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Comparison of pulse pressure variation and plethysmographic variability index to predict fluid responsiveness in anesthetized cats

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutora em Anestesiologia.

Orientador: Prof. Dr. Francisco José Teixeira Neto

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Palavras-chave: domestic cats; fluid responsiveness; goal-directed fluid therapy; plethysmographic variability index; pulse pressure variation.

Dedicatória

“A todos os animais que passaram pelas minhas mãos desde que posso me recordar, e aos que ainda passarão. Com eles aprendi muito sobre a Medicina Veterinária, sobre os ciclos da vida, sobre o amor, a empatia e o cuidado.”

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RESUMO

DALMAGRO, TL. **Comparação da variação da pressão de pulso e do índice de variabilidade pletismográfica para predição da fluido responsividade em gatos anestesiados com isoflurano.** Botucatu, 2023. 30 p. Tese (Doutorado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu.

Objetivo– Comparar a habilidade e acurácia da variação da pressão de pulso (VPP) e do índice de variabilidade pletismográfica (IVP) para predizer a fluido responsividade (FR) em gatos anestesiados.
Delineamente experimental– Estudo experimental prospectivo.
Animais– Trinta e um gatos hígidos (2,7–5,0 kg).
Material e Método– Durante anestesia com isoflurano sob ventilação mecânica controlada a volume [volume corrente (V_T): 12 mL/kg, pausa inspiratória de 30%], um cateter na artéria femoral foi utilizado para mensurar o volume sistólico por termodiluição transpulmonar (VS_{TDTP}) e a VPP. Um oxímetro de pulso posicionado na língua mensurou o IVP. As variáveis foram registradas antes e após o desafio volêmico (DV) com 10 mL/kg de Ringer Lactato administrados em 10 minutos. Com base no aumento percentual do VS induzido pelo DV, os gatos foram classificados como respondedores (VS_{TDTP} ≥15%) ou não respondedores (VS_{TDTP} <15%) à expansão volêmica.
Resultados– Quatro gatos foram excluídos da análise estatística por instabilidade hemodinâmica. O DV aumentou o VS_{TDTP} em 21,7 (17,5–38,1)% [mediana (intervalos)] nos respondedores (n = 15) e em 8.8 (-10,6–14,3)% nos não respondedores (n = 12). Em dois gatos, o monitor falhou em fornecer os valores do IVP. A área sob a curva "receiver operating characteristics" (ROC) e intervalos de confiança de 95% foi de 0,853 (0,664–0,959) para a VPP e 0,702 (0,490–0,914) para o IVP. A VPP >17% predisse respondedores à expansão volêmica com especificidade de 75% e sensibilidade de 86,7% (p <0,0001); o IVP não demonstrou habilidade preditiva (p = 0,062). O intervalo de valores de VPP associados à alta probabilidade de resultados falsos positivos (18–23%) foi maior e incluiu mais animais (11/27 gatos) que o intervalo associado à alta probabilidade de resultados falsos negativos (14–17% e 4/27 gatos, respectivamente).
Conclusões e relevância clínica– A VPP >17% predisse respondedores à expansão volêmica com alta probabilidade de resultados falsos positivos, sugerindo que o V_T de 12 mL/kg seja excessivamente alto para a predição acurada da FR em gatos. O IVP demonstrou aplicabilidade clínica limitada em gatos.

Palavras-chave gatos domésticos, fluidoterapia guiada por metas, fluido responsividade, variação da pressão de pulso, índice de variabilidade pletismográfica.

ABSTRACT

DALMAGRO, TL. **Comparison of pulse pressure variation and plethysmographic variability index to predict fluid responsiveness in anesthetized cats.** Botucatu, 2023. 30 p. Thesis (PhD) – São Paulo State University, School of Medicine, Botucatu.

Objective To compare the ability/accuracy of pulse pressure variation (PPV) and plethysmographic variability index (PVI) to predict fluid responsiveness (FR) in anesthetized cats.
Study design Prospective, experimental study.
Animal population Thirty-one healthy cats (2.7–5.0 kg).
Methods During isoflurane anesthesia and volume-controlled ventilation [tidal volume (V_T): 12 mL kg^{-1}, 30% of inspiratory pause] a femoral artery catheter was used to measure transpulmonary thermodilution stroke volume (SV_{TPTD}) and PPV. A pulse oximeter probe placed on the tongue measured PVI. Variables were recorded before and after a fluid challenge (FC) with 10 mL kg^{-1} of lactated Ringer´s over 10 minutes. Based on percent changes in SV_{TPTD} induced by the FC, cats were grouped into responders (SV_{TPTD} ≥15%) or nonresponders (SV_{TPTD} <15%) to volume expansion.
Results Four animals were excluded from analysis because of unstable hemodynamic conditions. The FC increased SV_{TPTD} by 21.7 (17.5–38.1)% [median (range)] in responders (n = 15) and by 8.8 (-10.6–14.3)% in nonresponders (n = 12). In two cats, the monitor failed to provide PVI values. The area under the receiver operating characteristics curve (95% confidence intervals) was 0.853 (0.664–0.959) for PPV and 0.702 (0.490–0.914) for PVI. PPV values >17% predicted responders to volume expansion with 75% specificity and 86.7% sensitivity (p <0.0001); PVI did not show predictive ability (p = 0.062). The range of PPV values associated with higher probability of false positives (18–23%) was larger and included more animals (11/27 cats) than the range associated with higher probability of false negatives (14–17% and 4/27 cats, respectively).
Conclusions and clinical relevance PPV >17% predicted responders to volume expansion with an increased probability of false positive results, suggesting that a V_T of 12 mL kg^{-1} is excessively large for accurate prediction of FR in feline species. PVI showed limited clinical application in cats.

Keywords domestic cats, goal-directed fluid therapy, fluid responsiveness, pulse pressure variation, plethysmographic variability index.

Introduction

According to the concept of fluid responsiveness (FR), intravascular volume expansion is beneficial only if it results in significant increases in stroke volume (SV) and cardiac output (CO). Based on the curvilinear relationship between preload and SV described by Frank Starling, responders to volume expansion are individuals where SV will increase by at least 10–15% in response to a fluid challenge (FC). Dynamic preload indexes, such as pulse pressure variation (PPV) and plethysmographic variability index (PVI) can predict if an increase in SV or CO will occur in response to a FC in mechanically ventilated dogs (Fantoni et al. 2017; Celeita-Rodríguez et al. 2019; Gonçalves et al. 2020; Dalmagro et al. 2021).

PPV is calculated from variations in arterial pulse pressure induced by mechanical breaths. In anesthetized dogs receiving volume-controlled ventilation, PPV values >15–16% reliably predict which individuals will present an increase SV or CO of least 15% in response to a FC (Fantoni et al. 2017; Celeita-Rodríguez et al. 2019; Gonçalves et al. 2020). PVI is calculated from changes in the plethysmographic waveform that nearly parallel changes in the arterial pulse pressure. The PVI measured from a clip-type pulse oximeter placed on the tongue has been reported to predict FR in mechanically ventilated dogs (Endo et al. 2017; Sano et al. 2018; Celeita-Rodríguez et al 2019). Although PPV >16% and PVI >11% were shown to be reliable predictors of FR according to one canine study, PVI was less accurate than PPV because the zone of diagnostic uncertainty (gray zone) around the cutoff value was larger for PVI (10–13%) than for PPV (15–16%) (Celeita-Rodríguez et al. 2019).

The ability of PPV and PVI to predict FR status has been extensively studied in dogs but there is a paucity of data on cats. Compared to dogs, cats have a smaller circulating blood volume (50–60 mL kg^{-1} versus 80–90 mL kg^{-1}, respectively) (Robertson et al. 2018), and appear to be more sensitive to volume overload than dogs. Therefore, *a priori* identification of FR status is particularly important in cats that present signs of poor tissue perfusion because it could prevent unnecessary intravenous fluid administration in this species.

The present study aimed to evaluate the ability/accuracy of PPV and PVI to predict the response to a FC with 10 mL kg^{-1} of lactated Ringer´s solution administered over 10 minutes in cats ventilated with a tidal volume (V_T) of 12 mL kg^{-1}. As a secondary objective, this study aimed to evaluate the precision of transpulmonary thermodilution technique to reliably discriminate responders to volume expansion, which were defined as animals were SV increased by at least 15% in response to FC administration (Monnet et al. 2011).

Materials and methods

Animals

The Animal Care Committee of São Paulo State University approved this study (protocol CEUA 0172/2017) and the ARRIVE guidelines were followed (Percie du Sert et al. 2020). After an informed owner consent was obtained, healthy adult cats (1–5 years old) scheduled for elective ovariohysterectomy or castration were selected for the study. Animals were considered healthy after physical evaluation and complete blood cell count/serum biochemistry values within the reference ranges. Sample size was calculated after the receiver operating characteristics curve (ROC) of PPV was generated for 10 cats. Twenty-six cats were necessary to reject the null hypothesis (no predictive value of PPV) with a statistical power of 80% and an alpha level of 1%. A total of 31 cats were enrolled in the study to obtain the 27 cats included in the statistical analysis. Conditions that lead to the exclusion of animals from the analysis are presented in the results section.

Instrumentation and monitoring

Cats were fasted for 6 hours before anesthesia, with free access to water until two hours before anesthesia. Ketamine (10 mg kg^{-1}; Cetamin; Syntec; São Paulo, Brazil), midazolam (0.3 mg kg^{-1}; Dormire; Cristália Ltda, São Paulo, Brazil), and morphine (0.2 mg kg^{-1}; Dimorf; Cristália Ltda) were administered intramuscularly as premedication. After a 22-gauge, 2.5 cm long, catheter (Insyte; Becton Dickinson, Minas Gerais, Brazil) was placed in a cephalic vein, anesthesia was induced with intravenous propofol (3.3 ± 1.1 mg kg^{-1}; Propovan; Cristália Ltda). Following intubation with a cuffed endotracheal tube, cats were positioned in dorsal recumbency and anesthesia was maintained with isoflurane (Isoforine; Cristália, Ltda) delivered in oxygen. A piston driven anesthesia ventilator capable of delivering a minimum V_T of 20 mL with increments of 5 mL in volume-control mode was used to ventilate the cats (Dräger Primus; Drägerwerk AG & Co., Lübeck, Germany). The volume delivered by the ventilator was adjusted to obtain an expired V_T close to 12 mL kg^{-1} with an inspiration-to-expiration ratio of 1:2 and zero end-

expiratory pressure. An inspiratory pause of 30% of total inspiratory time was adjusted to allow the measurement of plateau pressure (P_{plat}) and of quasistatic respiratory compliance [C_{qst} = expired V_T / (P_{plat} – end-expiratory pressure) x body weight^{-1}]. The end-tidal isoflurane (F_{E}´Iso) and end-tidal carbon dioxide (P_{E}´CO_2) were monitored by an infrared gas analyzer whose calibration was certified by the manufacturer before commencing the study (Dräger Primus; Drägerwerk AG & Co). The F_{E}´Iso was adjusted to achieve a moderate depth of anesthesia, characterized by absence of palpebral reflexes and jaw tone, and by the absence of spontaneous respiratory efforts during mechanical ventilation; the latter was certified by inspecting the inspiratory/expiratory flow and airway pressure waveforms on the screen of the anesthesia ventilator (Dräger Primus; Drägerwerk AG & Co.). The respiratory rate (f_R) was set to maintain the P_{E}´CO_2 between 35–40 mmHg.

A multiparameter monitor (Lifewindow LW9xVet; Digicare Animal Health, FL, USA) was used to monitor electrocardiography (lead II), hemoglobin saturation (SpO_2), and esophageal temperature, which was maintained above 36ºC by an electrical heating pad and a forced warm air device (Bair Hugger; Arizant Healthcare, MN, USA). Meloxicam (0.05 mg kg^{-1}) (Meloxicam, Eurofarma, São Paulo, Brazil) and ceftriaxone (25 mg kg^{-1}) (Triaxon, Laboratório Teuto, Goiás, Brazil) were administered intravenously after induction of anesthesia.

A 22-gauge, 10 cm long central venous catheter (Cateter Venoso Central Mono Lúmen, Alive Heart; Rio Grande do Sul, Brazil) was inserted into a jugular vein until its tip was positioned at the thoracic inlet. A 3-Fr, 7 cm long thermodilution catheter (PiCCO Catheter PV2013L07N; Pulsion Medical Systems, Feldkirchen, Germany) was inserted into a femoral artery. Both catheters were connected to pressure transducers (PiCCO Transducer MCC06882774; Pulsion Medical Systems) filled with heparinized saline (4 IU/mL). Central venous and femoral artery catheters were zeroed to atmospheric pressure at the level of the manubrium for monitoring central venous pressure (CVP) and mean arterial pressure (MAP), respectively, on the screen of the hemodynamic monitor (PulsioFlex Monitor; Pulsion Medical Systems, Feldkirchen, Germany).

Transpulmonary thermodilution cardiac output (CO_{TPTD}) was measured by injecting 2 mL of ice-cold saline solution (≤5ºC) over approximately three seconds into the central venous catheter; a thermistor at the tip of the thermodilution catheter detected the change in blood temperature induced by the thermal signal. This procedure generated the thermodilution curves used to calculate CO_{TPTD} (PulsioFlex Monitor; Pulsion Medical Systems).

Three boluses of ice-cold saline solution were injected to obtain three CO_{TPTD} measurements with <15% difference from each other. At the completion of each CO_{TPTD} measurement, the heart rate (HR) displayed by the hemodynamic monitor was recorded for calculating SV_{TPTD} ($SV_{TPTD} = CO_{TPTD}/HR$), and CO_{TPTD} and SV_{TPTD} were averaged from the three thermodilution curves. The cardiac index (CI_{TPTD}) and stroke volume index (SVI_{TPTD}) were calculated by indexing CO_{TPTD} and SV_{TPTD} to body surface area [BSA = (weight in grams)$^{2/3}$ x 10.1 x 10^{-4}] and body weight, respectively. Systemic vascular resistance index (SVRI) was calculated as $SVRI = (MAP – CVP)/CI_{TPTD}$ x 79.9.

Extravascular lung water (EVLW) was measured by transpulmonary thermodilution. For each time point, the EVLW indexed to body weight (EVLWI) was averaged from values yielded by the three-thermodilution curves.

The hemodynamic monitor (PulsioFlex Monitor; Pulsion Medical Systems) provided the automated measurement of PPV from the arterial pressure waveform. While the multiparameter monitor used to measure SpO_2 ((Lifewindow LW9xVet; Digicare Animal Health) incorporated a proprietary algorithm (Masimo SET Version 7.8.0.5; Masimo Corp., CA, USA) that displayed the PVI and the perfusion index (PI).

Experimental protocol and assessment of FR status

After the end of instrumentation, the FC with 10 mL kg^{-1} of lactated Ringer´s solution (Ringer lactato; Halex Istar Ind. Farm. S/A, Goiás, Brazil) prewarmed to 35ºC was administered over 10 minutes through the central venous catheter. The total volume was divided in 10 aliquots administered on a minute-by-minute basis by manual injection using a 60 mL syringe. Hemodynamic and respiratory variables

were recorded immediately before and after fluid administration. Based on percent changes in SV_{TPTD} induced by the FC, the cats were classified as responders (increases in SV_{TPTD} ≥15%) or nonresponders (increases in SV_{TPTD} <15%) to volume expansion.

After the end of data collection, animals underwent ovariohysterectomy or castration surgery and were recovered from anesthesia. Total duration of anesthesia and complications observed during the anesthesia and postoperative period were recorded. After discharge from the hospital, cats were followed for 15 days to monitor for possible complications.

Statistical Analysis

Data were analyzed using MedCalc Version 19.6.1.0 (MedCalc Software Ltd, Belgium) and GraphPad Prism Version 9.02 (GraphPad Software, San Diego, CA, USA). A Shapiro Wilk test was applied to determine if data fitted a normal distribution. Variables with symmetrical and asymmetrical distribution are presented as mean ± standard deviation and as median (lower–upper range), respectively.

For variables with symmetrical distribution, a two-way analysis of variance (ANOVA), followed by Bonferroni *post hoc* tests compared data between groups (responders versus nonresponders) and within each group (before versus after the FC). For variables with asymmetrical distribution, comparisons between and within groups were performed by a Mann-Whitney *U* test and a Wilcoxon signed rank test, respectively.

Receiver operating characteristics curve analysis was performed to evaluate the ability of PPV and PVI values recorded before the FC to predict FR status (DeLong et al. 1988). The best cutoff value that discriminates responders from nonresponders to volume expansion was taken from the Youden index, that is, the point that maximizes the specificity (true negative rate) and sensitivity (true positive rate) of the test.

The accuracy of dynamic preload indexes to predict FR was assessed by determination of the gray zone, which corresponds to the range of PPV and PVI

values around the best cutoff value that are associated with higher probability of false positive (gray zone above the cutoff point) and false negative (gray zone below the cuff point) results. Gray zone determination followed a two-step approach. Firstly, the 95% confidence intervals (CIs) of the Youden Index were calculated from a 1,000 bootstrap population. Secondly, the 95% CIs of the Youden Index were compared with the range of cutoff values that resulted in 90% specificity and 90% sensitivity; the largest of these intervals was retained as the gray zone.

To verify if SV_{TPTD} measurements presented an adequate precision to discriminate the "true" responsiveness status, the least significant change (LSC) of each triplicate SVI_{TPTD} measurement was calculated. The coefficient of variation (CV = standard deviation/mean) was calculated to later obtain the coefficient of error ($CE = CV/\sqrt{n}$) where n is the number of measurements. The LSC of each SV_{TPTD} measurement calculated as $CE \times 1.96 \times \sqrt{2}$.

Results

Group of responders and nonresponders to volume expansion

From the 31 cats enrolled in the study, four cats were excluded from the statistical analysis: one animal presented light depth of anesthesia, with spontaneous breathing efforts and hypertension (MAP >100 mmHg) persisting with elevated F_{E}´Iso (2.5%). The other three animals were excluded because the series of three CO_{TPTD} measurements presented variation >15% from each other.

Of the 27 cats included in the analysis, the FC increased SV_{TPTD} by 21.7 (17.5–38.1)% in 15 animals, which were classified as responders (56% of the population). The remaining 12 animals showed percent changes in SV_{TPTD} induced by the FC of 8.8 (-10.6–14.3)% and were classified as nonresponders (44% of the population). The LSC of triplicate SV_{TPTD} measurements [5.2 (1.1–17.4)%] was adequate to discriminate animals classified as responders to volume expansion (SV_{TPTD} ≥15%).

Effects of volume expansion on hemodynamic variables and extravascular lung water

Heart rate did not differ between groups and was decreased by the FC in the group of responders (p = 0.018) (Table 1). The SVI_{TPTD} was lower in responders than in nonresponders before volume expansion (p = 0.035). SVI_{TPTD}, CI_{TPTD}, and CVP were increased by the FC in responders (SVI_{TPTD} and CI_{TPTD}, p = 0.0001, CVP, p = 0.022) and nonresponders (SVI_{TPTD}, p = 0.02; CI_{TPTD}, p = 0.0034; CVP p <0.0001). For the SVRI, MAP and EVLWI there were no differences between and within groups, except for a decrease in SVRI after the FC in responders (p = 0.0038).

Table 1 Effects of a fluid challenge with lactated Ringer's solution (10 mL kg^{-1} over 10 minutes) on variables recorded in anesthetized cats that were responders (n = 15) and nonresponders (n = 12) to volume expansion.

Variable	Group	Fluid Challenge	
		Before	**After**
HR (beats minute^{-1})	Responders	139 ± 30	132 ± 32*
	Nonresponders	123 ± 27	126 ± 23
SVI_{TPTD} (mL beat^{-1} kg^{-1})	Responders	0.98 (0.66–1.23)†	1.18 (0.89–1.67)*
	Nonresponders	1.16 (0.91–1.54)	1.22 (0.86–1.70)*
CI_{TPTD} (mL min^{-1} m^2)	Responders	1.77 (1.42–2.88)	2.07 (1.77–3.81)*
	Nonresponders	2.0 (1.65–2.79)	2.29 (1.84–3.62)*
CVP (mmHg)	Responders	1 ± 1	2 ± 1*
	Nonresponders	1 ± 2	3 ± 2*
SRVI (dynes sec^{-1} cm^{-5} m^2)	Responders	2751 ± 461	2366 ± 557*
	Nonresponders	2379 ± 490	2167 ± 536
MAP (mmHg)	Responders	67 ± 13	68 ± 14
	Nonresponders	64 ± 8	66 ± 10
EVLWI (mL kg^{-1})	Responders	7.6 (5.0–11.8)	7.9 (5.0–15.8)
	Nonresponders	6.7 (5.8–15.1)	7.4 (5.6–10.4)

HR, heart rate; SVI_{TPTD}, stroke volume index measured by transpulmonary thermodilution; CI_{TPTD}, cardiac index measured by transpulmonary thermodilution; CVP, central venous pressure; SVRI, systemic vascular resistance index; MAP, mean arterial pressure; EVLWI, extravascular lung water index.

*Significant difference from before to after the fluid challenge ($p < 0.05$).

†Significant difference between responders and nonresponders ($p < 0.05$).

Effects of volume expansion on SV, PPV, PVI and PI

Stroke volume was lower in responders than in nonresponders before ($p = 0.0019$) and after ($p = 0.042$) the FC (Fig. 1a). Volume expansion increased SV in both groups (responders, $p = 0.0001$; nonresponders, $p = 0.042$). Pulse pressure variation was higher in responders than in nonresponders before the FC ($p < 0.0001$) (Fig 1b); volume expansion decreased PPV in both groups ($p < 0.0001$). In two cats (group of responders), the pulse oximeter failed to display PVI values. PVI values of 58% and 69% recorded before the FC were identified as outliers (Tukey 1977).

The PVI did not differ between groups (Fig. 1c). Volume expansion decreased PVI in both groups (responders, $p = 0.02$; nonresponders, $p = 0.006$). Median PI values were low (< 0.4) and there were no differences in PI between and within groups (Fig. 1 d).

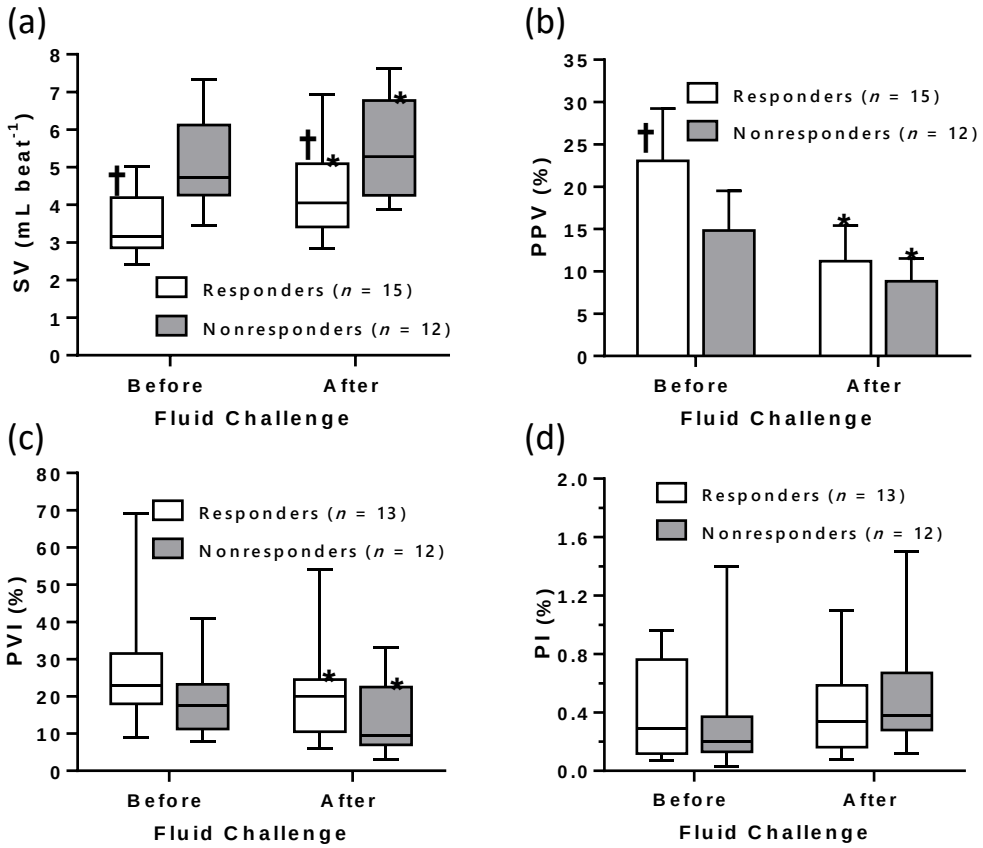

Figure 1 Changes in stroke volume (SV), pulse pressure variation (PPV), plethysmographic variability index (PVI) and perfusion index (PI) recorded in responders and nonresponders to a fluid challenge with 10 mL kg^{-1} of lactated Ringer´s solution over 10 minutes. Data in (a), (c) and (d) are presented as boxplots (the horizontal line within the box represents the median, the lower–upper limits of the box represent the interquartile range, and vertical bars represent the minimum and maximum values). The rectangles and bars in (b) represent the mean and the standard deviation, respectively.

*Significant difference from before to after the fluid challenge ($p < 0.05$).

†Significant difference between responders and nonresponders ($p < 0.05$).

Ability and accuracy of PPV and PVI to predict FR

The area under the ROC curve (AUROC) of PPV values recorded before the FC was significantly different from 0.5 (p <0.0001), denoting its ability to predict the response to volume expansion (Table 2 and Fig. 2a). Pulse pressure variation values >17% predicted responders to volume expansion with 25% of false positive results (100% minus the specificity of the test); while nonresponders were predicted by PPV values ≤17% with 13.3% of false negative results (100% minus the sensitivity of the test). The gray zone PPV cutoff values was 14–23% (Figure 2b). A total of 11/27 cats presented PPV values within the range associated with increased probability of false positive results, whereas 4/27 cats showed PPV values within the zone of high probability of false negative results.

The AUROC of PVI did not differ from 0.5 (p = 0.062) and could not predict responsiveness status (Table 2 and Fig. 2c). The gray zone of PVI was 16–41% (Figure 2d). From the 25 cats where PVI was obtained, 16 animals presented PVI values within the zone of diagnostic uncertainty.

Table 2 Receiver operating characteristics analysis for evaluating the ability of pulse pressure variation (PPV, n = 27) and of plethysmographic variability index (PVI, n = 25) to predict fluid responsiveness in cats that received a fluid challenge with 10 mL kg^{-1} of lactated Ringer's solution over 10 minutes.

Variable	AUROC (95% CI)	*p value* versus AUROC = 0.5	Best cutoff	Sensitivity (95% CI)	Specificity (95% CI)
PPV	0.853 (0.664–0.959)	<0.0001	>17%	86.7% (59.5–98.3)	75% (42.8–94.5)
PVI	0.702 (0.490–0.914)	0.062	>24%	46.2% (19.2–74.9)	91.7% (61.5–99.8)

AUROC, area under the receiver operating characteristics curve; CI, confidence intervals.

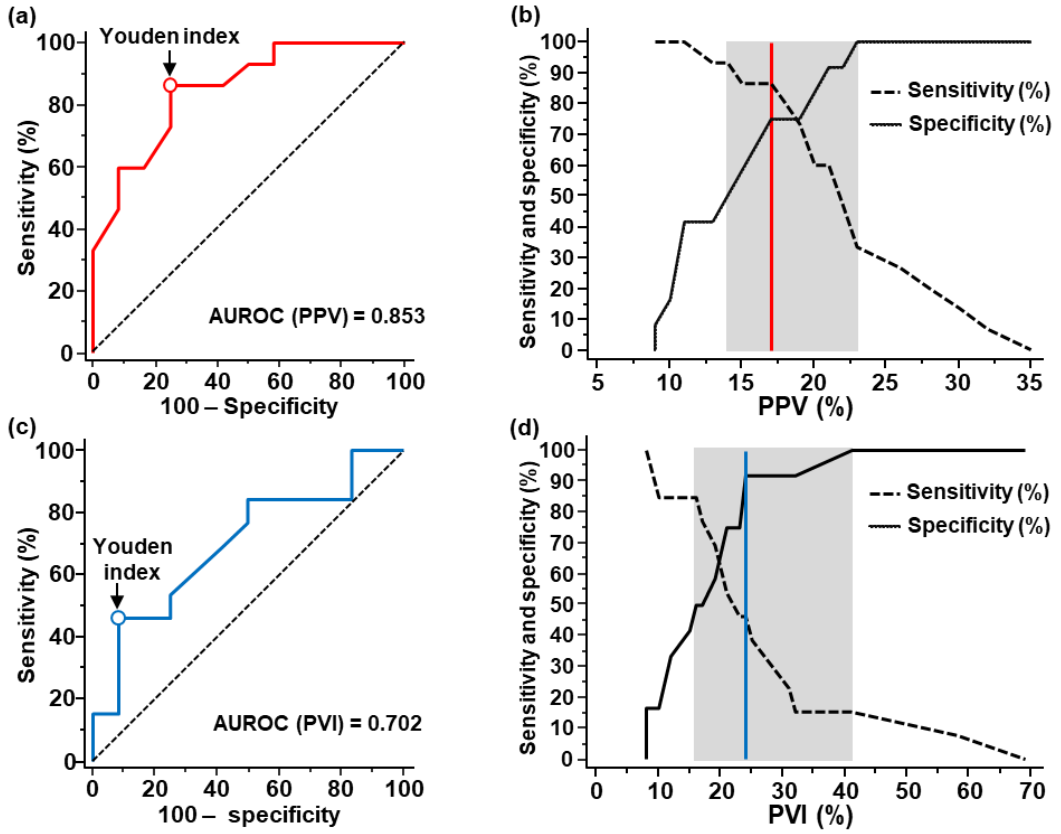

Figure 2 (a) Receiver operating characteristics (ROC) curve showing the point of maximum sensitivity and specificity (Youden index) and the area under the ROC curve (AUROC) of pulse pressure variation (PPV). (b) Simultaneous plot of sensitivity and specificity according to different PPV cutoff values showing zone of diagnostic uncertainty (gray shaded area) around the best cutoff value (vertical line). The ROC curve of the plethysmographic variability index (PVI) and the sensitivity and specificity curves showing zone of diagnostic uncertainty around best cutoff value of PVI (vertical line) are shown in (c) and (d), respectively.

End-tidal isoflurane, respiratory variables, demographic data and recovery from anesthesia

The F_E'Iso, respiratory variables and pulmonary mechanics did not differ between groups or withing groups. The pooled means ± standard deviation were: F_E'Iso, 1.24 ± 0.3%; expired V_T, 12.0 ± 0.5 mL kg^{-1}; f_R, 10 ± 2 breaths $minute^{-1}$; $P_E'CO_2$,35 ± 4 mmHg; C_{qst}, 1.8 ± 0.3 mL cmH_2O^{-1} kg^{-1}. The median (lower–upper

range) of pooled data of P_{plat} was 7 (5–12) cmH_2O.

Body weight was lower in responders (3.6 ± 0.6 kg) compared to nonresponders (4.3±0.5 kg) (p = 0.005). Total anesthesia time was 154 ± 31 minutes in responders and 138 ± 26 minutes in nonresponders to volume expansion (p = 0.618). Animals recovered from anesthesia without complications related to venous catheter placement, fluid administration (peripheral/pulmonary edema) or surgical procedure. All cats presented a small bruise at the point of femoral catheter placement that resolved spontaneously until seven days after anesthesia, as reported by the cat owners. Fifteen days after anesthesia no further complications were reported.

Discussion

This study showed that PPV recorded from an arterial catheter may be required to allow reliable prediction of FR in cats. Conversely, less invasive methods such as PVI may have limited clinical application in feline species. The ability of PPV to predict FR based on AUROC analysis (AUROC = 0.853) can be considered good (AUROC >0.75–0.90), but when the 95% CIs are considered (0.664–0.959), the predictive ability can vary from poor (AUROC >0.5–0.75) to excellent (AUROC >0.9) (Ray et. al. 2010). Such large variability was paralleled by a relatively large zone of diagnostic uncertainty denoting a poor level of accuracy of PPV to discriminate responders from nonresponders to volume expansion. The range of PPV values associated with a greater probability of false positive results (PPV = 18–23%) was larger and included more cats (11/27 animals) than the range of PPV values associated with a greater probability of false negative results (PPV = 14–17%, 4/27 cats). The increased probability of false positive prediction of responsiveness could have been caused by ventilation with an excessively large V_T for the feline species (12 mL kg^{-1}). Further studies are required to confirm if the accuracy dynamic preload indexes to predict responsiveness can be improved by mechanical ventilation using lower V_{Ts}.

The poor accuracy of PPV (wide gray zone) to predict FR was mainly attributable to the prediction of responders to volume expansion (PPV > 17%) in animals that were in fact nonresponders (increased probability of false positive results). However, heart rhythm irregularities, increased intraabdominal pressure secondary to pneumoperitoneum, and spontaneous breathing efforts during mechanical ventilation, which are known causes of false positive results (Michard 2015), were not observed in the animals evaluated.

Accurate prediction of FR by PPV and other dynamic preload indexes requires proper adjustment of the V_T delivered by the ventilator. Experimental studies point out that adjusting the V_T to 12 mL kg^{-1} with an inspiratory pause of 40% of inspiratory time may allow a more accurate prediction of FR in dogs because PPV values >16% predicted responders to volume expansion with high accuracy;

denoted by the absence of false positive results (100% specificity) and low incidence of false negatives (14% of false negatives, 86% specificity), and by the narrow zone of diagnostic uncertainty (15–16%) (Celeita-Rodríguez et al. 2019). However, evidence from the present study suggest that this V_T may be excessively large for accurate prediction of FR in cats because it was associated with a 25% false positive rate (75% specificity) and a relatively large zone of diagnostic uncertainty associated with higher probability of false positive results (18–23%). An excessively large V_T will increase variations in SV and pulse pressure induced by mechanical breaths (Kim and Pinsky 2008), potentially increasing PPV to values above the threshold that predict responders (PPV >17% in cats) in animals that are in fact nonresponders to volume expansion according to the reference method (transpulmonary thermodilution). Although the V_T set in the present study (12 mL kg^{-1}) may be excessively high to allow accurate prediction of FR by dynamic preload indexes, recent studies suggest that this V_T may not be elevated from a physiological standpoint in feline species (Martins et al. 2022). In anesthetized cats, adjusting the airway pressure (P_{plat}) to a maximum of 7 cm H_2O in pressure control mode (zero end expiratory pressure) was recommended to prevent lung overinflation assessed by computed tomography (Martins et al. 2022). Because pressure-controlled ventilation adjusted to deliver an inspiratory pressure of 7 cm H_2O resulted in a V_T that is close to the V_T adjusted in volume control mode in the present report (10.9 ± 3.9 mL kg^{-1}), it is unlikely that mechanical ventilation settings of the study reported here caused significant overinflation of the lungs.

Collective analysis of recent reports suggest that respiratory system (lung and chest wall) compliance recorded during mechanical ventilation is larger in cats than in dogs (Celeita-Rodríguez et al. 2019, Asorey et al. 2020, Martins et al. 2022). Considering that this difference could be attributed, at least in part, to a greater lung compliance in feline species, mechanical ventilation with the same V_T indexed to body weight has the potential to result in greater transmission of inspiratory/alveolar pressures to the intrathoracic cavity in cats than in dogs, which could in turn result in greater decreases in venous return and SV with each mechanical breath in feline species. Therefore, one could expect that the same V_T could result in larger

variations in SV and in pulse pressure in animals with more compliant lungs, potentially leading to false positive results, because PPV could be increased to values above the threshold that identifies responders in cats that are in fact nonresponders to volume expansion.

The inability of PVI to predict preload responsiveness in the present study could have been the result of poor perfusion in the site of pulse oximeter probe placement resulting in low PI values (Broch et al. 2011). It is possible that an excessive pressure applied by the clip-type pulse oximeter sensor compromised perfusion to the tongue and caused the very low PI values observed in the present report. Poor perfusion caused by the clip-type sensor can also explain the failure of the monitor to display PVI and PI values in two cats of the group of responders to volume expansion. According to one report in humans, PVI showed predictive value only in the group of individuals presenting PI values ≥ 4 (Broch et al. 2011). The PI recorded in the present study (median values ranging from 0.20 to 0.38) were substantially lower than PI values reported in anesthetized dogs (mean values ranging from 2.6 to 5.2) (Celeita-Rodríguez et al. 2019). Higher PI values observed in dogs may explain why PVI reliably predicted FR in canine species (Celeita-Rodríguez et al. 2019).

Studies have shown that PVI is a useful predictor of FR in humans and dogs (Cannesson et al. 2008; Zimmermann et al 2010; Julien et al. 2013; Siswojo et al. 2014; Endo et al. 2017; Sano et al. 2018; Celeita-Rodríguez et al. 2019). Although ROC curve analysis showed that PVI was unable to predict responsiveness in the cats of the present study, there was a statistical trend towards reaching a significance level ($p = 0.062$) when the AUROC of PVI (0.702) was compared with 0.5 (no predictive ability). *Post hoc* sample size calculation showed that a total of 62 cats would be necessary to demonstrate a significant predictive ability of PVI (AUROC >0.5), assuming a statistical power of 80% and an alpha level of 5%.

The reference method used to discriminate responders from nonresponders to volume expansion is a possible source of bias/inaccuracy in studies evaluating FR (Michard et al. 2015, Teixeira-Neto and Valverde. 2021). Methods with inadequate ability to detect changes in SV or CO over time, that is, with poor

trending ability, may lead to incorrect discrimination between responders and nonresponders to volume expansion. Although CO measured by transpulmonary thermoditution was reported to overestimate CO measured by pulmonary artery thermodilution in cats, this method resulted in acceptable trending ability with the clinical gold standard over a wide range of CO values in feline species (Kütter et al. 2014). The LSC is the minimum percent change that needs to be measured by a device to recognize the change as real, not attributed to random effects or to lack of precision of the method (Monnet et al. 2011). Results of the present report also showed that level of precision of triplicate SV_{TPTD} [LSC = 5.2 (1.1–17.4)%] was adequate to reliably discriminate responders (SV_{TPTD} ≥15%) from nonresponders (SV_{TPTD} <15%) to volume expansion.

Evaluation of FR in a population of healthy euvolemic cats was a limitation of the present study. Although intravenous volume expansion is not indicated in euvolemic animals, some important data could be obtained from the results of the present study. With the use of transpulmonary thermodilution as the reference method to discriminate the response to a FC, previous reports have shown that 83 to 100% of healthy euvolemic dogs respond to a single FC with increases in SV_{TPTD} > 15% (Celeita-Rodrígues et al. 2019, de Oliveira et al. 2021). Otherwise, the proportion of responders (56%) and nonresponders (44%) to one single fluid challenge observed in the present report approaches the proportion observed in critically ill humans, where the condition of preload dependency is less often observed (Marik et al. 2009). Comparison of the response to one single FC in dogs and cats corroborates with the clinical impression that the feline species is more susceptible to volume overload than dogs. Nearly 50% of cats were nonresponders to volume expansion with 10 mL kg^{-1} of lactated Ringer´s solution and therefore were already closer to the flat portion of the Frank Starling curve. According to the Marik-Philips curve it may be undesirable to promote volume expansion until animals that are positioned at the flat portion of the Frank Starling curve because the there is an increased risk of pulmonary edema (increased EVLWI) (Marik and Lemson 2014, Teixeira-Neto and Valverde 2021). Although EVLWI was not increased after FC administration in both responders and nonresponders, these

results should be pondered by the fact that this response was observed in healthy cats, which may differ from critically ill animals. If a FC is administered to cats whose heart is already positioned on the flat portion of the Frank Starling, and animals concomitantly present inflammatory lung disease or sepsis, larger increases in EVLWI and pulmonary edema may occur as sequelae of volume expansion (Marik and Lemson 2014, Teixeira-Neto and Valverde 2021).

In summary, PPV was able to predict FR with poor accuracy in cats ventilated with a V_T of 12 mL kg^{-1}. The relatively high percentage of false positive prediction of responders to volume expansion, and the wide gray zone of PPV associated with increased probability of false positive results, suggests that the V_T adjusted in the present report is excessively large to allow accurate prediction of FR in feline species. Despite its noninvasive nature, PVI showed limited clinical application in the cats of the present study. Future studies can explore the effect of smaller V_{Ts} on the predictive ability of dynamic preload indexes in cats.

References

Asorey I, Pellegrini L, Canfrán S, Ortiz-Díez G, Aguado D. (2020) Factors affecting respiratory system compliance in anaesthetised mechanically ventilated healthy dogs: a retrospective study. J Small Anim Pract 61, 617–623.

Broch O, Bein B, Gruenewald M, Höcker J, Schöttler J, Meybohm P, et al. (2011) Accuracy of the pleth variability index to predict fluid responsiveness depends on the perfusion index. Acta Anaesthesiol Scand 55, 686–693.

Cannesson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, et al. (2008) Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude predict fluid responsiveness in the operating theatre. Br J Anaesth 101, 200–206.

Celeita-Rodríguez N, Teixeira-Neto FJ, Garofalo NA, Dalmagro TL, Girotto CH, Oliveira GCV, et al. (2019) Comparison of the diagnostic accuracy of dynamic and static preload indexes to predict fluid responsiveness in mechanically ventilated, isoflurane anesthetized dogs. Vet Anaesth Analg 46, 276–288.

Dalmagro TL, Teixeira-Neto FJ, Celeita-Rodríguez N, Garofalo NA, López-Castañeda B, Nascimento-Junior PD. (2021) Comparison between pulse pressure variation and systolic pressure variation measured from a peripheral artery for accurately predicting fluid responsiveness in mechanically ventilated dogs. Vet Anaesth Analg 48, 501–508.

de Oliveira GCV, Teixeira-Neto FJ, Dalmagro TL, Alfonso A, Celeita-Rodríguez N, Lobo CPC, et al. (2021) Use of aortic flow indexes derived from transthoracic echocardiography to evaluate response to a fluid challenge in anesthetized dogs. Vet Anaesth Analg 48, 187–197.

DeLong ER, DeLong DM, Clarke-Pearson DL. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44, 837–845.

Endo Y, Kawase K, Miyasho T et al. (2017) Plethysmography variability index for prediction of fluid responsiveness during graded haemorrhage and transfusion in sevoflurane-anaesthetized mechanically ventilated dogs. Vet Anaesth Analg 44, 1303–1312.

Fantoni DT, Ida KK, Gimenes AM, Mantovani MM, Castro JR, Patrício GCF, et al. (2017) Pulse pressure variation as a guide for volume expansion in dogs undergoing orthopedic surgery. Vet Anaesth Analg 44, 710–718.

Gonçalves LA, Otsuki DA, Pereira MA, Nagashima JK, Ambrosio AM, Fantoni DT. (2020) Comparison of pulse pressure variation versus echocardiography-derived stroke volume variation for prediction of fluid responsiveness in mechanically ventilated anesthetized dogs. Vet Anaesth Analg 47, 28–37.

Julien F, Hilly J, Sallah TB, Skhiri A, Michelet D, Brasher C, et al. (2013) Plethysmographic variability index (PVI) accuracy in predicting fluid responsiveness in anesthetized children. Paediatr Anaesth 23, 536–546.

Kim HK, Pinsky MR. (2008) Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. Crit Care Med 36, 2858–2862.

Kütter AP, Bektas RN, Hofer CK, Larenza Menzies MP, Bettschart-Wolfensberger R. (2015) Trending ability and limitations of transpulmonary thermodilution and pulse contour cardiac output measurement in cats as a model for pediatric patients. J Clin Monit Comput 29, 377–383.

Marik PE, Cavallazzi R, Vasu T, Hirani A. (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37, 2642–2647.

Marik PE, Lemson J. (2014) Fluid responsiveness: an evolution of our understanding. Br J Anaesth 112, 617–620.

Martins ARC, Ambrósio AM, Fantoni DT, Pinto ACBCF, Villamizar-Martinez LA, Soares JHN, et al. (2022) Computed tomography assessment of tidal lung overinflation in domestic cats undergoing pressure-controlled mechanical ventilation during general anesthesia. Front Vet Sci 9, 10.

Michard F, Chemla D, Teboul JL. (2015) Applicability of pulse pressure variation: how many shades of grey? Crit Care 19, 144.

Monnet X, Persichini R, Ktari M, Jozwiak M, Richard C, Teboul JL. (2011) Precision of the transpulmonary thermodilution measurements. Crit Care 15, R204.

Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et. al. (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol 18, 12.

Ray P, Le Manach Y, Riou B, Houle TT. (2010) Statistical evaluation of a biomarker. Anesthesiology 112, 1023–1040.

Robertson SA, Gogolski SM, Pascoe P, Shafford HL, Sager J, Griffenhagen GM. (2018) AAFP Feline anesthesia guidelines. J Feline Med Surg 20, 602–634.

Sano H, Seo J, Wightman P, Cave NJ, Gieseg MA, Johnson CB, et al. (2018) Evaluation of pulse pressure variation and pleth variability index to predict fluid responsiveness in mechanically ventilated isoflurane-anesthetized dogs. J Vet

Emerg Crit Care 28, 301–309.

Siswojo AS, Wong DM, Phan TD, Kluger R. (2014) Pleth variability index predicts fluid responsiveness in mechanically ventilated adults during general anesthesia for noncardiac surgery. J Cardiothorac Vasc Anesth 28, 1505–1509.

Teixeira-Neto FJ, Valverde A. (2021) Clinical application of the fluid challenge approach in goal-directed fluid therapy: What can we learn from human studies? Front Vet Sci 8, 25.

Tukey, JW. (1977) Exploratory data analysis 2, 131–160.

Zimmermann M, Feibicke T, Keyl C, Prasser C, Moritz S, Graf BM, et al. (2010) Accuracy of stroke volume variation compared with pleth variability index to predict fluid responsiveness in mechanically ventilated patients undergoing major surgery. Eur J Anaesthesiol 27, 555–561.