LUCAS ALAIÃO GONÇALVES

AVALIAÇÃO DA RESPONSIVIDADE A FLUIDO POR MEIO DE ÍNDICES DINÂMICOS EM CÃES MECANICAMENTE VENTILADOS E SUBMETIDOS A DIFERENTES TIPOS DE CIRURGIA

São Paulo

2018

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Tese apresentada ao Programa de Pós-Graduação em Clínica Cirúrgica Veterinária da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo para obtenção o título de Doutor em Ciências

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Orientadora

Profª Drª Denise Tabacchi Fantoni

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CERTIFICADO

Certificamos que a proposta intitulada "AVALIAÇÃO DA RESPONSIVIDADE A FLUIDO POR ÍNDICES DINÂMICOS EM CÃES SUBMETIDOS A CIRURGIA ABDOMINAL", protocolada sob o CEUA nº 6613081116, sob a responsabilidade de **Denise Tabacchi Fantoni** *e equipe; Lucas Alaião Gonçalves* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **aprovada** pela Comissão de Ética no Uso de Animais da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo (CEUA/FMVZ) na reunião de 15/03/2017.

We certify that the proposal "ASSESSMENT OF FLUID RESPONSIVENESS BY DYNAMIC INDICES IN CANINE ABDOMINAL SURGERYY", utilizing 50 Dogs (males and females), protocol number CEUA 6613081116, under the responsibility of **Denise Tabacchi Fantoni** *and team; Lucas Alaião Gonçalves* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **approved** by the Ethic Committee on Animal Use of the School of Veterinary Medicine and Animal Science (University of São Paulo) (CEUA/FMVZ) in the meeting of 03/15/2017.

Finalidade da Proposta: Pesquisa

Vigência da Proposta: de 11/2016 a 06/2018   Área: Anestesiologia

Origem:	Animais de proprietários						
Espécie:	Cães	sexo:	Machos e Fêmeas	idade:	1 a 16 anos	N:	50
Linhagem:	Misto			Peso:	7 a 60 kg		

Resumo: A hipotensão não corrigida pode causar distúrbios ácido-base, isquemia, lesão renal em vários órgãos, dependendo do grau do déficit vascular. A reanimação volêmica é a primeira linha de tratamento para a maioria dos casos, assim como importante passo para o início da terapia baseada em metas. Dessa forma, na ultima década, vários tipos de monitorização minimamente invasiva têm sido desenvolvidos. Dentre elas, as técnicas que avaliam índices dinâmicos e intermitentes apresentam melhores resultados. O objetivo desse trabalho será de avaliar comparativamente dois índices de responsividade a fluido em cães submetidos a celiotomia mediana, correlacionando aos valores entre os métodos no abdômen fechado e aberto. A avaliação terá início com o animal já anestesiado, após bloqueio neuromuscular, e será dividido em: antes da incisão no peritônio (TAF □ tempo abdômen fechado) e após a incisão no peritônio (TAA □ tempo abdômen aberto). Serão utilizados como parâmetros para intervenção a detecção de PAM < 65 mmHG. Um desafio hídrico de 15 mL/Kg de Ringer com Lactato intravenoso em 15 minutos; sendo que a cada 5 min serão obtidos novos valores tanto do ?pp quanto da avaliação ecocardiográfica. Os dados serão testados para normalidade pelo teste de Sharpiro-Wilk, em seguida os grupos serão comparados pela Anova seguida do teste t-student pareado. Ainda, será utilizada a curva ROC para comparação dos testes diagnósticos. Será considerado um nível de significância de 5% para todos os testes.

Local do experimento: Hospital Veterinário da Universidade de São Paulo - Setor de Obstetrícia e ou Cirurgia.

São Paulo, 28 de setembro de 2017

Profa. Dra. Anneliese de Souza Traldi
Presidente da Comissão de Ética no Uso de Animais
Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo

Claudia Madalena Cabrera Mori
Vice-Presidente
Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo

FOLHA DE AVALIAÇÃO

Autor: GONÇALVES, Lucas Alaião

Título: **Avaliação da responsividade a fluido por meio de índices dinâmicos em cães mecanicamente ventilados e submetidos a diferentes tipos de cirurgia**

Tese apresentada ao Programa de Pós-Graduação em Clínica Cirúrgica Veterinária da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Data: _____/_____/_____

Banca Examinadora

Prof. Dr.____

Instituição:__________________________ Julgamento:______________________

Prof. Dr.____

Instituição:__________________________ Julgamento:______________________

Prof. Dr.____

Instituição:__________________________ Julgamento:________________________

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A Deus pela oportunidade da vida, pela saúde e força para superar as dificuldades.

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Para todos que contribuíram para a realização desse trabalho, o meu muito obrigado.

RESUMO

GONÇALVES, L. **A. Avaliação da responsividade a fluido por meio de índices dinâmicos em cães mecanicamente ventilados e submetidos a diferentes tipos de cirurgia.** [Evaluation of fluid responsiveness by dynamics indices in mechanically ventilated dogs undergoing diferente types of surgery]. 2018. 69 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2018.

A prova de carga com cristaloides é uma das intervenções mais comumente realizadas diante da hipotenção trans-anestésica, contudo, nem todo animal que apresenta hipotensão é responsivo a fluidoterapia. Por esta razão, na ultima década, vários índices que avaliam a responsividade a fluido foram desenvolvidos com o intuito de otimizar o emprego da fluidoterapia no paciente hemodinamicamente instável. . O objetivo desse trabalho foi avaliar três diferentes índices de responsividade, quais sejam: a variação da integral velocidade-tempo (ΔIVT), variação da velocidade de pico do fluxo aórtico (ΔVFAO) e variação da pressão de pulso (VPP) no que tange a sua capacidade diagnóstica. Para tanto, foram utilizados 40 cães submetidos a anestesia inalatória associada a anestesia epidural. Em caso de detecção de pressão arterial média < 65 mmHg, foi realizado uma prova de carga com cristalóde de 15 ml/kg durante 15 minutos. Volume sistólico (VS) obtido por meio da ecocardiografia transesofágica foi utilizado para definir a responsividade a fluido, sendo que os cães responsivos foram aqueles em que um aumentou no VS igual ou superior a 15% foi observado após o desafio com o cristalóide. Os dados foram avaliados pela análise da curva ROC para comparação dos testes diagnósticos, assim como a análise da curva cinzenta e também pela probabilidade pré e pós-teste. Trinta cães (75%) foram responsivos a fluidoterapia e 10 (25%) não eram responsivos. Tanto a ΔVFAO quanto a ΔIVT apresentaram boa capacidade discriminativa pela análise da Área sob a curva (0.89 e 0.93), assim como a VPP (0.88). Além disso, a análise da área cinzenta e da probabilidade pós-teste sugeriram uma melhor capacidade em diagnosticar os animais responsivos a fluido do que não-responsivos. Os valores de corte que distinguem responsivos a fluidoterapia de não-responsivos foram semelhantes aos observados na literatura. Sobe ventilação controlada e após a anestesia epidural, os índices ecocardiográficos de responsividade a fluido apresentaram boa capacidade discriminativa.

Palavras-chave: Transesofágico. Pré-carga. Prova de carga. Ecocardiografia.

ABSTRACT

GONÇALVES, L. A. **Evaluation of fluid responsiveness by dynamics indices in mechanically ventilated anesthetized dogs undergoing diferente types of surgery.** [Avaliação da responsividade a fluido por meio de índices dinâmicos em cães mecanicamente ventilados e submetidos a diferentes tipos de cirurgia]. 2018. 69 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2018.

Intravenous fluid resuscitation is the first therapeutic choice used against arterial hypotension, however, not every animal with arterial hypotension is responsive to fluids. In the past decade, many indices of fluid responsiveness were introduced and plenty of studies covering many scenarios on the surgery context have been published. Therefore, the aim of this study was to evaluate the diagnostic accuracy of velocity-time integral variation (ΔVTI), peak aortic velocity variation (ΔVpeak) and pulse pressure variation (PPV). Forty dogs were included in this study. Whenever a mean arterial pressure < 65 mmHg, a 15 ml/kg fluid challenge with crystalloids over 15 minutes was administered. Responders to fluids were defined by means of transesophageal echocardigraphy if an increase equal to or greater than 15% in stroke volume was observed after the fluid challenge. For the statistical evaluation, ROC curve analysis, gray zone approach, and pre-test, post-test probability were used to estimate the diagnostic capability of each index. Thirty (75%) dogs were responders and 10 (25%) were non-responders. Both velocity-time integral variation (ΔVTI) and aortic blood velocity variation (ΔVpeak) showed a good diagnostic capability according to the Area under curve analysis (0.89 e 0.93), as well as PPV (0.88). Moreover, the gray zone approach and the post-test probability suggests a greater ability to detect fluid responders. The optimum cutoff value to discriminate responders from non-responders for all dynamics indices were similar to that observed in the literature. After the epidural anesthesia and under mechanical ventilation, all dynamic índices showed good diagnostic ability in predicting fluid responsiveness.

Keywords: Transesophageal. Preload. Fluid challenge. Echocardiography

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LISTA DE ABREVIAÇÕES

DC – Débito cardíaco

ET'CO2 – Dióxido de carbono corrente final

FIO2 – Fração inspirada de oxigênio

IVT – Integral velocidade tempo

PAOP – Pressão de oclusão da artéria pulmonar

PEEP – Pressão expiratória final positiva

PVC – Pressão venosa central

UTI – Unidade de terapia intensiva

VDFVD – Volume diastólico final do ventrículo direito

VS – Volume sistólico

VVS – Variação do volume sistólico

VSVD – Volume sistólico final do ventrículo direito

VSVE – Volume sistólico final do ventrículo esquerdo

ΔPP – Variação da pressão de pulso

ΔIVT – Variação da integral velocidade tempo

ΔVFAo – Variação da velocidade do fluxo aortico

ALT – Alanine aminotransferase

AP – Alkaline phosphatase

AUC – Area under the curve

CO – Cardiac output (CO)

FE´Iso – End-tidal isoflurane

FE – Fluid expansion

fR – Respiratory rate

HR – Heart rate

IV - Intravenously

MAP – Mean arterial pressure

PEEP – Positive end-expiratory pressure

PE′CO2 – End-tidal carbon dioxide

PPV – Pulse pressure variation

ROC – Receiver Operating Characteristic

SD – Standard deviation

SVR – Systemic vascular resistance (SVR)

SVV – Stroke volume variation

VE – Volume expansion

Vt – Tidal volume

ΔVTI – Velocity time integral variation

ΔVpeak – Peak aortic velocity variation

ΔVpeak – Peak aortic velocity variation

ΔCO – Cardiac output variation

1 Introdução geral

1 INTRODUÇÃO

A mortalidade anestésica no âmbito da Medicina Veterinária varia entre 0,05 a 3,12%, em cães e 0,11 a 3,33% em gatos, sendo os maiores valores pertencentes aos animais classificados como ASA III – V (CLARKE; HALL, 2009). Os principais fatores envolvidos nessa mortalidade incluem agentes anestésicos, equipamentos anestésicos, monitoração multiparamétrica, cuidados trans e pós-operatórios e aumento de programas de qualificação em anestesiologia (DESMONTS, 1994; SIGURDSSON; MCATEER, 1996).

Nesse contexto, a monitoração transoperatória contribuiu significativamente para uma anestesia mais segura, através dos mais variados tipos de dispositivos de vigilância e prevenção (CAULKETT et al., 1998; BODEY; DIAMOND, 1994). Esses aparelhos permitem a monitoração de vários sistemas do organismo animal, além de guiar a terapia em momentos de instabilidade (BODEY; DIAMOND, 1994; DE LAFORCADE; ROZANSKI, 2001; CHEN et al., 2005). Uma das intervenções mais comuns durante o procedimento anestesico é a expansão volêmica, que é indicada como a primeira conduta em face a hipotensão arterial (MONNET et al., 2016; FEISSEL et al., 2001). Contudo, nem todo episódio hipotensivo é responsivo a fluidoterapia (pré-carga dependente), tornando essa conduta empírica e podendo levar ao insucesso na terapia (RUBENFELD et al., 2012; HERNANDEZ et al., 2013). Adicionalmente, a utilização de fármacos vasoativos em animais hipovolêmicos pode prejudicar a perfusão de órgãos (MARAKAWA et al. 1988).

Dessa forma, a avaliação da volemia e do *status* cardiovascular é essencial para guiar a terapia, e vários índices minimamente invasivos da avaliação da responsividade a fluido, têm sido propostos (MARIK; CAVALLAZZI, 2013; VALVERDE et al., 2011). Dentre elas, as técnicas que avaliam as flutuações da pressão de pulso e aqueles relacionados à ecocardiografia apresentam resultados promissores (CAMEL et al., 2015; MARIK; CAVALLAZZI, 2013; VALVERDE et al., 2011).

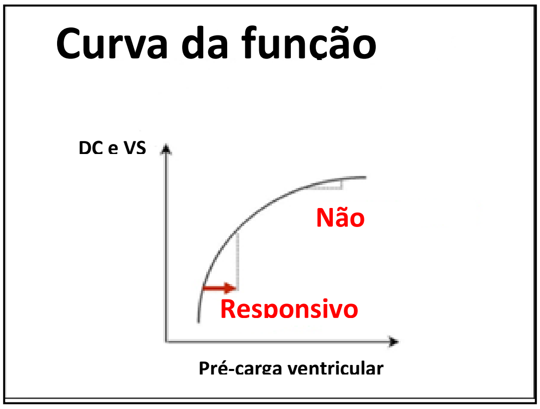
Poucos trabalhos abordaram essa temática de índices de responsividade a fluido no contexto anestesia, e muitas vezes está relacionado com cães submetidos a procedimentos específicos, dentre a mais variada gama de cenários existentes (FANTONI et al. 2017; BUCCI et al. 2017b; ENDO et al. 2017). A extrapolação de valores de corte deve ser feita com cautela, pois assim como observado em alguns trabalhos, esses índices são afetados por vários fatores, tornando indispensável a individualização de cada situação (MARIK; CAVALLAZZI, 2013; VALVERDE et al., 2011; VINCENT et al., 2011).

2 REVISÃO DE LITERATURA

A avaliação do volume intravascular para o restabelecimento do equilíbrio volêmico é ainda hoje um dos grandes desafios da Medicina moderna (MARIK et al., 2009; VINCENT et al., 2011). Tradicionalmente, um coração normal ajusta o volume sistólico (VS) de acordo com a variação do volume diastólico final de seu ventrículo, pela relação que existe entre a energia de contração e o comprimento das fibras cardíacas (pré-carga) após a diástole. Essa relação, também conhecida como mecanismo de Frank-Starling, permite entender o conceito dos métodos de monitoração da pré-carga, que em sua maioria, avaliam diretamente ou indiretamente a interação entre os grandes vasos e sistema respiratório com o coração (GUYTON, 2006).

A interação descrita por Frank-Starling também permite a construção de sua curva (Figura 1), que sintetiza todo o conceito de responsividade a fluido, pois, através de seu formato sigmóide possibilita entender que animais localizados na parte ascendente estão mais propensos a aumentar seu débito cardíaco (DC) após o aumento de sua pré-carga ventricular, ou seja, através de um desafio volêmico. Por outro lado, animais localizados no platô da curva muito provavelmente terão um acrescimo ínfimo em seu DC após um desafio volêmico (MULLER et al.; 2011; MARIK et al.; 2010). Pensando em números, ser responsivo a fluido significa apresentar um aumento do DC ou VS de 15% após o desafio volêmico de 500 ml, segundo diversos estudos na medicina (MARIK 2010; FEISSEL et al. 2001; DE BACKER et al. 2005, GUYTON, 2006). Em contra partida, o indivíduo não responsivo é aquele em que o aumento do DC/VS é menor que 15 %, após desafio volêmico (FANTONI et al. 2017; BUCCI et al. 2017a).

Figura 1 – Curva de Frank Starling demonstrando a relação entre a pré-carga e o débito cardíaco.



Fonte: Adaptado de Guyton, (2006).

2.1 Índices estáticos

Considerando novamente a curva de Frank-Starling (Figura 1), um animal responsivo a fluido, isto é, na parte ascendente da curva, sugere estar mais propenso a apresentar valores de volume e ou pressão de enchimento mais baixos. Assim, é dessa forma que os primeiros marcadores de pré-carga estáticos foram propostos na literatura, se baseando nessas duas variáveis (pressão e volume) da interação de Frank-Starling (GUERIN et al., 2013; MARIK, 2010).

Nesse contexto, vários métodos estáticos de avaliação da pré-carga foram sugeridos, e muitos deles ainda são utilizados, os exemplos mais comuns incluem: pressão venosa central (PVC), pressão de oclusão da artéria pulmonar (POAP) e volume diastólico final do ventrículo direito (VDFVD). Dentre eles a avaliação da pressão venosa central é um dos principais representantes desse grupo (GUERIN et al., 2013; MARIK et al., 2008). Devido a localização próxima ao átrio direito, esse método avalia o retorno de sangue pelas veias cavas e conseqüentemente a pressão gerada, que por sua vez é utilizado como um substituto da pressão do átrio direito. Assim, o seu valor absoluto ou a variação dessa pressão antes e após um desafio volêmico foi sugerida como teste de responsividade a fluido (MARIK et al., 2010; GUERIN et al., 2013).
Outro método importante a destacar, é o cateter de artéria pulmonar (GANZ et al., 1970). A utilização do cateter de artéria pulmonar permite a avaliação da pressão de oclusão da artéria pulmonar (POAP), que por sua vez, foi descrito como um índice de avaliação da volemia,

principalmente como guia durante a fluidoterapia (NAHOURAII; ROWELL, 2010; GUERIN et al., 2013).

Contudo, apesar da popularidade dos métodos estáticos citados acima, uma série de estudos levantaram evidências que suportam a sua baixa correlação com marcadores dinâmicos de responsividade a fluido (KUMAR et al., 2004; MARIK, 2010). Da mesma forma, muitos autores e vários consensus não recomendam mais esse métodos para esse fim, (VINCENT et al., 2011; NAHOURAII; ROWELL, 2010).

Por outro lado, é importante destacar que atrelado a esses métodos estáticos, vários trabalhos renomados por seu impacto na comunidade médica surgiram, como por exemplo o protocolo de abordagem de pacientes sépticos descrito por Rivers et al. no qual a PVC era o parâmetro empregado para guiar a fluidoterapia (2001).

2.2 Índices dinâmicos

Os índices dinâmicos surgem no cenário de unidades de terapia intensiva (UTI) como um método promissor e considerado atualmente como o método com maior acervo de evidências a seu favor (MARIK, 2010; VINCENT et al., 2015; VINCENT et al., 2011).

Se por um lado os índices estáticos avaliam a variabilidade de uma variável (pressão ou volume) após um desafio volêmico, os índices dinâmicos avaliam a variabilidade da relação que existe entre o VS e a respiração (MONNET et al., 2016; CHERPANATH et al., 2013). Mais precisamente, os índices dinâmicos avaliam a variabilidade da variação do VS durante a ventilação controlada. Isso se deve pela interação cardiopulmonar, já que o sistema cardiovascular é alterado durante cada inspiração (CHERPANATH et al., 2013). De maneira geral sob ventilação controlada, o período inspiratório eleva a pressão pleural, gerando uma diminuição no retorno venoso e conseqüentemente no DC, já no período expiratório esses efeitos são atenuados, levando a uma normalização (aumento) do DC (CHERPANATH et al., 2013). Além da diminuição do retorno venoso, o aumento da pressão torácica, durante a inspiração, eleva a pressão transpulmonar, que por sua vez aumenta a pós carga do ventrículo direito, diminuindo, principalmente, o VS do lado direito (CHERPANATH et al., 2013; MONNET et al., 2016). Juntos, esses fatores contribuem para a redução do DC/VS do ventrículo direito, que posteriormete resulta em uma diminuição do DC/VS do ventrículo esquerdo, e assim podendo tornar os ventrículos pré-carga dependentes (CHERPANATH et al., 2013).

A variação do volume sistólico (VVS) foi um dos primeiros métodos desenvolvidos para a avaliação dinâmica da responsividade a fluido (MONNET et al., 2016; MICHARD, 2005). A monitoração do VS é feita através de acessos arteriais acoplados a monitores que calculam essa variável por meio da análise do contorno do pulsos e suas flutuações durante a ventilação controlada (VINCENT et al., 2015; LANSDORP et al., 2012).

A variação da pressão de pulso (ΔPP) é outro método dinâmico que avalia a responsividade a fluido através da diferença entre as pressões sistólicas e diastólicas, durante o ciclo respiratório (MAHJOUB et al., 2014; LANSDORP et al., 2012). Esse método além de ser minimamente invasivo, é o que apresenta maior acurácia, até o momento, no que diz respeito a responsividade a fluido (SOLIMAN et al., 2015; MACDONALD et al., 2015; MICHARD, 2005). Na medicina, os valores de corte entre 12 – 15% são descritos, já na medicina veterinária valores entre 13 – 15% foram propostos para suínos e cães (Noel-Morgan, J. et al., 2013 FANTONI et al., 2017).

2.3 Ecocardiografia

Nos últimos anos, várias técnicas não invasivas ou minimamente invasivas ecocardiograficas foram propostas como alternativa a avaliação da responsividade a fluido (FEISSEL et al., 2001). Essas técnicas ocupam seu lugar principalmente nos casos em que outros tipos de monitoração não são possíveis, ou como um complemento na monitoração (FEISSEL et al., 2001; SKULEC et al., 2009). O período perioperatório de animais gravemente acometidos ou em choque é um exemplo comum em que sua utilização é necessária, pois muitas vezes cursam com prejuízo na entrega de oxigênio e consumo de oxigênio. Assim, devido ao fato da entrega de oxigênio ser determinada pelo DC e o conteúdo arterial de oxigênio, a manutenção e monitorização do DC é um pilar nas condutas terapêuticas do paciente gravemente doente (PORTER et al., 2015; VINCENT et al., 2011).

Nesse contexto, alguns índices ecocardiográficos podem ser utilizados para a monitorização do VS, na avaliação do status volêmico e também para o cálculo do DC (PORTER et al., 2015).

Com o auxílio do Doppler pulsátil o VS pode ser estimado através do cálculo do IVT pela área de corte transversal (cm²), tanto da via de saída do ventrículo direito (VSVD) como pela VSVE. Ainda, o valor do VS multiplicado pela freqüência cardíaca fornece o valor do

DC (PORTER et al., 2015; VINCENT et al., 2011).

Dessa forma, mediante um episódio de hipotensão, vários índices ecocardiográficos podem ser utilizados como guia terapêutico, através da diferenciação dos responsivos a fluido dos não responsivos. Os índices com maior destaque incluem a variação da integral velocidade-tempo (ΔIVT) e variação da velocidade do fluxo aórtico (ΔVFAo). Uma comparação feita entre o ΔPP e a ecocardiografia em relação à responsividade a fluido, demonstrou que a ΔIVT apresentou uma correlação positiva com os valores da ΔPP (CAMEL et al., 2015). Outro trabalho correlacionou de forma positiva a responsividade a fluido pelo índice integral velocidade-tempo (IVT) da VSVE com as mudanças cíclicas na respiração controlada (FEISSEL et al., 2001; PORTER et al., 2015). Adicionalmente, a ecocardiografia também permite a avaliação da resposta a fluido por outros índices, como a colapsabilidade da veia cava ou diâmetro da veia cava (MANDEVILLE; COLEBOURN, 2012).

No acervo da Medicina Veterinária, apenas um trabalho investigou a acurácia de um índice ecocardiográfico de responsividade a fluido (ΔIVT e ΔVFAo), com um valor de corte de 7,2 e 13 %, respectivamente (FANTONI et al., 2017).

A abordagem transtorácica, com probe tradicional são descritos mais comumente, porém em muitas cirurgias não é possível sua utilização, e nesses casos a abordagem transesofágica oferece maior facilidade na avaliação (REBEL et al., 2012). Outro ponto importante para o funcionamento desses índices é a manutenção da interação cardiorespiratória, ou seja, é necessário que o animal esteja em ventilação controlada, com um volume corrente de 8 – 10 ml/kg, complacência normal e com seus músculos respiratórios paralisados (CHERPANATH et al., 2013; DÍAZ et al., 2015). Também podem interfirir nessa avaliação, animais arrítmicos, taquicárdicos e com algum grau de insuficiência sistólica, animais submetidos a terapia com vasoativos (CHERPANATH et al., 2013; HADIAN et al., 2011) e dexmedetomidina (DINIZ et al., 2014), e ainda, animais submetidos a cirurgias torácicas (CHERPANATH et al., 2013).

2.4 Responsividade a fluido em vários cenários

Índices que avaliam a pré-carga de forma dinâmica são em sua maioria resultado da interação cardio-pulmonar durante a ventilação mecânica, e é através dessa interação que alguns trabalhos demonstraram sua acurácias diagnóstica (MICHARD, 2005; DE BACKER et al. 2005). Contudo, é importante salientar que a maioria desses estudos apresentam populações sob ventilação controlada com volume corrente entre 8 – 10 ml/kg, relação FC e FR de 3-1, ausência de arrítmias e de esforço respiratório espontânea e sob nenhum efeito de vasoativos. Isto é, quando tais índices são aplicados em outros contextos clínico-cirurgicos, muita cautela deve ser tomada visto que o tipo de cirurgia, anestesia e outras condições podem variar e influenciar a acurácia diagnóstica de cada índice (MARIK et al., 2009; MICHARD; TEBOUL, 2002).

A extrapolação de valores de corte de um cenário para outro também podem influenciar as características diagnósticas de cada índice. Como exemplo, a procalcitonina, um biomarcador diagnóstico, apresenta uma sensibilidade maior para diagnosticar infecções bacterianas em pacientes com meningite quando comaparado em pacientes com pielonefrite (LEMIALE et al., 2007). Dessa forma, a individualização das características diagnósticas dos índices dinâmicos devem ser levado em consideração, principalmente quando o cenário do trabalho original diferir (MARIK et al., 2009; MICHARD, 2005).

Um cenário relativamente comum em centros cirúrgicos veterinários é a cirurgia abdominal, que classicamente influência os índices de responsividade a fluido pela relação que existe entre a pressão abdominal e as pressões torácicas. A variação da pressão abdominal influencia diretamente a resistência do diafragma a mudanças, agindo como uma força opositora ou facilitadora a ventilação mecânica. O aumento da pressão abdominal, por exemplo, leva a uma diminuição da complacência torácica, que por sua vez eleva as pressões intratorácicas, exacerbando a variação dos índices dinâmicos (JACQUES et al. 2011). Outro cenário comum é a cirurgia com bloqueio epidural, o qual altera a resistência vascular sistêmica, podendo influenciar o sistema cardiovascular. Um mecanismo comum da alteração da resistência vascular sistêmica é a hipovolemia relativa, que acontece pela re-distribuição do volume vascular que mimetiza um quadro de hipovolemia (SHIBATA K, YAMAMOTO Y 1989). Diversos trabalhos investigaram a acurácia diagnóstica de índices dinâmicos nos mais variados cenários clínicos, de cirurgias cardíacas, abdomen aberto, sepse e insuficiência respiratória (MANDEVILLE; COLEBOURN 2012; YI et al. 2017). Contudo, a influência dos cenários cirúrgicos sobre os índices de responsividade a fluido em cães, foram pouco estudados.

Dessa forma, o objetivo desse trabalho foi de avaliar a acurácia diagnistica de índices de responsividade a fluido em cães submetidos a anestesia epidural, cães sépticos e provenientes de cirurgias de rotina em que a infusão de fentanil foi necessária

Capítulo 2

Evaluation of three dynamic indices of fluid responsiveness in dogs undergoing epidural anesthesia

3 EVALUATION OF THREE DYNAMIC INDICES OF FLUID RESPONSIVENESS IN DOGS UNDERGOING EPIDURAL ANESTHESIA

Abstract

Arterial hypotension is one of the most common complications observed during general anesthesia, especially when it is combined with epidural anesthesia. Since fluid overload was showed to be as harmful as hypovolemia, to evaluate wether the animal need fluids or vasopressor is essencial, and dynamic indices of fluid responsiveness can be used to discriminate fluid responders from nonresponders. Therefore, the purpose of this study was to evaluate the diagnostic accuracy of peak aortic velocity variation (ΔVpeak), velocity time integral variation (ΔVTI) and pulse pressure variation (PPV), in dogs submitted to epidural anesthesia. Fourty dogs were submitted to a 15 ml/kg infusion of crystalloid solution over 15 minutes, if mean arterial pressure (MAP) < 65 mmHg was detected. The fluid expansion was considered effective (fluid responders) if an increase by $\geq 15\%$ in the stroke volume was observed by transesophageal Doppler. Receiver operating characteristcs (ROC) curves, gray zone approach and post-test probability were used to evaluate the diagnostic capability of the dynamic indices. Thirty (75%) dogs were responsive to fluids and 10 (25%) were non-responders. The area under the ROC curve for PPV was (0.89 ± 0.10), for ΔVpeak was (0.88 ± 0.10) and ΔVTI (0.93 ± 0.09). Considering the gray zone approach, the percentage of dogs that fell into it inconclusive area for ΔVTI was 10% (4/40), 17.5% (7/40) for PPV and 17.5% (7/40) for ΔVpeak. In addition, positive post-test probability analysis showed a relatively high value for all indices, and negative post-test probability value of all dynamic indices decreased poorly. Meaning that those indices have a good capability to diagnose fluid responders and a median capability to detect nonresponders. In conclusion, all three dynamic indices have a good capability to predict fluid responsiveness in dogs submitted to epidural anesthesia.

Key-words: Hipotension, crystalloids, fluid responders, hypovolemia.

3.1 Introduction

Epidural anesthesia is a common anesthetic procedure performed to manage pain. It accounts for a wide range of surgical scenarios, including procedures in the limbs, hip, tail, lower abdomen and cesarean section (Jones 2001; Valverde 2008; Torske & Dyson 2000). In addition to analgesia, epidural anesthesia can also provide muscle relaxation, faster recovery, shorter length of stay in the hospital and reduced amount of anesthetics needed (Mccally et al. 2015; Valverde 2008). However, a frequent adverse effect observed during epidural anesthesia is arterial hypotension, as a result of a decrease in systemic vascular resistance (SVR) caused by the sympathetic block (Triffterer et al. 2017; Bosmans et al. 2011; Shibata K, Yamamoto Y 1989). Furthermore, a decrease in cardiac output (CO) due to a redistribution of central volume can contribute to a relative hypovolemia, worsening hypotension (Triffterer et al. 2017; Raux et al. 2004). To address this issue, many authors suggest pre-filling with crystaloids before anesthesia, but the need for volume expansion before the epidural block, as well as the amount of fluids to be administered, remain controversial (Xu et al. 2014; Skupski et al. 2010; Preload & Work 2016).

Dynamic indices of fluid responsiveness were shown to be a successful tool to predict fluid responsiveness in dogs undergoing mechanical ventilation (Fantoni et al. 2017; Endo et al. 2017; Drozdzynska et al. 2018). By assessing the volume status, those indices can help optimize hemodynamic instability in a more accurate and objective way (Marik 2010; Vincent et al. 2011; Auler et al. 2008), since it indicates which patients will benefit the most from either therapy with fluids or with vasoactive drugs. Among the several parameters employed to predict fluid responsiveness, pulse pressure variation (PPV) was shown to be one of the most reliable methods in humans (Auler et al. 2008; Marik 2010; Michard et al. 2000), dogs (Endo et al. 2017; Fantoni et al. 2017; Klein et al. 2016) and pigs (Noel-Morgan et al. 2013; Ana et al. 2012). Likewise, several studies in humans have shown that respiratory variation in echocardiographic markers, such as velocity-time integral (ΔVTI), and peak aortic velocity (ΔVpeak) can predict fluid responsiveness in ventilated patients (Feissel et al. 2001; Soliman et al. 2015), in hemorrhagic animal model (Slama et al. 2002) and in sevoflurane-anesthetized animal model (Endo et al. 2017).

To our knowledge, no study evaluated the use of dynamic indices to assess fluid responsiveness in dogs under epidural anesthesia. Furthermore, one cannot extrapolate hemodynamic characteristics from one scenario to another, especially in cases where general and epidural anesthesia are combined (Triffterer et al. 2017). Therefore, the aim of this study was to evaluate the diagnostic accuracy of three dynamic indices of fluid responsiveness; such as ΔVpeak, ΔVTI and PPV, in dogs submitted to epidural anesthesia, after a 15 ml/kg infusion of crystalloid solution over 15 minutes. As a secondary objective, we compared the diagnostic accuracy among the dynamics indices.

3.2 Materials and methods

This study was approved by the institutional Ethics Committee for Animal Use (no. 6613081116) in the Veterinary Teaching Hospital of the University of São Paulo. A written consent of the owner was obtained for each patient before its inclusion in the study.

Patients

This was a prospective observational clinical study conducted over a period of 14 months, (June, 2017 – July, 2018). Inclusion criteria were dogs aged at least 1 year old, weighing at least 7 kg, undergoing epidural anesthesia that presented arterial hypotension over 5 minutes. Exclusion criteria were: cardiac arrhythmias, which included tachyarrhythmias, bradyarrhythmia, premature ventricular contractions and any degree of atrioventricular block; any cardiomyopathy, namely dilated, hypertrophic, or restrictive; history of esophageal diseases, any degree of anemia (< 35%) and any dermatologic disease that could prevent the epidural procedure. Additionally, all the evaluation was performed with the animals in the dorsal decubitus position.

All animals underwent the department's standard clinical pre-operative evaluation, which include: complete blood count, liver function tests (ALT, AP, albumin and total proteins), kidney function tests (creatinine, urea), electrocardiography and echocardiography if needed (in the presence of murmurs and clinical sign).

Anesthesia

Dogs were premedicated with acepromazine (0.02 mg/kg; Apromazin 1%, Syntec) and meperidine (3 mg/kg, Petidine, União Química) intramuscularly (IM). Twenty minutes later, the animals were transferred to the operating room so that the electrodes of a two-lead (DII, DIII) electrocardiogram were atthached (Philips Dixtal multiparameter monitor 2020, Brazil) and a 20-gauge catheter (Angiocath; BD, Brazil) was placed in the right cephalic vein. For induction of general anesthesia, propofol (3 - 5 mg/kg to effect) was administered intravenously (IV), and maintenance was achieved with isoflurane (FE´Iso 1.3%) diluted in oxygen (FIO_2 0.6 – 0.7) both titrated with the help of a sidestream, non-dispersive infrared gas analyzer (Poet IQ2; Critcare Systems, WI, USA).

After tracheal intubation, neuromuscular block was performed with rocuronium at 0.6 mg/kg (Rocurom, rocuronium bromide, Cristália) and repeated if any spontaneous respiration was detected by the ventilometer. Volume-controlled ventilation was instituted in all animals (Fabius Tiro, Drager), with the tidal volume (Vt) set at 8 – 10 ml/kg, an inspiratory to expiratory ratio of 1:2, a positive end-expiratory pressure (PEEP) of 2 cmH20 and the respiratory rate (*fR*) was adjusted according to end-tidal carbon dioxide (PE′CO2 30 – 40 mmHg, 5 - 6 kPa) values. Respiratory parameters were monitored by the anesthetic machine's ventilometer. Additionally, the ventilator was calibrated before each experiment, the circuit was tested for air leaking, airflow and oxygen sensors were also tested.

A 22-gauge catheter (0.9 x 25 mm; Angiocath; BD) was placed in the dorsal podal artery in order to monitor the arterial pressure invasively, with the help of an extension tubing connected to the transducer and to the multiparameter data collection system (Philips Dixtal 2020, Biomédica Indústria e Comércio). The pressure transducer was placed at the level of the scapulohumeral joint and the line was flushed from time to time with heparinized saline solution (2 UI/ml). Calibration of the arterial line was performed immediately after catheter insertion. Also, the dogs were positioned over an electric heating blanket to avoid hypothermia.

After anesthesia stabilization, animals were placed in the sphinx position for the epidural anesthesia, which was performed with lidocaine (4 mg/kg, lidocaine hydrochloride, Cristália) and morphine (0.1 mg/kg, Morphine Sulfate, Cristália) diluted in saline solution to a final volume of 0.26 ml/kg into the epidural space at the lumbosacral junction. A Tuohy epidural needle (Uniever UNISIS corp, Japan) was used and the proper positioning of the needle was confirmed by the drip infusion technique and by the ease of injection of the epidural solution.

Indices of fluid responsiveness

An echocardiographic 2 - 5 MHz probe (6Tc-RS TEE KN100104, Vivid Q; General Electrics Healthcare, IL, USA) was introduced into the mouth and pushed into the oesophagus up to the point where the aortic valve could be identified through the transverse caudal view. The transverse area section of the left ventricle outflow tract was then obtained at the level of the aortic valve annulus, to further allow the calculation of the stroke volume (SV = velocity–time integral × transverse area section). Subsequently, the transducer was inserted into the gastric cavity, flexed ventrally and rotated approximately 90 - 120°. This transgastric approach was used to measure VTI and Vpeak via pulsed-wave Doppler, as described elsewhere (Mantovani et al. 2017). After the first assessment, the probe was left in place in freeze mode throughout each evaluation for immediate measurements at each time point (Stoddard et al. 2017.; Descorps-Declère et al. 1996). Images were only recorded when the ascending aorta was parallel or less than 20° from the ultrasound beam and, if needed, images could be improved by slight adjustments of the transducer by rotation or flexion/extension movements.

All echocardiographic indices, as well as SV calculation, were evaluated in triplicate over a 5 heart beats image, to comprise an entire respiratory cycle (inspiration/expiration). The velocity time integral variation (ΔVTI(%) = 100 x (VTImax – VTImin) / [VTImax + VTImin)/2]) and the peak aortic velocity variation (ΔVpeak) (ΔVpeak(%) = 100 x (Vpeakmax – Vpeakmin) / [Vpeakmax + Vpeakmin)/2]) were then calculated offline from the stored images.

The PPV was calculated by the multiparameter monitor (DX2020; Philips Dixtal Biomédica Indústria e Comércio). To calculate the PPV, the multiparameter system uses the synchronized values from the invasive arterial pressure (the difference between systolic and diastolic arterial pressures) and the capnography modules. So that the difference between maximum and minimum pulse pressure values could be used to calculated PPV (%) = 100 (PPmax –PPmin)/([PPmax + PPmin]/2), as described elsewhere (Auler et al. 2008). Data were collected only if the factors described to interfere with this measurement were absent (Auler et al. 2008), that is, if all of the following requirements were fulfilled: absence of respiratory efforts; mechanical ventilation set to cycles of *f*R 10 – 25 breaths minute^{-1} and Vt of 8 - 10 ml kg^{-1}; sinus rhythm; HR: *f*R > 3.6. Additionally, all respiratory parameters and inhalant gases were held unchanged during the fluid challenge.

Study design

After the epidural anesthesia, if a MAP < 65 mmHg for 5 minutes was detected, a fluid challenge with 15 ml/kg of lactated Ringer’s solution (lactated Ringer’s, Fresenius Ltda) was administered in 15 minutes by an infusion pump (Fresenius Kabi, USA). The animals were considered to be responders to fluids when an increase greater than or equal to 15% in SV was observed after the fluid challenge and nonresponders when an increase of less than 15% in SV was detected. All echocardiographic measurements were performed by a single evaluator, while the maintenance of anesthesia was performed by a second observer. Measurements of echocardiography (ΔVTI, ΔVpeak) and PPV were recorded immediately before the fluid challenge and by the end of it.

Statistical analysis

The final sample size depends on the interest of the researcher. If sensitivity and specificity are equally important for the study, determine the sample size for both sensitivity and specificity, separately. The final sample size of the study would be the larger of these two.

For the sample size determination, we focused on the magnitude of the test's sensitivity and specificity. Therefore, the size of the sample was calculated considering Indrayan (2017) nomogram, thus considering a 10% precision level. It was suggested that a minimum of 40 dogs was required for this study. Data were expressed as mean ± SD or median (interquartile range). Normal distribution of data was verified by means of the Shapiro Wilk test. To evaluate the equality of variances between groups, the Levene test was used. Hemodynamic and respiratory variables related to the responders/nonresponders were analyzed using an unpaired *t*-test or Mann-Whitney test. Also, to investigate temporal responses a paired *t*-test or Wilcoxon test was used.
Receiver operator characteristic (ROC) curves were constructed using the bootstrap methodology (1000 samples), to evaluate the ability of PPV, ΔVTI, and ΔVpeak to predict fluid responsiveness. The accuracy of each index cut-offs in predicting fluid responsiveness is given by the area under the ROC curve (0 = not accurate; 1 = 100% accurate) (DeLong et al. 1988), which allowed the calculation of the most accurate cut-off values for each variable, by means of the highest Youden index (sensitivity + (specificity - 1)). A contingency table was used to estimate both sensitivity and specificity, which also allowed the calculation of the positive likelihood ratio (sensitivity / (1 - specificity), negative likelihood ratio (1 - sensitivity) / specificity) and post-test probabilities. The post-test probability was evaluated by means of the Fagan (1975) nomogram. For further understanding, in the present study a positive test/result refers to responders and a negative test/result refers to non-responders.
The gray zone approach was used to provide a range of values for which conclusive information cannot be provided. A two-step procedure was performed to determine the gray zone (Cannesson et al. 2011). First, the best threshold in each of the 1000 bootstrapped

populations for each index was determined. The 95% CI of the best threshold was defined by the observed distributions of the thresholds in 1000 populations. In the second step, we determined the values for inconclusive responses (sensitivity <90% or specificity <90%). The two steps were complementary, and the largest interval was defined as the gray zone.

A p value < 0.05 was considered to be statistically significant. RStudio, Version 0.99.903 – © 2009-2016 RStudio, Inc, and R package (pROC) and (epiR) were used for statistical analysis. In addition, both post-test probabilities were calculated by an online nomogram table, available at: http://araw.mede.uic.edu/cgi-bin/testcalc.pl.

3.3 Results

A total of 49 animals were included in this study and 9 dogs had to be excluded because adequate images could not be obtained (4), due to cardiac arrhythmia (3) and due to partial conclusion of the fluid challenge (2). Ortophedic surgery performed in 19 dogs (47%) was the most common intervention in the present study, followed by tumor exeresis in 10 (25%), lower gastrointestinal surgery in 6 (15%) and lower urinary tract surgery in 5 (13%).

The characteristics of the population and respiratory variables were divided between responders and nonresponders and presented at table 2.

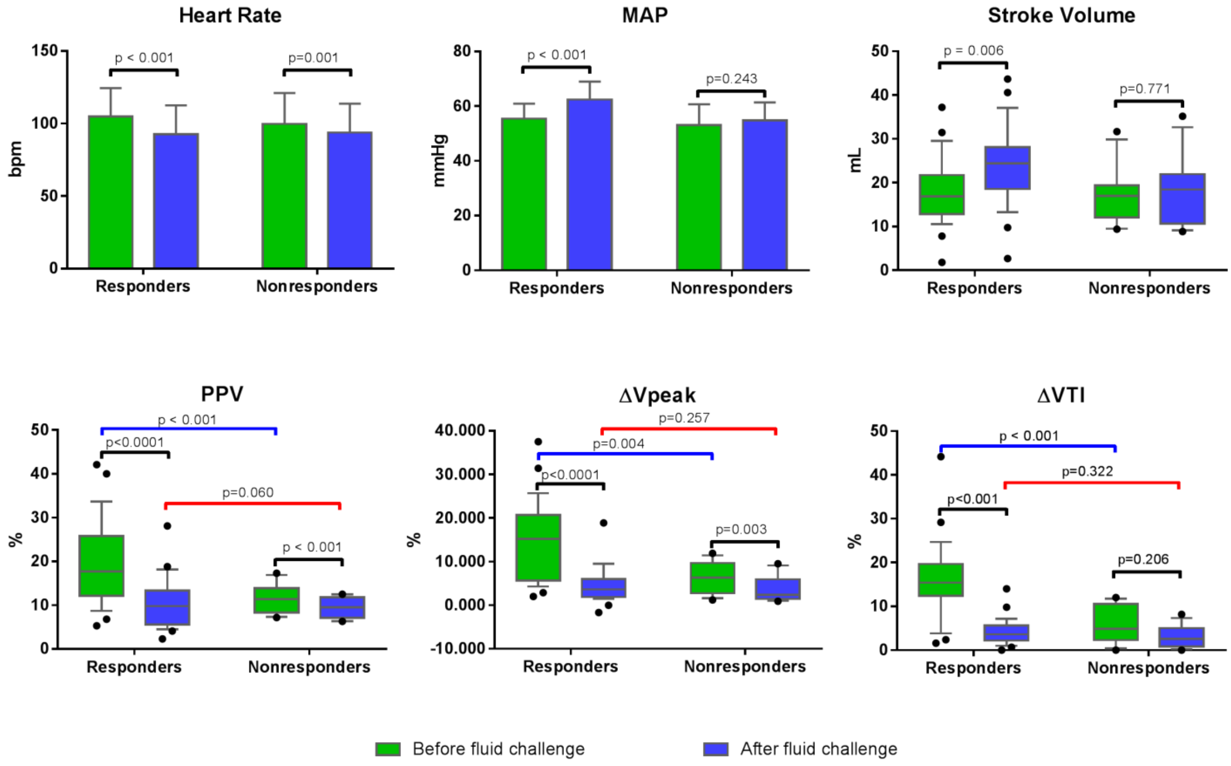
Table 2 - Main characteristics and repiratory variables of the 40 dogs enrolled in the study, divided between responders and nonresponders.

Variables	**All animals (n = 40)**	**Responders (*n* = 30)**	**Nonresponders (*n* = 10)**	***p* value**
Age (years)	6.1 ± 3.2	6.9 ± 3.0	5 ± 3.5	0.136
Weight (kg)	25.9 ± 11.6	27.8 ± 10.8	21.5 ± 12.9	0.121
Sex (M/F)	22/18	15/14	7/4	0.128
PE’CO_2	35.1 ± 6.8	35.1 ± 4.5	35 ± 3.1	0.993
Vt	9.5 ± 1.2	9.6 ± 1.05	9.5 ± 1.4	0.637
FiO_2	62.9 ± 7.4	64.6 ± 7.8	57.2 ± 6.7	0.165
PE’ISO	1.3 (1.2/1.3)	1.3 (1.3/1.4)	1.3 (1.2/1.3)	0.208

M, male; F, female; PE’CO_2, end-tidal carbon dioxide; Vt, tidal volume; FiO_2, inspired oxygen concentration; PE’ISO, end-tidal isoflurane. Values are expressed as mean ± standard deviation or median (interquartile range).

Thirty (75%) dogs were responsive to fluids and 10 (25%) were non-responders. Responders had a mean increase of 26.3% ± 9.1% in SV (p = 0.006) after the fluid challenge, while the increase in non-responders 7.13% ± 4.8% was not statistical significant (p = 0.771). Also, a statistical difference was observed (p < 0.001) after the fluid challenge in hemodynamic and echocardiograpfic variables, at responders (Figure 1). Additionally, in the non-responder group, both ΔVpeak and PPV have significantly decreased after the fluid challenge. Heart rate significantly decreased in the responders group (p < 0.001), and in the non-responders (p = 0.01). Likewise, MAP significantly increased in the responders group (p < 0.001). There were no significant differences in the respiratory parameters and inhalant gases between groups (p > 0.05), (Table 2).

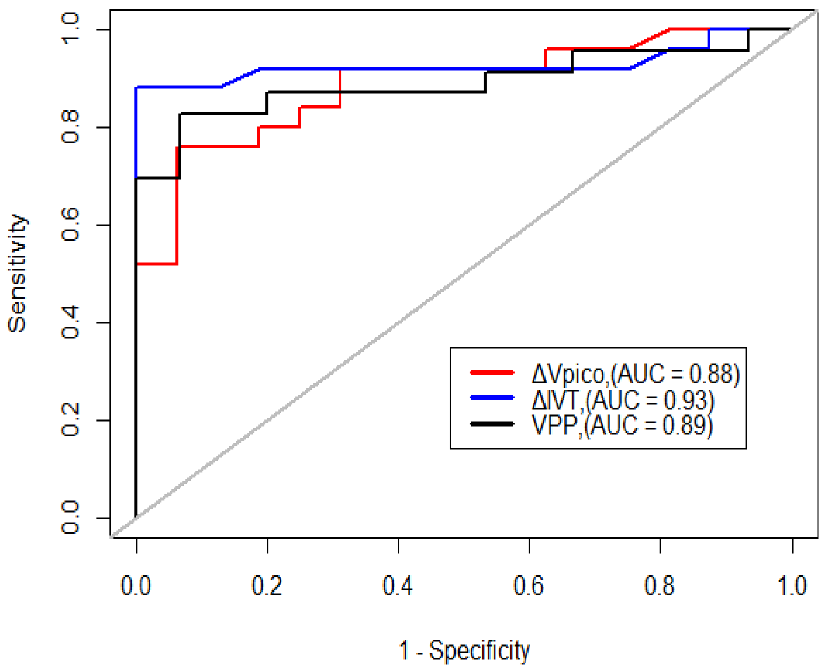
Fig 1 – Hemodynamic and echocardiographic variables of the study population, changes are presented before and after the 15 ml/kg fluid challenge over 15 minutes.



bpm, beats per minute; mmHg, millimeter of mercury; ΔVTI, velocity time integral variation; ΔVpeak, peak aortic velocity variation; PPV, pulse pressure variation; mL, milliliters.

The area under the ROC curve for PPV was (0.89 ± 0.10), along with the following echocardiographic indices: ΔVpeak (0.88 ± 0.10) and ΔVTI (0.93 ± 0.09), (Figure 2). Regarding the AUCs for the macro hemodynamic parameters, HR was (0.60 ± 0.19) and for the MAP was (0.51 ± 0.20). Additionally, when comparing the AUC's between ΔVTI, ΔVpeak and PPV, none of the indices showed a significant difference, for the values before fluid challenge ($p > 0.05$).

Figure 2 - The receiver operating characteristic (ROC) curve measured before fluid challenge for ΔVpeak, ΔVTI, PPV, HR and MAP and after infusion with 15 ml/kg of crystalloid.



ΔVpeak, peak aortic velocity variation; ΔVTI, velocity time integral variation; PPV, pulse pressure variation; HR, heart rate; MAP, Mean arterial pressure; AUC, area under the curve.

The optimum cut-off values able to distinguish responders from nonresponders were: 15.8% for PPV (sensitivity, 82%; specificity, 93%); 13% for ΔVpeak (sensitivity, 76%; specificity, 93%); and 11.7% for ΔVTI (sensitivity, 88%; specificity, 87%), all measured before the fluid challenge.

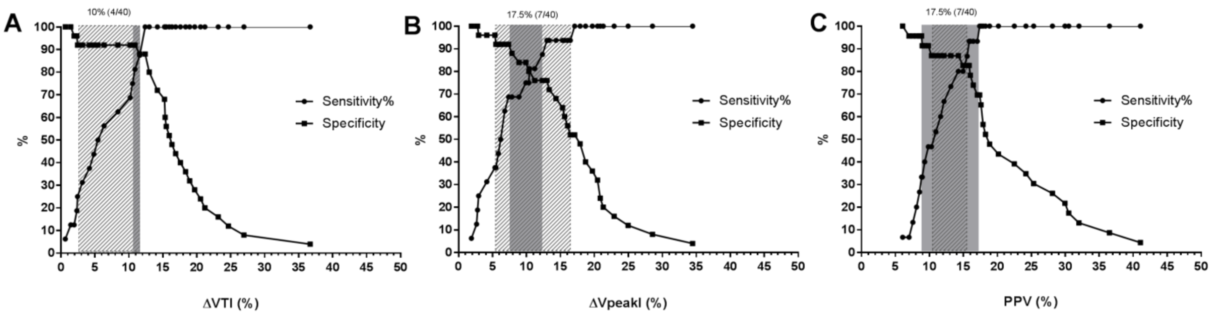
Table 3 - Receiver operating characteristics (ROC) curve statistics of three dynamics indices and two macro hemodynamic parameters to predict fluid responsiveness after a fluid challenge with crystaloids with 15 ml/kg over 15 minutes.

Variables	AUC	95% CI AUC	p value	Cut-off	Gray zone area	Sensitivity (%)	Specificity (%)
HR baseline	0.60	0.41 – 0.79	0.266	94	81 – 142	72	50
MAP baseline	0.51	0.30 – 0.71	0.916	48.5	48.5 – 63.5	91	26
PPV baseline	0.89	0.78 – 0.99	<0.001	15.8	9.9 – 15.8	82	93
ΔVpeak baseline	0.88	0.78 – 0.98	<0.001	13.0	7.3 – 13.0	76	93
ΔVTI baseline	0.93	0.83 – 1.0	<0.001	12.4	10.9 – 12.4	88	100

HR, heart rate, MAP, mean arterial pressure; PPV, pulse pressure variation; ΔVpeak, peak aortic velocity variation; ΔVTI, velocity time integral variation.

Considering the gray zone approach, the percentage of dogs that fell into it inconclusive area for ΔVTI was 10% (4/40), 17.5% (7/40) for PPV and 17.5% (7/40) for ΔVpeak (Figure 3).

Figure 3 – Gray zone approach of the three dynamic indices of fluid responsiveness, containing the number os dogs that fell into the inconclusive area.



ΔVpeak, peak aortic velocity variation; ΔVTI, velocity time integral variation; PPV, pulse pressure variation

The number of true positives, false positives, false negatives and true negatives between the dynamic indices and the fluid responsiveness classification, were the following: ΔVpeak (19, 1, 10, 10); for ΔVTI (23, 0, 7, 10) and for PPV (24, 0, 7, 9). Positive likelihood ratio and negative likelihood ratio, as well as the post-test probability, considering a pre-test probability of 75% (prevalence of responders), were summarized in table 4.

Table 4 - Diagnostic test characteristics (likelihood ratios) and the post-test probability of responders given the pre-test probability and test characteristics

Variables	Positive test result		Negative test result	
	LHR+	Post-test probability	LHR -	Post-test probability
PPV baseline	Inf	100%	0.25	45%
ΔVpeak baseline	7.2	95%	0.37	50%
ΔVTI baseline	Inf	100%	0.23	40%

LHR +, positive likelihood ratio; LHR -, negative likelihood ratio; PPV, pulse pressure variation; ΔVpeak, peak aortic velocity variation; ΔVTI, velocity time integral variation; Inf, infinite.

3.4 Discussion

Fluid theraphy is the cornerstone of the treatment of hypovolemic shock, hypotension, sepsis, and hemodynamic instability in general. Consequently, monitoring the patient's volume status has become increasingly important during anesthesia and in the intensive care unit. Pulse pressure variation is a well established preload marker in humans being utilized in several studies at different settings (Marik 2010; Cecconi et al. 2015). It is easily obtained and several multiparameter monitors usually provide its measurement. Although it is a relatively new indicator in veterinary medicine when compared to medicine, it was shown to be a reliable marker in mechanically ventilated dogs undergoing orthopedics surgery (Fantoni et al. 2017), as well as in dogs after experimentally induced hemorrhage (Klein et al. 2016), and in 63 client-owned dogs submit to abdominal surgery (Drozdzynska et al. 2018).

On the other hand, echocardiographic indices of fluid responsiveness are relativelly new in veterinary medicine, and even though they are not new in human medicine, it was found that they are used by only 2% of anesthesiologists in Europe, according to a cohort study (Cecconi et al. 2015). Most of the human studies reported ΔVpeak as a good predictor of fluid responsiveness in mechanically ventilated adults patients and specially in children (Feissel et al. 2001; Desgranges et al. 2015; Durand et al. 2008). Likewise, ΔVTI is also an echographic index derived from aortic blood flow that are commonly reported in human literature, with a satisfactory diagnostic accuracy in predicting fluid responsiveness (Monnet et al. 2016; Dave et al. 2018; Messina et al. 2018). Nevertheless, echocardiographic indices are a noninvasive option for assessing fluid responsiveness and measuring cardiac output, they are also good predictors of inotropic response (Porter et al. 2015; Kanji et al. 2014).

This study showed that PPV, ΔVpeak and ΔVTI can predict fluid responsiveness in anesthetized dogs undergoing epidural anesthesia with satisfactory accuracy, distinguishing animals that are responsive to fluids from the non-responders. The AUC's of the three dynamic indices was greater than 0.75, which is considered a good diagnostic value for biomarkers in general. Moreover, the AUC for ΔVTI at baseline was above 0.90, a characteristic of an excellent diagnostic index (Ray et al. 2010; Cohen et al. 2016). The similar diagnostic performance between the indices, considering the AUCs, was also influenced by their 95% confidence intervals, that in fact, also had their lower limit higher than 0.75. In comparison with existing studies, veterinary literature and experimental studies with animals reports AUCs ranging from 0.89 to 1.0 (Endo et al. 2017; Bucci et al. 2017; Fantoni et al. 2017), which was in concordance with the present study.

The ROC curve analysis is a global assessment of the test accuracy that is easily appreciated and generally used for statistical comparison versus other diagnostic tests (Ray et al. 2010). In the present study, this approach allowed the authors to suggest the good diagnostic capability of the dynamics indices. However, a single method of estimating diagnostic accuracy is not able to fulfill the needs of a clinical evaluation (Ray et al. 2010; Cohen et al. 2016). As mentioned, the ΔVTI showed a great AUC value, implying a good diagnostic capability to distinguish responders from non-responders. This is also strengthened by its higher sensitivity and specificity values. However, despite this fact, all dynamic indices had a comparable effect on detecting true positives and true negatives (that is, similar false positives/negatives), especially when comparing ΔVTI and PPV. In other words, we can take into account the pre-test and post-test probability, which indicates the probability of the presence of a condition (such as fluid responders) before and after a diagnostic test (dynamics indices). This evaluation allows the anesthesiologist to estimate whether an animal is responsive to fluids or not, with an improved clinical approach. The high positive post-test probability seen in all dynamic indices greatly increases the probability that a positive result (a cut-off value that identify responders) is in fact an animal that is responsive to fluids. In other words, this means that the probability of being responsive to fluids when evaluating an animal with ΔVTI, increases from 75% to 100% (95% CI, 77 – 100%) when the ΔVTI value is greater than its cut-off value of 12.4. This is frequently observed in diagnostic tests, when the prevalence of the disease (75% of responders in this study) and a great LHR+ value, increases the probability that an individual is positive to the “disease”, after a positive test result (Akobeng 2007). On the other hand, even with this maximum probability of being responder after a positive test, many animals fell into the false negatives (specially ΔVpeak). This result is probably related to the relatively high prevalence of responders, that is, as the prevalence increases, the chance that a positive test is true increases (more true positives), but also the false negatives.

The diagnostic accuracy to predict non-responders was rather regular for several reasons. First, the negative post-test probability value of all dynamic indices decreased poorly, which means it had an unsatisfactory diagnostic capability to rule out responders. For instance, if an evaluation with PPV results in a cut-off value that identifies non-responders (i.e, lesser than 15.8), the probability that this animal is indeed a non-responder decreases little (from 75% to 45%), which might lead to more false positive cases. Second, regarding LHR-, all three indices were whithin the same range (0.2 – 0.5), which according to Ray et al. (2010) indicates a poor diagnostic value. And third, the inconclusive area of the gray zone approach was wider in the first cut-off value for all dynamic indices, which can impair the exclusion of the diagnosis (namely, detection of non-responders). Even though, the capability of the dynamic indices to detect non-responders was regular, only one case was a false positive (in ΔVpeak), which is probably due to the prevalence of responders in the study, as previously explained. As prevalence increases, the chance of getting a false positive decreases (Akobeng 2007).

Therefore, all dynamic indices showed good diagnostic accuracy to detect fluid responders, however, if the evaluation results in a cut-off value lower than its original cut-off value, suggesting a non-responder, one may consider pursuing additional information to improve their decision. This is even more important in scenarios with high prevalence of responders, such as in Fantoni et al. (2017) (prevalence of 76%) and Sasaki et al. (2017) (prevalence of 63%) studies. In contrast, the diagnostic capability to predict non-responders would be increased in studies with lower prevalence of responders, just as reported by Bucci et al. (2017) (37%) and Endo et al. (2017), (35%). In this case, the LHR is a robust analysis to be considered, since post-test probabilities can be affected by prevalence (Akobeng 2007). Additionally, the anesthesiologist should consider different cut-off values, according to the clinical scenario and to whether they want to be more sensitive or more specific regarding fluid responsiveness (Cannesson M, Le Manach Y et al. 2011). Another option would be performing the “tidal volume challenge”, a transient increase in tidal volume to 12 ml/kg over

1 - 3 minutes, which might improve diagnostic accuracy, especially in patients within the inconclusive area (Myatra et al. 2017; Min et al. 2017; Biais et al. 2014). Min et al. (2017) reported in a study with 39 patients undergoing laparotomy, an increase in the diagnostic capability (by AUCs analysis) after the “tidal volume challenge”.

Regarding the dynamics indices cut-off values, variation among the studies is expected, since some aspects, such as populations, comorbidities and the types of surgery involved can vary immensely (Cecconi et al. 2015). In the present study, the ΔVTI cut-off value (12.4%) was similar to those in humans studies (11 - 19%), (Muller et al. 2011; Wu et al. 2014). A study evaluated 30 dogs undergoing cardiac surgery and found a similar cut-off value of 13,5%, with a specificity of 84.2% and sensitivity of 72.7% (Sasaki et al. 2017). The PPV cut-off value with maximum accuracy was 15.8% (sensitivity 82%, specificity 93%), which was in accordance or close with most of the studies (10 – 16%) conducted in humans in various settings (Mahjoub et al. 2014; Cecconi et al. 2015; Michard et al. 2000). Furthermore, a previous study with mechanically ventilated dogs undergoing ortophedics surgery and fentanyl infusion showed a similar cut-off value (15%) compared with the present study (Fantoni et al. 2017). As regards to ΔVpeak cut-off values, Bucci et al. (2017) showed that a variation of 9.4% can predict fluid responders with a good sensitivity 88% and specificity 100% in dogs during elective surgery. Human literature refers a cut-off values ranging from 7 to 20%, with sensitivity of 92% (95% CI: 84 – 96%) and specificity 85% (95% CI: 75 – 92%) in children after cardiac and neurosurgery (Desgranges et al. 2015), and cut-offs values of 12% (sensitivity 100%, specificity 89%) in septic shock patients under mechanical ventilation (Feissel et al. 2001). Both veterinary studies and most of the human studies regarding ΔVpeak, showed consistent findings when compared to the present study.

The ratio between responders and nonresponders animals was one fourth, a finding that was not expected due to the well-know depression of the sympathetic tone related to the epidural block (Triffterer et al. 2017; Shibata K, Yamamoto Y 1989; Bosmans et al. 2011). Epidural anesthetics can block the sympathetic response of the cardiovascular system, leading to vasodilatation and consequently hypotension, which usually is considered to be responsive to therapy with vasoactive drugs (Triffterer et al. 2017). However, several authors suggest that this decrease in SVR may cause a redistribution of the central volume, leading to a status of relative hypovolemia, what could explain our ratio of patients that are responsive to fluids (Westphal et al. 2010). Previous studies with rats have compared hemorrhage-induced hypotension (absolute hypovolemia) with pharmacologic vasodilatation (relative hypovolemia) and found a similar pattern for PPV in both shock models (Westphal et al. 2010; Pizov et al. 1988).

Considering the complex response of the cardiovascular system after the association of epidural and general anesthesia, hypotension might be a result of both hypovolemia (decreased preload) and the decrease in SVR (decreased afterload). In the present study a 25.9% increase in SV was noticed after the fluid challenge, while in previous studies, where anesthetized dogs were maintained with isoflurane and continuous infusion of fentanyl, the increase was around 40% (Fantoni et al. 2017). This difference could be related to the different mechanisms that contributes to the hypotension in each studied population. Probably, in the population undergoing general anesthesia, a decreased preload was the main cause of hypotension, while in the epidural population, hypotension was generated by a decreased preload and afterload as mentioned. The Frank-Starling curve supports this concept because, the lower the preload, the greater the increase in cardiac output after fluid administration. Therefore, it is reasonable to assume that blood volume monitoring with dynamics indices of fluid responsiveness should be taken into account in this scenario (Marik 2010).

This study had some limitations - first, our study population consisted of different breeds, with different thoracic shapes and compliances which could result in different peak pressures. However, the tidal volume was shown to be the variable that interferes with the cardiopulmonary interaction, and that was rigorously monitored thoroughly. Secondly, the overall diagnostic accuracy of the dynamic indices presented in this study should be extrapolated with caution in other populations. Finally, we used the transesophageal echocardiography to evaluate the change in systolic volume or cardiac output which has been validated in previous studies in humans (Cannesson M, Le Manach Y et al. 2011; Feissel et al. 2001) and in dogs (Mantovani et al 2017) but its not the gold standard.

3.5 Conclusion

In conclusion, dynamic indices derived from echocardiography as ΔVTI and ΔVpeak, and from PPV, are reliable predictors of fluid responsiveness in dogs submitted to epidural anesthesia. The diagnostic capability to detect fluid responders was comparable between the dynamic indices, and poor to detect non-responders. If the index result suggests a non-responder, aditional information should be persue.

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Capítulo 3

Evaluation of three dynamic indices of fluid responsiveness after a bolus of 5 and 10 ml/kg with Ringer's lactate solution

4 EVALUATION OF THREE DYNAMIC INDICES OF FLUID RESPONSIVENESS AFTER A BOLUS OF 5 AND 10 ML/KG OF RINGER'S LACTATE SOLUTION

Abstract

The assessment of fluid responsiveness in dogs undergoing anesthesia have changed considerable in the last few years. New protocols have emerged to improve the evaluation of preload responsiveness in a wide variety of scenarios. Therefore, the objective of this study was to evaluate the diagnostic accuracy of stroke volume variation (SVV), cardiac output variation (ΔCO) and pulse pressure variation (PPV), after a fluid expansion with crystalloids of 5 ml/kg and 10 ml/kg over 5 and 10 minutes respectivelly. Ninety dogs, monitored and undergoing mechanical ventilation, were studied. Hemodynamic and echocardiographic variables were evaluated before and after fluid challenge. Responders were classified by ≥ 15% increase in stroke volume. The ability to predict fluid responsiveness by the indices was evaluated by ROC curve analysis and post-test probabilities. Stroke volume significantly increased 25.8% ± 8.8% ($p < 0.001$) in the responders group 64/90 (71%), compared to the no significant increase in 8.7% ± 4% ($p = 0.439$) in the nonresponders 26 (29%). After a fluid expansion of 5 ml/kg, PPV (0.78), ΔCO (0.70) and SVV (0.75) showed a median to poor diagnostic capability. However, after an infusion of 10 ml/kg both echocardiographyc indices showed a good diagnostic capability. In addition, the ability to predict responders were good (LHR**+,** ΔCO10 89%, SVV10 97%) according to the post-test probability, and median to predict nonresponders (LHR**-,** ΔCO10 29%%, SVV10 19%). In conclusion, a fluid expansion with 10 ml/kg can predict fluid responsiveness better when comapared with a mini fluid challenge of 5 ml/kg. The echocardiographic indices showed a great diagnostic capability when compared with pulse pressure variation.

Key-words: Hypotension, mini-fluid challenge, dynamic indices.

4.1 Introduction

Intravenous fluid challenge is one of the most frequent procedures performed during general anesthesia and it is considered by many anesthesiologists to be the first therapeutic choice for arterial hypotension (Cecconi et al. 2015; Messina et al. 2018). However, the decision on whether fluids or vasopressors should be used is sometimes arbitrary, since arterial hypotension may result from diverse mechanisms (Monnet et al. 2016; Cherpanath et al. 2013). Low blood pressure secondary to decreased preload can take place due to, for example, blood loss or epidural anesthesia (relative hypovolemia); another reason for hypotension can be vasodilatation, secondary to inhalational anesthetics, or even because of an impaired cardiac contractility (Marik 2010; Cherpanath et al. 2013). Nonetheless, these may also vary through time depending on the events that might occur during anesthesia and surgery.

Whichever the case, considering that the patient's systolic function is normal, a hypovolemic animal is more likely to be on the ascending portion of the Frank-Starling curve, which means that this animal will probably benefit from fluid expansion, leading to an increase of cardiac output (CO) (Guerin et al. 2013; Marik 2010; Cherpanath et al. 2013). On the other hand, if the animal is on the flat portion of the curve, further fluids can be detrimental. Therefore, tracing the patients' position on the Frank-Starling curve is an essential step to guide an optimal therapeutic strategy and prevent the deleterious effects of unnecessary fluid expansion (Auler et al. 2008; Marik 2010; Monnet et al. 2016).

Over the last decade, most of the studies on dynamic indices of fluid responsiveness have stated that a fluid responder is characterized by a 15% increase in stroke volume (SV) or cardiac output (CO) after a fluid expansion (Toscani et al. 2017; Yi et al. 2017; Dave et al. 2018). However, to achieve the intended vascular expansion, the fluid challenge requires an adequate volume in a rapid infusion rate (Cerda et al. 2010; Besen 2015; Kim et al. 2017). In humans, this adequate volume and rate of infusion were reported to vary considerably between institutions and therefore, no standard protocol regardless fluid expansion can be found in the literature (Cecconi et al. 2015; ENDO et al. 2017; Bucci et al. 2017b). Most studies in veterinary medicine have reported volumes to be infused in a fluid challenge ranging from 15 – 30 ml/kg, which is greater than the values found in humans researches (Berkenstadt et al. 2005; Fantoni et al. 2017; ENDO et al. 2017; Toscani et al. 2017). In veterinary, the fluid expansion characteristics also varies considerably, and in a recent study, we have demonstrated that 15 ml/kg can be used to predict fluid responsiveness in dogs undergoing orthopedic surgery (Fantoni et al. 2017).

Since excessive fluid expansion was shown to be as harmful as hypovolemia, in the present study, we hypothesized that a low volume (5 ml/kg) of crystalloid infused rapidly (5 minutes) could predict fluid responsiveness with the same accuracy of that observed with a bolus of 10 ml/kg. Therefore, the aim of this study was to estimate the diagnostic accuracy/capability of the administration of a bolus of 5 and 10 ml/kg with crystalloids to predict fluidresponsiveness by means of velocity-time integral variation (ΔVTI), cardiac output variation (ΔCO) and pulse pressure variation (PPV), in dogs undergoing surgery. We also aimed to compare the diagnostic accuracy among the three dynamic indices.

4.2 Methods

This was a retrospective observational study conducted in the Veterinary Teaching Hospital of the University of São Paulo. The study protocol was approved by the institutional Ethics Committee for Animal Use (no. 6613081116). The perioperative data were identified through medical records over the period of March 2017 to August 2018. The perioperative data collected for the present study included: age, body weight, gender, type of surgery, anesthetics agents used to induce and maintain anesthesia, respiratory variables, hemodynamic variables related to the cardiovascular system, pulse pressure variation and two echocardiographic parameters derived from aortic blood flow such as stroke volume variation (SVV) and cardiac output variation (ΔCO).

4.2.1 Inclusion and Exclusion Criteria

Mechanically ventilated dogs with at least 1 year old and weighing at least 10 kg, undergoing routine surgery to whom a fluid expansion was indicated, were eligible for the current study. If an animal received more than one fluid expansion, only the first was considered for the study. Animals with cardiac arrhythmias (atrio-ventricular block, extrasystole contractions and tachyarrhythmias), dilated or hypertrophic cardiomyopathy, any degree of anemia and undergoing vasopressor therapy, were excluded. Also, any animal with missing data regard the variables already mentioned was excluded.

4.2.2 Anesthesia procedures data

To improve the homogeneity of the study population, some aspects of the anesthesia procedure that could interfere with the preload index were evaluated within the medical records. For this purpose, animals included in the study should be anesthetized with isoflurane diluted in oxygen (FIO2 0,6 – 0,7). The animals also required to be temporarily paralyzed by neuromuscular blocking agents, to improve ventilation and to allow cardiopulmonary interactions. Mechanical ventilation was another requisite, in either volume or pressure control mode, ensuring a tidal volume (Vt) of 8 – 10 ml/kg and PEEP 2 cmH2O. The optimal ratio between the heart rate and respiratory rate was HR;fR > 3.6, to assure proper echocardiographic evaluation. Additionally, a fluid expansion (FE) volume of 15 ml/kg, infused over 15 minutes was established in this study to evaluate the diagnostic capability of the two fluid expansion volumes already mentioned.

4.2.3 Hemodynamic and preload markers data

The overall variables were collected in four time points, which is, before initiation of FE (Tb), within 5 ml/kg of the FE (T5 – minutes), after 10 ml/kg (T10 – minutes) and again after the 15 ml/kg of the FE (T15 – minutes).

We also recorded stroke volume (SV), cardiac output (CO) and pulse pressure variation (PPV) in triplicate, in all time points described above. For the evaluation of fluid responsiveness, the SVV was calculated, (SVV(%) = 100 x (SVVtx – SVVb) / [SVVtx + SVVb)/2]), comparing the increase between baseline and T5 (SVV5), baseline and T10 (SVV10), and again baseline with T15 (SVV15). The same procedure was applied to ΔCO, in all time points. Similarly, the decrease in PPV was calculated using (PPV(%) = 100 x (PPVtx – PPVb) / [PPVtx + PPVb)/2]). To differentiate fluid responders (Rs) from nonresponders (NRs), stroke volume (SV = velocity time integral × transverse area section) was used. Animals were considered fluid responders when an increase equal or greater than 15%, in stroke volume, was observed after the FE with 15 ml/kg infused over 15 minutes. Conversely, animals were considered nonresponders when the increase in SV was inferior than 15%.

4.2.4 Statistical analysis

Data are expressed as mean ± SD or median (25/75th percentiles). Normal data distribution was verified by means of the Shapiro-Wilk normality test, and if necessary Bartlett test was used to test if the samples had equal variances. For the comparison of the hemodynamic variables between responders and nonresponders, *t*-student test or Mann-Whitney test was used. Also, for the comparison of the same variables within the time points, ANOVA one way or Kruskal-Wallis test was used. Receiver operating characteristic curves (ROC) were generated to evaluate the ability of each index to predict fluid responsiveness. The ROC curves were created by using the bootstrap methodology (1000 samples), and the area under

ROC curve (AUC) was calculated and compared using the Delong, Delong and Clarke-Pearson method (Delong et al. 1988). The cut-off values for each preload marker were chosen with the highest Youden index, calculated as (sensitivity + (specificity - 1)). Positive likelihood ratio (LHR+: sensitivity / (1 - specificity)) and negative likelihood ratio (LHR-: (1 - sensitivity) / specificity) were used to evaluate the probability of a test results in responders or non-responders, given the presence or not of fluid responsiveness. LHR evaluation was based on the sensitivity and specificity generated by the contingency table (2x2) of the true positive, false positive, true negative and false negative ratio, according to each indices cut-off. In the present study, LHR was only calculated for dynamic indices that presented AUCs greater than 0.80, Also, to evaluate the probability of the presence of a condition (such as fluid responder) before and after the diagnostic test, the pre-test and post-test probability, was calculated using Fagan (1975) nomogram. A p value < 0.05 was considered to be statistically significant. Sigmaplot (Sigmaplot for Windows 11.1), Prism (GraphPad Prism 5 for Windows), R software (R3.2.2, 2015-08-14) and R packages (pROC), (rROC), were used for statistical analysis. Additionally, post-test probabilities were calculated by an online nomogram table, available at: http://araw.mede.uic.edu/cgi-bin/testcalc.pl.

4.3 Results

After the assessment of 115 dogs in the database, 90 dogs were included in this study. Three animals had to be excluded from the study due to anemia and two dogs because of cardiac arrhythmia (Atrio-ventricular block). Secondary exclusion of 20 animals was due to missing data of hemodynamic variables (12) and not completion of the fluid expansion (8). Table 1 summarizes all the characteristics of the animals, including age, sex and body weight, respiratory parameters and the type of surgical procedure.

In this study, seventy-one percent (71%) of the dogs (64/90) were responders and 29% of the dogs (26/90) were nonresponders. Responders had a mean increase of 25,8% ± 8,8% (p < 0.001) in stroke volume, while nonresponders had an increase of 8,7% ± 4% (p = 0.439).

Table 1 - Characteristics of the study population, respiratory parameters and types of surgery. Values are expressed as mean (standard deviation) or median (interquartile range).

Characteristics	**All animals (n = 90)**	**Responders (*n* = 64)**	**Nonresponders (*n* = *26*)**	***p* value**
Age (yr)	7.9 ± 3.6	7.6 ± 3.5	8.5 ± 3.8	0.318
Sex (m/f)	(38/52)	(29/35)	(21/15)	0.243
Body weight (kg)	25 ± 11.6	24.3 ± 11.9	25 ± 10.7	0.817
Tidal volume (ml/kg)	9 ± 0.68	9 ± 0.5	9 ± 0.78	0.798
Respiratory rate (mpm)	15 (14/21)	15 (14/22)	15 (14/20)	0.963
FiO2	65.8 ± 7.6	64 ± 7.4	66.9 ± 7.6	0.118
ETCO2	36.5 ± 4.2	36.2 ± 4.3	36.7 ± 4.2	0.647
ETIso	1.3 (1.2/1.3)	1.3 (1.2/1.3)	1.3 (1.2/1.3)	0.115

m/f, macho/fêmea; mpm, movimentos por minuto, FiO2, fração inspirada de oxigênio; ETCO2, dióxido de carbono expirado; ETIso, isoflurano expirado.

The increase in SV between time points ($p < 0.001$) was significantly greater in all responders. Conversely, the increase in cardiac output, between time points, was not statistically significant in both Rs and NRs. With exception of SV at baseline, there were no statistical difference between Rs and NRs with regard to echographic indices ($p > 0.05$). PPV was significantly different baseline and other time points, both in Rs and in NRs. The overall comparison between groups (Rs and NRs) and moments (baseline, 5, 10 and 15 ml/kg) is summarized in Table 2.

Table 2 – Hemodynamic and preload markers variables during fluid expansion, stratified by fluid responders and non-responders. Data are expressed as median (interquartile range).

Variables	**Baseline**	**5**	**10**	**15**	***p* value**
HR (bpm)					
Responders	101 (91.7/115)	98.5 (89.5/110)	94.5 (87/105)	93 (84/106.5)	0.158
Nonresponders	101 (91.7/115)	91 (85/100)	88 (83/105.7)	88 (83/102)	0.865
MAP (mmHg)					
Responders	56 (49/59)	57 (52.7/63)*	59 (53/62)*	62 (57/65.5)*†	<0.001
Nonresponders	53.5 (48/56.7)	55 (50/59.7)	55 (50.5/59)	57 (52.5/60)§	0.321
SV (ml)					
Responders	16.8 (14.2/25)§	19 (15/26.8)*	20.7 (17/30.5)*†	23.9 (17.9/33.7)*†	<0.001
Nonresponders	17.7 (14.1/25.3)	18 (14.6/26.1)	19 (15.3/26.1)	19 (16.1/26.7)	0.596
CO (l/min)					
Responders	1.77 (1.45/2.64)	1.97 (1.42/2.87)	2.0 (1.47/2.98)	2.26 (1.6/3.18)	0.100
Nonresponders	1.8 (1.15/2.18)	1.85 (1.15/2.42)	1.87 (1.26/2.33)	1.9 (1.12/2.39)	0.965
PPV (%)					
Responders	18.4 (16/26.3)	14.2 (9.8/19.7)*	11.9 (8/16.2)*	9.7 (6.4/13)*†	<0.001
HR (bpm)	10.3 (7.9/13.6)§	8.3 (6.8/10.4)§	7.2 (6.2/8.8)*§	6.6 (4.7/7.6)§*†	<0.001

HR, heart rate; bpm, beats per minute; MAP, mean arterial pressure; mmHg, millimeters of Mercury; SV, stroke volume; CO, cardiac output; PPV, pulse pressure variation.
§ $p < 0.05$ between responders and nonresponders.
* $p < 0.05$ when comparing with baseline.
† $p < 0.05$ when comparing with T5.

The ROC curve analysis (Table 3) showed a significant difference between the AUCs of all preload markers. When comparing the indices' AUCs, a non-significant differences were observed among SVV5, ΔCO5 and PPV5 ($p > 0.05$). There were significant differences between the AUCs for SVV10 and ΔCO10 ($p < 0.01$), and for SVV10 and PPV10 ($p < 0.001$), however, between ΔCO10 and PPV10 there was not ($p = 0.09$). Additionally, a significant difference was observed between the AUCs for SVV15 and ΔCO15 ($p < 0.01$), for SVV15 and PVV15 ($p < 0.0001$), and for ΔCO15 and PPV15 ($p < 0.001$). Regarding SVV, its AUCs showed statistical differences when comparing the beginning of the fluid expansion (SVV5) with SVV10 and with SVV15 ($p < 0.001$). Additionally, there was no significant difference between the AUCs for SVV10 and SVV15 ($p > 0.05$). Furthermore, the AUC for ΔCO5 was also statistically different from ΔCO10's and ΔCO15's ($p < 0.001$), as were the AUCs for ΔCO10 and ΔCO15 ($p = 0.011$). The best cut-off values through all the FE and their sensitivity/specificity is displayed in table 3.

Table 3: Receiver operating characteristics (ROC) curve statistics of three dynamic indices of fluid responsiveness during fluid expansion with 5, 10 and 15 ml/kg.

Variables	**AUC**	**95% CI AUC**	***p* value**	**Cut-off**	**Sensitivity (%)**	**Specificity (%)**
PPV 5	0.78	0.69 – 0.87		12.85	60	96
PPV 10	0.77	0.67 – 0.86		7.5	82	68
PPV 15	0.70	0.59 – 0.81		7.8	66	75
ΔCO5	0.70	0.59 – 0.81		1.6	78	60
ΔCO10	0.85	0.78 – 0.93		3.8	93	64
ΔCO15	0.92	0.86 – 0.97		11.2	82	87
SVV5	0.75	0.64 – 0.85		6.8	67	80
SVV10	0.97	0.95 – 1.00		11.8	92	92
SVV15	1.00	1.00 – 1.00		14.2	96	100

HR, heart rate, MAP, mean arterial pressure; PPV, pulse pressure variation; ΔCO, cardiac output variation; SVV, stroke volume variation.

The likelihood ratios and post-test probabilities, given a pre-test probability of 71%, are summarized in table 4. Regarding the contingency table (2 x 2) results of each dynamic index, ΔCO10 was (59, 8, 6, 16), and ΔCO15 was (52, 3, 12, 19), as well as for SVV10 (60, 1, 5, 23), and for SVV15 (62, 0, 3, 24).

Table 4: Positive and negative likelihood ratio and the post-test probability given the pre-test probability of 71%, between the echographic indices of fluid responsiveness.

Variables	**Positive test result**		**Negative test result**	
	LHR+	**Post-test probability**	**LHR -**	**Post-test probability**
ΔCO10	2.7	89%	0.13	29%
ΔCO15	3.3	94%	0.30	40%
SVV10	23	97%	0.07	19%
SVV15	Inf	100%	0.05	12%

ΔCO, cardiac output variation; SVV, stroke volume variation. Inf, infinito.

4.4 Discussion

This study showed that the ability of SVV5 to predict fluid responsiveness was inferior to SVV10's and SVV15's. ΔCO displayed a similar pattern, as ΔCO5 was less accurate than ΔCO10 and ΔCO15. Regarding PPV, it showed poor diagnostic accuracy in predicting fluid responsiveness in all FE protocols.

Fluid expansion with crystalloids is performed with the objective of increasing preload and consequently cardiac output. However, if FE does not increase cardiac output or their surrogates, giving fluids will grant no benefit to the animal. Therefore, administering the smallest necessary amount of fluids to evaluate fluid responsiveness is an interesting strategy to pursue during anesthesia. In recent years, many minimally invasive techniques to evaluate fluid responsiveness have been investigated, and SVV is one of the indices that have accumulated a large amount of evidence both in humans (Monnet et al. 2016; Dave et al. 2018; Messina et al. 2018) and animals (Endo et al. 2017; Sasaki et al. 2018; Sasaki et al. 2017; Bucci et al. 2017b). Regarding ΔCO, this echocardiographic index is infrequently reported in the literature, probably because is obtained through the same method (same echographic view) as SVV, with aortic pulsed Doppler. Conversely, pulse pressure variation have been shown to be a reliable index for predicting fluid responsiveness across several settings (Endo et al. 2017; Berkenstadt et al. 2005; Fantoni et al. 2017; Renner et al. 2008).

Even though SVV5 and ΔCO5 did not show a satisfactory diagnostic accuracy, considering the ROC analysis and an AUC lower than to 0.75 (Ray et al. 2010), both SVV10-15 and ΔCO10-15 appear to be an adequate option for predicting fluid responsiveness. One may consider using the smallest amount of fluids during the evaluation, since many animals may be non-responders (29% in the present study) and will receive unnecessary fluids. Therefore, both SVV10 and ΔCO10 should be used to titrate FE and limit the amount of fluids infused. This is also supported by the fact that no statistical difference was observed between the AUCs of those time points (T10 – T15), as well as the number of animals in the inconclusive area and their LHR. More importantly, the probability of an animal is indeed responsive to fluids after a positive test result (i.e SVV10 cut-off > 11.8), is equally high from T10 to T15, suggesting that little increase in the diagnostic accuracy will be present after the completion of the bollus. Additionally, the increase in the negative post-test probability value between ΔCO10 to ΔCO15 might lead to more false positive cases. Therefore, evidences suggest that a FE with 10 mL/kg was the optimum choice in the present study.

In the present study, the diagnostic accuracy of ΔCO10 was inferior when compared with SVV10, suggested by several factors. First, the AUC is considered good when it is higher than 0.75 and as excellent when is more than 0.90, meaning that SVV10 was superior when compared with ΔCO10. Additionally, the AUC 95% CI of SVV10 was narrow, far from the identity line and from ΔCO10, especially at the lower limit which was still superior than 0.90. Secondly, the specificity value for ΔCO10 was small when compared to SVV10, which can explain the higher number of false positives seen in ΔCO10. This is also strengthened by it poorly LHR value, compared with SVV10, which resulted in a small positive post-test probability (more false negatives) and high negative post-test probability (more false positives). Third, the ΔCO cut-off values were rather low both in ΔCO5 - 10, which could decrease its practical value since it is more difficult to detect such a small difference in the daily practice. This difference observed between these two echocardiographic indices could be attributed to the variability of the heart rate, which can be easily influenced during anesthesia.

Studies often report SVV cut-off values ranging from 8% to 22% in several settings, from cardiac surgery to pediatric intensive care unit patients (Yi et al. 2017; Messina et al. 2018).

The present study found a SVV cut-off value that is in concordance with previous studies both in veterinary medicine and in humans. Endo et al. 2017 in an experimental study with 5 euvolemic sevoflurane anesthetized adult dogs, reported an SVV cut-off value of 11% (sensitivity 100%; specificity 100%) to predict an increase of 15% in SV after FE with lactated Ringer's solution and hydroxyethyl starch solution at 30 ml/kg/hr. Another experimental study with mechanically ventilated dogs undergoing an haemorrhage model reported an SVV cut-off value of 9,5% to predict an increase of SV after FE with a colloid solution (Berkenstadt et al. 2005). A recent study with 45 mechanically ventilated dogs evaluated the ability of SVV to predict an increase of 10% in stroke volume index after FE with 10 mL kg^{-1} lactated Ringer's solution infused over 15 minutes and reported the best cut-off value to be 13,5% (75% sensitivity and 86% specificity), (Sasaki et al. 2018). This heterogeneity in the reported SVV cut-off values through all the studies can be attributed to the variety among the studied populations, to the types of surgery/disease involved and to the FE protocols used, which are factors that, according to two multicenter studies, Cecconi et al. (2015) and Toscani et al. (2017), are highly variable even in humans.

Regarding ΔCO cut-off value, Wu and colleagues reported that a 6% increase in ΔCO have a good predictive capability (AUC 0.95 ± 0.03) based on AUC analysis, in 55 mechanically ventilated patients underwent a mini fluid challenge (Wu et al. 2014)

The magnitude of variation in diagnostic accuracy of the dynamic indices of fluid responsiveness appears to depend on the characteristics of the FE used. The type of fluid, total volume administered and the rate of infusion are three aspects of FE that vary immensely among the studies (Cecconi et al. 2015; Min et al. 2017). Some aspects of the FE were summarized and evaluated in a systematic review and meta-analysis in human literature, which concluded that the type and volume of fluid or even the duration of the assessment do not seem to have any effect on the detection of fluid responsiveness (Toscani et al. 2017). Moreover, according to the Frank-Starling cardiac function curve, to achieve a great increase in stroke volume, a faster rate of fluid administration could theoretically enhance preload and thus SV, especially if the patient is in the steep portion of the curve. Therefore, an increase in the rate of the FE (particularly less than 5 minutes) could be employed to evaluate whether a small FE, such as 5 ml/kg can predict fluid responsiveness with better diagnostic accuracy than the present study.

In human literature, Muller et al. (2011) reported a good AUC (0.92) after an infusion of 100 ml of hydroxyethyl starch solution over 1 minute, in thirty-nine critically ill ventilated and sedated patients with acute circulatory failure. Another study with 55 mechanically ventilated patients also reported a good predictability (ΔVTI, AUC 0.92) after a FE with 50 ml of crystalloids infused as fast as 10 seconds (Wu et al. 2014). Indeed, a previous study in veterinary literature with 24 mechanically ventilated healthy dogs showed that a FE with 5 ml/kg of lactated Ringer's solution over 1 minute was able to predict an increase ≥ 15% in VTI (Bucci et al. 2017a). However these author's also reported having used a high tidal volume per kg during the evaluation of (14 mL kg^{-1} - 13/15), which could have influenced the findings, since the cyclical changes in stroke volume during mechanical ventilation have been reported to predict fluid responsiveness in tidal volumes ranging from 8 – 10 ml kg^{-1} in all studies (Min et al. 2017; Cecconi et al. 2015; De Backer et al. 2005; Vistisen et al. 2010; Marik 2010). Some studies even described "tidal volume challenges" as a transitory increase in the tidal volume to intensify the variation in intrathoracic pressure and thus produce a significant variation in the preload marker, however even the temporary increase in tidal volume ranged from 8 to 12 ml/kg (Myatra et al. 2017; Min et al. 2017).

The present study had some limitations, first, the retrospective aspect of the analysis carries its own limitations. Heterogeneity is expected among patients since variation in the illness, underlying diseases and their severity is likely to be present. However, in the selection for the study, animals with severe disease experiencing severe hemodynamic deficit or undergoing any type of vasopressor therapy were excluded. The present study also had a good homogeneity regarding weight, sex, and age. Variety in overall management of the anesthesia and in the FE protocol it is another factor that could influence the results. However, the unicenter aspect of the study contributes to a better homogeneity of the protocols and procedures.

4.5 Conclusion

In conclusion, both SVV10 and ΔCO10 are reliable predictors of fluid responsiveness when compared with the other FE protocols. However, PPV did not showed the same discriminative capability. In addition, an increase in SSV of 11.8% after an infusion of 10 mL kg^{-1} with crystaloids over 10 minutes, was the fluid expansion protocol with higher diagnostic accuracy in the present study.

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5 Considerações gerais

O presente estudo confirma a efetividade dos índices dinâmicos de responsividade a fluido em alguns cenários cirúrgicos comuns no dia a dia. Destacando as diferenças e particularidades entre cada índice, assim como possíveis soluções para cada situação. Independente do tipo de índice dinâmico utilizado, nossos dados suportam o uso de tais índices como guia intraoperatório de fluidoterapia e encoraja novos estudos na área, para que no future uma abordagem individualizada possa impactor positivamente em desfechos clínicos para os animais.

6 Referências gerais

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