CO increases.[19,25] In such hypotensive patients, Ea_{dyn} may aid in guiding clinicians toward vasopressors as the prime treatment for stabilizing ABP instead of continued fluid administration that will potentiate risks for fluid overload. Moreover, for the same increment in CO, the greater the preinfusion Ea_{dyn}, the greater the improvement in ABP after a fluid challenge.[21,24,25] Our canine study was a preliminary attempt to report the relationship between AL variables and SV during sudden hemodynamic shifts in blood volume. We found that at lower SV and MAP during HYPO-30, Ea and Ea_{dyn} were higher, but C_a was lower. With stabilization of the blood volume, SV and MAP improved significantly, and this coincided with a decrease in Ea and Ea_{dyn} and an increase in C_a. We speculate that the Ea was higher during hypovolemia as a result of the sympathetic activation triggering ventricular-arterial decoupling in an attempt to maintain tissue perfusion.

Our study exhibited multiple limitations. The sample size was small because of ethical considerations. As a result, the predictive values, cutoffs, sensitivity, and specificity for the Doppler-derived indices and AL variables could not be calculated. The sequence of the experimental blood volume stages was not randomized because this specific order was critical to evaluate the study variables during assessment of FR in these dogs. This was also necessary to avoid the carryover effect of hypervolemia if demonstrated prior to hypovolemia. The gold standards for assessing ventricular-arterial coupling and AL are invasive measurement of ventricular volumes and pressures (pressure-volume loops) using a conductance catheter and arterial impedance, respectively.[18,19] Instead, we quantified Ea_{dyn} and used it as an index for ventricular-arterial coupling, considering its measure relies on the SV-pulse pressure relationship. Arterial impedance can be challenging to measure and interpret; therefore, we opted for a 2-element or resistance-compliance Windkessel model of arterial circulation for evaluating AL in our study using static (SVR) and dynamic (C_a, Ea_{dyn}) components. Also, Ea served as an integrative measure that was common between the 2 components. As a result of the sparse literature available regarding the impact of anesthetics on ventricular-arterial coupling and AL, it cannot be ruled out whether this factor influenced our study data.

Our study was one of the first exploratory studies to report the values for Doppler-derived indices and dynamic variables using the CardioQ-EDMV+, along with AL variables during assessment of FR in anesthetized healthy dogs undergoing experimental and sudden changes in blood volume. It was observed that StrokeD, FTc, SDV, and PVV could be used as surrogates for guiding changes in SV during occurrence of acute hemorrhage followed by correction of blood volume. During hypovolemia-induced hypotension, C_a, Ea, and Ea_{dyn} may be able to guide therapeutic decisions favoring improvement in ABP on the basis of their relationship with SV and MAP. The minimally invasive EDM could be advantageous in clinical settings to perform GDFT during general anesthesia in canine patients. Moreover, including AL variables may help clinicians to differentiate between FR and pressure responsiveness. Further clinical studies are warranted to investigate the performance and prediction values of Doppler-derived indices and AL variables in critically ill canine patients.

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