Respiratory variation in aortic blood peak velocity and caudal vena cava diameter can predict fluid responsiveness in anaesthetised and mechanically ventilated dogs

Original Article

Respiratory variation in aortic blood peak velocity and caudal vena cava diameter can predict fluid responsiveness in anaesthetised and mechanically ventilated dogs

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Abstract

Dynamic preload indices, such as systolic pressure variation (SPV), aortic flow peak velocity variation (ΔVpeak) and distensibility index of the caudal vena cava (CVCDI), are reliable indices for predicting fluid responsiveness in humans. This study aimed to investigate the ability of these indices to predict fluid response in healthy dogs undergoing general anaesthesia and mechanical ventilation. The study included 24 dogs. ΔVpeak, CVCDI, and SPV were calculated before and after volume expansion (5 mL/kg bolus of lactated Ringer's solution). Dogs were considered responders (group R, n = 9) when the aortic velocity time integral (VTI) increase was ≥15% and non-responders (group NR, n = 15) when the increase was <15%. ΔVpeak, CVCDI, and SPV before volume expansion were higher in group R than in group NR ($P = 0.0009$, $P = 0.0003$, and $P = 0.0271$, respectively). Receiver operating characteristic (ROC) curves were plotted for the three indices. The areas under the ROC curves for SPV, ΔVpeak, and CVCDI were 0.91 (CI 0.73–0.99; $P = 0.0001$), 0.95 (CI 0.77–1; $P = 0.0001$), and 0.78 (CI 0.56–0.92; $P = 0.015$), respectively. The best cut-offs were 6.7% for SPV (sensitivity, 77.78%; specificity, 93.33%), 9.4% for ΔVpeak (sensitivity, 88.89%; specificity, 100%), and 24% for CVCDI (sensitivity, 77.78%; specificity, 73.33). In conclusion, ΔVpeak, CVCDI, and SPV are reliable predictors of fluid responsiveness in dogs undergoing general anaesthesia and mechanical ventilation.

Keywords: Anaesthesia; Dog; Fluid responsiveness; Mechanical ventilation; Preload indices

Introduction

One of the major task for the anaesthetist, in order to optimize cardiac output and tissues perfusion, is to evaluate the perioperative fluid responsiveness which is commonly defined as an increase in the stroke volume by 15% after intravenous administration of an adequate bolus of IV fluid, and a responder is considered as a subject who reacts to such an increase. Stroke volume (SV) monitoring and prediction of fluid responsiveness are crucial to optimised hemodynamic and to avoid a detrimental fluid overload in non-responder subjects (Vellet et al., 2013).

Dynamic indices of preload, such as systolic pressure variation (SPV), aortic flow peak velocity variation (ΔVpeak), and distensibility of the inferior vena cava, are associated with heart-lung interactions (Jardin et al., 1983; Pinsky, 1997), allow beat-to-beat monitoring, and have been shown to be reliable predictors of fluid responsiveness in subjects undergoing general anaesthesia and controlled mechanical ventilation (CMV) (Gan et al, 2013;Rabozzi and Franci, 2014; Desgranges et al., 2016). The literature concerning the use of these dynamic indices in dogs is quite scarce and incomplete. Recently, SPV has been studied in anaesthetised dogs undergoing CMV at 8 cm H2O of airways pressure and has been shown to be a good predictor of fluid responsiveness (Rabozzi and Franci, 2014).

Ideally, an index of fluid responsiveness should be sensitive to changes in ventricular preload, predictive of fluid responsiveness, reproducible, simple to use, non-invasive, and widely available, in order to be conveniently used in the operating theatre or in the intensive care unit (Michard and Teboul, 2002; Marik et al., 2009). Echography offers the possibility to obtain indices correlated with preload, with many of these desired characteristics. Unfortunately, none sonographic index of fluid responsiveness can be currently used in dogs in clinical practice because the lack of validated cut-off values in this specie.

As mentioned above monitoring of SV is a mandatory aspect of studying indices of fluid responsiveness. Sonography has also been used as a non-invasive, painless and widely available method for beat-to-beat monitoring of the variation of stroke volume (SV) in experimental setting. Authors measured the aortic velocity time integral (VTI), using its percentage variation (ΔVTI) in the same subject after a fluid challenge, as a surrogate for SV variation (Pereira de Souza Neto et al., 2011; Brun et al., 2012; de Oliveira et al., 2016). In a pulsatile and accelerated flow detected with Doppler trace, the VTI (expressed in cm) is the integral under the velocity-time curve and represents the length covered by a systolic ejection flow. Previous studies have shown a high correlation between VTI variation, measured with transthoracic echocardiography (TTE), and SV variation in the same human subject measured by invasive methods (Lewis et al., 1984; Nguyen et al., 2006).

The present study aimed to evaluate the ability of SPV, ΔVpeak, and of the caudal vena cava distensibility index (CVCDI) to predict an increase equal to or greater than 15% in ΔVTI, after a fluid challenge, in mechanically ventilated dogs under general anaesthesia.

Materials and Methods

This prospective clinical study was approved by the Ethics Committee of the University of Padua (protocol no. 2422824). This study investigated 24 client-owned dogs, who were referred to the Veterinary Teaching Hospital of the University of Padua for elective surgeries. Written informed consent was obtained from each owner.

Preoperative physical examination and routine blood analysis (packed cell volume, haemoglobin, total protein, creatinine, urea, and electrolytes) were performed in each dog. The dogs were aged greater than 12 months, and dogs with arrhythmia, a history or clinical signs of cardiovascular or thoracic diseases, and systemic diseases were excluded.

After inserting a venous catheter into the cephalic vein, general anaesthesia was induced with fentanyl (Fentanest, Pfizer, Latina, Italy) administered at 0.003 mg/kg, followed by propofol (Vetofol, Norbrook, Carlisle, UK) administered to effect. Once intubated, each dog was maintained in left lateral recumbency and the tracheal tube was connected to an anaesthesia machine (ADU, Datex-Ohmeda, Helsinki, Finland). CMV was immediately started, and the tidal volume was set such that a plateau pressure of 10 cmH_2O was maintained. No positive end-expiratory pressure or inspiratory pause was applied. Anaesthesia was maintained with an infusion of propofol (18–25 mg/kg/h) using a syringe pump (3500, Graseby, Watford, UK). The respiratory rate was set such that a partial pressure of end-tidal CO_2 ($PE'CO_2$) between 4.6 and 6 kPa was maintained. The inspired fraction of oxygen was set between 35% and 40%.

Electrocardiography (three derivations), pulse oximetry, rectal temperature monitoring, capnography (side-stream system), and spirometry (pitot based) were performed throughout the entire procedure (AS/5, Datex-Ohmeda). Arterial blood pressure was measured invasively using an arterial catheter placed in the dorsal pedal artery, and the arterial line transducer was zeroed and maintained at the level of the right atrium.

After ensuring that the dog had completely adapted to mechanical ventilation and confirming the absence of spontaneous inspiratory effort on the spirometry trace, the maximum and minimum systolic arterial pressures (SAPmax and SAPmin) were measured over three respiratory cycles.

For measuring the SAPmax and SAPmin, we used the ‘wedge pressure’ menu of the Datex-Ohmeda AS/5 monitor, which allows the freezing of the arterial pressure trace, as performed by Rabozzi and Franci (2014). Median values over three respiratory cycles were used to calculate SPV using the following formula (Perel et al., 1987):

$$SPV\ (\%) = (SAPmax - SAPmin) / ([SAPmax + SAPmin] / 2) \times 100$$

Maximum Vpeak (Vpeak max) and minimum Vpeak were measured over three respiratory cycles using a cardiological probe (Z One Ultra, Zonare Mountain View, CA) at a frequency of 4-8 MHz. A standard subxifoid diaphragmatico-hepatic long axis view allowed to visualize the left ventricular outflow tract (LVOT) and aorta in order to obtain a pulsed Doppler traces over three respiratory cycles. Aortic valve and aortic annulus were identified as landmarks. The median values were used to calculate ΔVpeak using the following formula (Feissel et al., 2001): ΔVpeak (%) = (Vpeak max – Vpeak min) / ([Vpeak max + Vpeak min] / 2) × 100

VTI was measured as the median value over three respiratory cycles. ΔVTI was calculated as follows: ΔVTI (%) = ([VTI after volume expansion – VTI before volume expansion] / VTI before volume expansion) × 100.

CVC image was obtained using a 4-9 MHz convex probe (Z One Ultra, Zonare Mountain View, CA) at the level of the tenth to twelfth intercostal space, just few centimetres ventrally to the vertebral column, in the lateral short axis view in order to obtain a good image of the porta hepatis. Aorta, CVC and portal vein cross sections were identified as landmarks. In this view CVC appears slightly elliptical. The short axe calibre was measured according to the approach presented by Meneghini et al. (2015). Maximum CVC diameter (CVCmax) and minimum CVC diameter (CVCmin) were measured from the recorded cine-loop images of three respiratory cycles. The median values were used to calculate the caudal vena cava distensibility index (CVCDI) using the following formula (Feissel et al., 2004): CVCDI (%) = (CVCmax – CVCmin) / ([CVCmax + CVCmin] / 2) × 100.

A volume expansion was performed with a bolus of 5 mL/kg of lactated Ringer's solution administered intravenously over one minute using preloaded 50 mL syringes. One minute later,

142 systolic pressure, Doppler aortic trace, and cine-loop images of the caudal vena cava were again
143 obtained and stored.
144
145 All measurements (before and after volume expansion) were taken for three respiratory
146 cycles, and the median values were recorded for statistical analyses and calculation of haemodynamic
147 indices. Synchronization of the measurements with the inspiratory and expiratory phases of the
148 respiratory cycles was verified with the trace of airway pressure and the capnogram. After obtaining
149 all measurements, the dog was positioned as required to perform the scheduled surgical procedure.
150
151 *Statistical methods*
152 The distribution of normality for each variable was assessed using the visual inspection of the bar
153 graph and performing the Shapiro-Wilk test. Data that were not normally distributed are expressed
154 as median and interquartile range (25th-75th percentiles). Normally distributed variables are
155 expressed as mean ± standard deviation (SD). Fisher's exact test was used for categorical data, the
156 independent Student's *t*-test for continuous normally variables while Wilcoxon rank-sum test was
157 used to assess changes of not normally distributed variables.
158
159 The effects of VE on haemodynamic parameters were assessed using a non-parametric
160 Wilcoxon rank-sum test. Assuming that a 15% increase in the VTI was needed for clinical
161 significance, dogs showing a ΔVTI ≥15% after VE were classified as responders (R) and those
162 showing a ΔVTI <15% were classified as non-responders (NR). Receiver operating characteristic
163 (ROC) curves were plotted for SPV, ΔVpeak, and CVCDI in order to evaluate their ability to predict
164 fluid responsiveness. A *P*-value <0.05 was considered significant.
165
166 All measurements were performed by the same operator (MB). Intra-observer and inter-
167 observer variabilities of echographic measurements were determined through repetition of

168 measurements (VTI, Vpeak, and CVC diameters) in eight randomised dogs by the same operator and
169 by a second operator. The second observer was an expert sonographer (CG).
170
171 **Results**
172 This study included 24 dogs (female, 14; male, 10). The median age of the dogs was 27 (16–
173 52) months, and the median weight was 8.2 (7.5–12.6) kg. All dogs were ventilated at a plateau
174 pressure of 10 cmH_2O, and the median tidal volume per kg was 14 (13.8–15.4) mL. VE induced a
175 VTI increase of ≥15% in nine dogs (group R) and <15% in 15 dogs (group NR). There were no
176 significant differences in baseline characteristics between groups R and NR (Table 1). The effects of
177 volume expansion on haemodynamic parameters are summarised in Table 2. Before volume
178 expansion, heart rate, systolic pressure, and mean arterial pressure were not significantly different
179 between groups R and NR. SPV (Fig. 1), ΔVpeak (Fig. 2), and CVCDI (Fig. 3) before volume
180 expansion were higher in group R than in group NR ($P = 0.0009$, $P = 0.0003$, and $P = 0.0271$,
181 respectively). ROC curves for SPV, ΔVpeak, and CVCDI are presented in Fig. 4. The areas under the
182 ROC curves for SPV, ΔVpeak, and CVCDI were 0.91 (CI 0.73–0.99; $P = 0.0001$), 0.95 (CI 0.77–1;
183 $P = 0.0001$), and 0.78 (CI 0.56–0.92; $P = 0.015$), respectively. The best cut-offs were 6.7% for SPV
184 (sensitivity, 77.78%; specificity, 93.33%), 9.4% for ΔVpeak (sensitivity, 88.89%; specificity, 100%),
185 and 24% for CVCDI (sensitivity, 77.78%; specificity, 73.33%).
186
187 For VTI, Vpeak, and CVC diameters, the inter-observer variabilities (expressed as the mean
188 percent errors and SDs) were 3.8 ± 3%, 3.5 ± 3.2%, and 5.7 ± 4.6%, respectively, and the intra-
189 observer variabilities were 5.5 ± 4%, 4.8 ± 3.7%, and 6 ± 3.8%, respectively.
190
191 **Discussion**
192 To our knowledge, this is the first study to show that the preload dynamic indices ΔVpeak
193 and CVCDI can predict the response to a fluid bolus in anaesthetised adult dogs undergoing

194 mechanical ventilation.

195

196 All three indices tested in this study can be used to predict the fluid responsive status of an
197 anaesthetized and mechanically ventilated dog, as it has been proposed in humans (Feissel et al.,
198 2001; Feissel et al., 2004; Barbier et al., 2004; Pereira de Souza Neto et al., 2011). The ΔVpeak had
199 the best predictive value of the three indexes. The best performance of ΔVpeak may be explained,
200 on one hand, by the fact that arterial compliance has a lower influence on this index than on other
201 dynamic indices (Durand et al., 2008). On the other, Vpeak can be a major component of the VTI,
202 especially when left ventricle ejection time is short. CVCDI had the worst performance as index of
203 fluid responsiveness in this study. One reason which may explain this performance is that CVCDI
204 measurement may be influenced by movements of the area to be scanned during ventilation, which
205 can result in measurement errors. The fact that the ultrasound scanning of the vena cava in dog can
206 be difficult in some subjects may have been another source of error.
207 Based on this study SPV can be regarded as an excellent predictor of fluid responsiveness. This is
208 the first study which tests SPV as index of fluid responsiveness using a SV measurement or a
209 surrogate of it. Previously, the HR or MAP variation, comparing baseline and post fluid challenge
210 values, were used to analyse the ability of the baseline SPV to predict 10% decrease in HR or
211 increase in MAP (Rabozzi & Franci 2014). Considering the important difference regarding the
212 response variables between this study and the previous on SPV, not surprisingly, two differences
213 cut-off values were found: 4.5% Vs 6.7%. The higher SPV cut-off value found in this study can be
214 even partially explained by the higher airway pressure of ventilation used. Studies have shown that
215 a higher airway pressure is associated with a greater cut-off value that is able to discriminate
216 between responders and non-responders (da Silva Ramos et al., 2011; Michard, 2005).

217

218 Even though, there are reports which suggest that SPV is less accurate than pulse pressure
219 variation (()), in our opinion it retains one important practical advantage over others dynamic

indices. In clinical veterinary practice it is uncommon to have monitors which provide dynamic index values to the clinician. In order to measure them one has to use the modality presented by Rabozzi & Franci (2014) and used in this paper, which is already rather time consuming for SPV. Pulse pressure variation needs twice the manual measurements than SPV.

In our study, there were not significant differences of the heart rate and mean arterial pressure in the two groups (R and NR). This implies that the monitoring of blood pressure or heart rate may not be a reliable way to evaluate preload-dependence of an anaesthetized and ventilated subject.

The dynamic indices considered in this study are based on cyclical interactions between the heart and lungs during mechanical ventilation, and the extent of their variations is proportional to the magnitude of hypovolaemia. The inspiratory phase of positive-pressure ventilation causes a decrease in both the venous return from the CVC and the ventricular preload (Pinsky, 1997; Luecke and Pelosi, 2005). From this point of view, mechanical ventilation itself can be considered as a rhythmic volaemic challenge. For this reason, the above-mentioned preload indices can better predict fluid responsiveness in subjects fully adapted to mechanical ventilation, because all the aspects of the breathing cycle are predetermined and constantly maintained breath-by-breath..

In this study, the VTI was measured as a SV surrogate both before and after volume expansion to evaluate the SV variation in the same dog. In several studies in humans, the VTI has been used as a SV surrogate to measure the variation of left ventricular ejection in the same subject (Pereira de Souza Neto et al., 2011; Brun et al., 2012; de Oliveira et al., 2016). This approach to monitor cardiovascular function has several advantages both in clinical and experimental settings in veterinary medicine. It provides non-invasive beat-to-beat monitoring of SV, without further pain and distress.

Although SPV is an invasive index, its use is advantageous during the intraoperative period. In the majority of surgical procedures, monitoring ΔVpeak or CVCDI is not feasible owing to incorrect positioning or difficulties in reaching the body area for scanning. In some dogs, it might be difficult to obtain good images of the CVC owing to rhythmic interposition of the lungs, and both ΔVpeak and CVCDI can be difficult to evaluate in large dogs with a profound chest. The cut-off values identified are of value only within the clinical setting presented, as different airway pressures will produce different cut-off values. Respiratory diseases, which cause relevant changes in chest and/or lung compliance or are associated with lung hyperinflation and the development of auto-PEEP, can reduce the clinical applicability of the data obtained in this study. Dynamic indices of fluid responsiveness are difficult to use in dogs with respiratory diseases, as well as dogs with cardiac conditions that impede venous return or aortic blood flow and dogs with profound alteration of the Frank-Starling curve owing to end-stage myocardial degeneration. CVCDI should not be used with increased abdominal pressure, as the CVC size can reduce in this condition. Moreover, all conditions that cause direct mechanical action, such as restriction, compression, and thrombosis of the CVC, may invalidate the applicability of CVC ultrasound to estimate fluid responsiveness (Via et al., 2016).

Decisions with regard to fluid therapy, irrespective of the clinical setting, are among the most important tasks that veterinarians face daily, considering that hypervolaemia and hypovolaemia can increase the risk of mortality (Han et al., 2003; Rosenberg et al., 2009; Boyd et al., 2011). The only reason for a fluid challenge is to increase the SV. When an animal is a non-responder, a fluid challenge should be potentially harmful, at least in the most fragile animals. Careful fluid administration should be considered even in anaesthetised animals, as there is evidence that anaesthesia can cause a drastic change in fluid distribution across the body (Hahn, 2010). In this clinical setting, there is a steep increase in the amount of administered fluids distributed in the interstitial space, and this can be more pronounced and detrimental in

hypervolaemic or ill animals (Lee and Slutsky, 2010; Bruegger et al., 2005). Therefore, the advantages of a fluid challenge should be well weighted against the potential risks. Further studies recruiting a larger number of dogs could be useful in understanding whether the use of indices of fluid responsiveness to manage fluid therapy in the perioperative period can improve the outcome in subjects undergoing surgical procedures.

Conclusion

SPV, ΔPV and CVCDI are reliable predictors of fluid responsiveness in dogs undergoing general anaesthesia and mechanical ventilation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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386
387

388 **Table 1**

389 Baseline characteristics of the dogs

	Total	R	NR	*P*-value
No. of dogs	24	9	15	
Sex (male/female)	10/14	4/5	6/9	0.280*
Age (months)	27 (16–52)	26 (18–48)	30 (16–52)	0.445**
Weight (kg)	8.2 (7.5–12.6)	9.2 (6.8–11.8)	7.8 (7.2–12.6)	0.322**
Type of surgery (No.)	Ovariectomy (10) Orthopaedic surgery (TPLO) (9) Skin surgery (5)	Ovariectomy (3) Orthopaedic surgery (TPLO) (4) Skin surgery (2)	Ovariectomy (7) Orthopaedic surgery (TPLO) (5) Skin surgery (3)	
TV/kg (mL/kg)	14 (13–15)	13 (12–16)	14 (13–15)	0.932**
Respiratory rate (breaths/min)	14 (12–14)	14 (12–14)	14 (12–14)	1**
Plateau pressure (cmH_2O)	10	10	10	
I:E ratio	1:2	1:2	1:2	

390

391 Data are presented as median (25th-75th percentiles) or numbers.

392 *Fisher's exact test; **Independent Student's *t*-test

393 R, Responders; NR, Non-responders; TV, Tidal volume; TPLO, Tibial plateau levelling osteotomy

Table 2

Haemodynamic parameters in group R and group NR before and after volume expansion

	Before fluid challenge		*P*-value*	After fluid challenge		*P*-value*
Group	R	NR		R	NR	
Dogs (No.)	9	15		9	15	
HR (beats/min)	91 (76–105)	78 (65–90)	0.0889	81 (70–98)	75 (60–83)	0.4732
SAP (mmHg)	98 (96–101)	110 (94–112)	0.189	105 (101–108)	114 (102–118)	0.2201
DAP (mmHg)	58 (57–63)	54 (50–62)	0.2616	61 (60–76)	55 (50–62)	0.0828
MAP (mmHg)	71 (70–72)	71 (68–79)	1	74 (74–77)	76 (70–79)	0.8812
SPV (%)	6.9 (6.8–7.1)	5.2 (4.5–6.3)	0.0009	2.9 (2.2–3.4)	4.4 (3.8–5.6)	0.0031
ΔVpeak (%)	11 (10.7–12.2)	7.3 (6.3–8.9)	0.0003	6.8 (4–7.5)	7 (4.6–8.3)	0.9286
CVCDI (%)	33 (30–38)	21 (19–30)	0.0271	25 (15–30)	19 (12–22)	0.2201

Data are presented as median (25th-75th percentiles) or numbers.

*Wilcoxon rank-sum test

R, Responders; N, Non-responders; HR, Heart rate; SAP, Systolic arterial pressure; DAP, Diastolic arterial pressure; SPV, Systolic arterial Pressure; ΔVpeak, Aortic flow peak velocity variation; CVCDI, Caudal vena cava distensibility index

Figure Legends

Fig. 1

Box-plot of the systolic pressure variation (SPV) index before volume expansion (VE), comparison between responders and non-responders group (P=0.0009)

Fig. 2

Box-plot of the aortic flow peak velocity variation (ΔVpeak) index before volume expansion (VE), comparison between responders and non-responders group (*P*=0.0003)

Fig. 3

Box-plot of the caudal vena cava distensibility index (CVCDI) before volume expansion (VE), comparison between responders and non-responders group (*P*=0.0271)

Fig. 4

Receiver operating characteristic (ROC) curves comparing the ability of the ΔVpeak, CVCDI and SPV to predict fluid responsiveness. The area under the curve is 0.95 (CI 0.77–1; *P* = 0.0001) for the ΔVpeak, 0.91 (CI 0.73–0.99; *P* = 0.0001) for the SPV and 0.78 (CI 0.56–0.92; *P* = 0.015) for the CVCDI.