



Clinical Application of the Fluid Challenge Approach in Goal-Directed Fluid Therapy: What Can We Learn From Human Studies?

Francisco José Teixeira-Neto^{1*} and Alexander Valverde²

¹ Departamento de Cirurgia Veterinária e Reprodução Animal, Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista, Botucatu, Brazil, ² Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada

OPEN ACCESS

Edited by:

Charlotte Sandersen,
University of Liège, Belgium

Reviewed by:

Francesco Staffieri,
University of Bari Aldo Moro, Italy
Sônia Campos,
University of Liège, Belgium

*Correspondence:

Francisco José Teixeira-Neto
francisco.teixeira@unesp.br

Specialty section:

This article was submitted to
Veterinary Emergency and Critical
Care Medicine,
a section of the journal
Frontiers in Veterinary Science

Received: 29 April 2021

Accepted: 06 July 2021

Published: 03 August 2021

Citation:

Teixeira-Neto FJ and 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. 8:701377.
doi: 10.3389/fvets.2021.701377

Resuscitative fluid therapy aims to increase stroke volume (SV) and cardiac output (CO) and restore/improve tissue oxygen delivery in patients with circulatory failure. In individualized goal-directed fluid therapy (GDFT), fluids are titrated based on the assessment of responsiveness status (i.e., the ability of an individual to increase SV and CO in response to volume expansion). Fluid administration may increase venous return, SV and CO, but these effects may not be predictable in the clinical setting. The fluid challenge (FC) approach, which consists on the intravenous administration of small aliquots of fluids, over a relatively short period of time, to test if a patient has a preload reserve (i.e., the relative position on the Frank-Starling curve), has been used to guide fluid administration in critically ill humans. In responders to volume expansion (defined as individuals where SV or CO increases ≥ 10 –15% from pre FC values), FC administration is repeated until the individual no longer presents a preload reserve (i.e., until increases in SV or CO are < 10 –15% from values preceding each FC) or until other signs of shock are resolved (e.g., hypotension). Even with the most recent technological developments, reliable and practical measurement of the response variable (SV or CO changes induced by a FC) has posed a challenge in GDFT. Among the methods used to evaluate fluid responsiveness in the human medical field, measurement of aortic flow velocity time integral by point-of-care echocardiography has been implemented as a surrogate of SV changes induced by a FC and seems a promising non-invasive tool to guide FC administration in animals with signs of circulatory failure. This narrative review discusses the development of GDFT based on the FC approach and the response variables used to assess fluid responsiveness status in humans and animals, aiming to open new perspectives on the application of this concept to the veterinary field.

Keywords: fluid challenge, fluid responsiveness, goal-directed fluid therapy, shock, cardiac output

INTRODUCTION

Patients that are critically ill or that are undergoing major surgery are frequently presented with inadequate tissue oxygen delivery due to poor circulating volume. Under these conditions, rapid volume expansion *via* intravenous fluid administration should optimize tissue perfusion but such benefit is not without risks. Iatrogenic hypervolemia due to a liberal fluid administration strategy causes tissue/lung edema and worsens patient outcome (1). Otherwise, insufficient fluid administration due to a restrictive fluid therapy strategy can perpetuate hypovolemia/poor tissue perfusion and increase the rate of complications such as renal failure and death (1). According to guidelines published in veterinary medicine, when signs of circulatory failure/hypovolemia are present, aggressive fluid administration can be initiated *via* rapid administration of isotonic crystalloids using 25% of the “shock dose” (15–20 ml/kg in dogs and 10 mL/kg in cats), while monitoring the patient’s the response (e.g., blood pressure, capillary refill time, lung sounds) (2). Based on the response to initial volume expansion, additional aliquots (25% of shock dose) can be administered, or a synthetic colloid can be considered if 50% of crystalloid shock volume did not cause sufficient improvement (2). However, there are opened questions regarding the goals and endpoints that should guide volume resuscitation in animals.

In the human medical field, fluid resuscitation guided by assessment of fluid responsiveness [i.e., the ability of an individual to increase stroke volume (SV) and cardiac output (CO) in response to volume expansion] appears to reduce patient mortality, duration of stay in the intensive care unit (ICU), and duration of mechanical ventilation (3). The use of a fluid challenge approach (i.e., the rapid administration of a relatively small amount of fluids) guided assessment of fluid responsiveness status allows rapid replacement of intravascular volume deficits as long as the individual has a cardiac preload reserve (i.e., is positioned on the ascending limb of the Frank-Starling curve). Because additional amounts of fluids are administered only if the individual presents an improvement in SV and CO, the fluid challenge approach can improve tissue perfusion and minimize the risks associated with hypervolemia and fluid overload (1, 3). This article will review the physiological basis of goal-directed fluid therapy (GDFT), the fluid challenge approach for treating circulatory failure, and the target variables used to evaluate the response to volume resuscitation. Most of the current literature originates from research on the human side, whether conducted in the clinical setting, or from bench research in animals. More recently, veterinary studies have used this information in several animal species. This article aims to critically review the development of the fluid challenge approach in human and veterinary medicine, with the objective of shedding light on the possible applications of this concept to the veterinary field.

References from PubMed database since January 2000 were included in this narrative review. Primary search terms were fluid challenge, GDFT, and fluid responsiveness. Human and animal studies (dogs and cats, and other species if relevant) involving the above mentioned terms were selected. To approach the target variables used to assess the response to a fluid challenge, studies comparing newer CO measurement technologies with reference

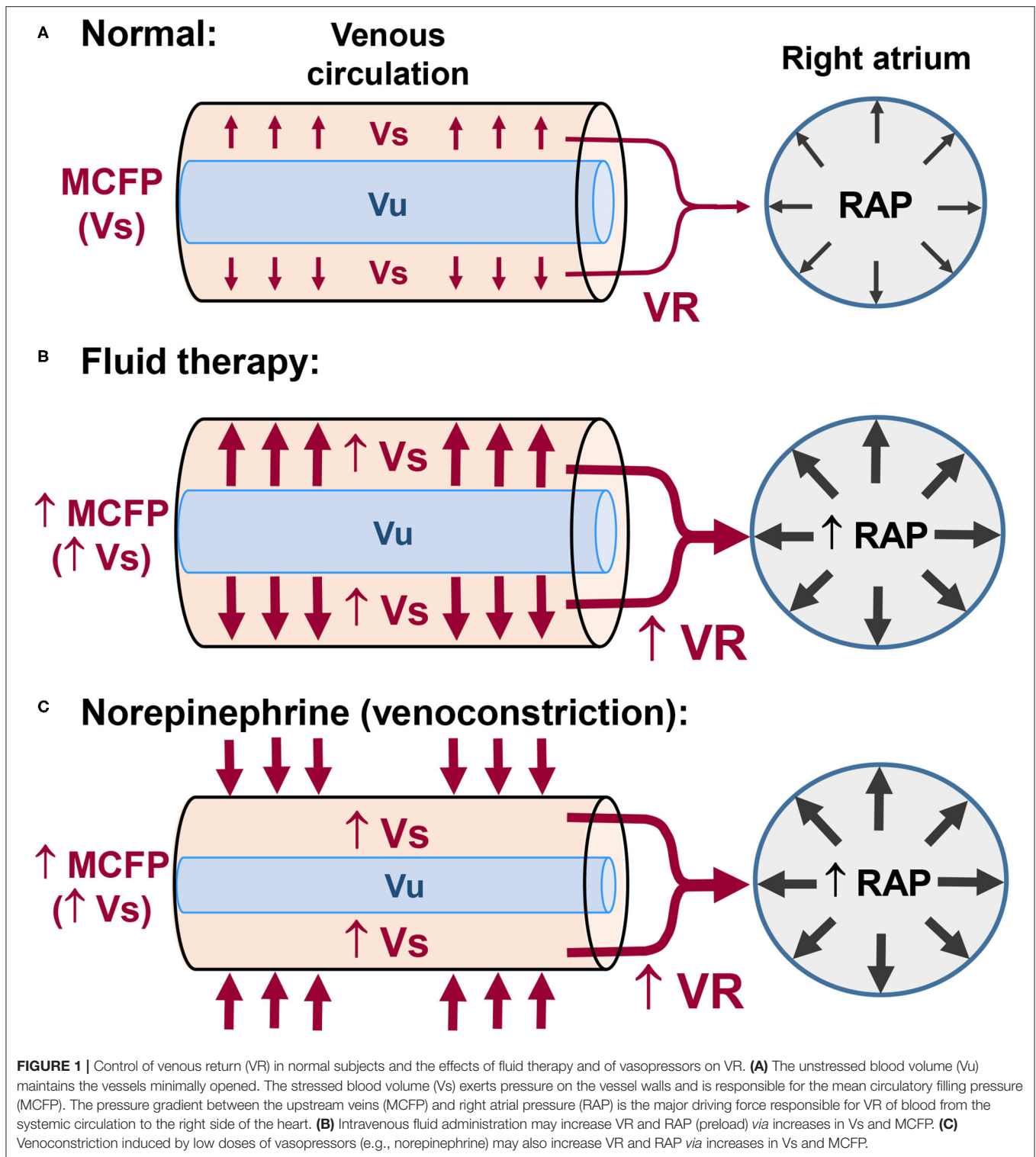
methods of CO measurement in humans, dogs, and cats were selected. Studies published before 2000 considered seminal for understanding the current state of knowledge were also included in the review.

THE PHYSIOLOGICAL BASIS OF GOAL DIRECTED FLUID THERAPY

The venous system is composed of highly compliant capacitance vessels (i.e., vessels that can accommodate a large volume of blood without a large increase in intravascular pressure) which contain ~70% of blood volume (4, 5). Based on its physiological role in the circulation, blood volume is subdivided into unstressed and stressed volumes (V_u and V_s , respectively), which represent 70% and 30% of total blood volume, respectively (4, 5). The V_u is the blood volume that maintains the vessels minimally opened and does not influence transmural pressure (i.e., the difference between intravascular pressure and the pressure exerted on the outside of the vessel wall). The V_s is the blood volume that stretches the vessel walls, effectively increasing transmural pressure (4, 5). The V_s represents the blood that moves fast within the circulatory system and is the major determinant of venous return (VR) (4, 5). During steady state conditions, VR from the systemic and pulmonary circulations equals CO. Venous return is the product of the gradient between mean circulatory filling pressure (MCFP) and right atrial pressure (RAP), divided by the resistance to blood flow in the venous circulation (**Figure 1A**). The effects of a fluid challenge on VR, SV, and CO may be the result of an unpredictable distribution of the infused fluid between the V_s and V_u , which may explain why ~50% of critically ill human patients do not respond to a fluid challenge with significant increases in SV and/or CO (6). If intravenous fluids are distributed mainly to V_u there will be no increase in VR, SV, and CO (6). Otherwise, a fluid challenge will result in the desired increase in VR, SV, and CO if it augments MCFP *via* an effective increase V_s (**Figure 1B**). Another frequently unappreciated physiological concept is the fact that fluids do not hold the monopoly of improving VR, SV, and CO. Venoconstriction may also shift blood from V_u to V_s , thereby, increasing VR due to an increase in MCFP (**Figure 1C**). Lower doses of vasopressor agents (e.g., norepinephrine and phenylephrine) may increase VR, SV, and CO through a venoconstrictive effect (6, 7). Otherwise, higher doses of vasopressors, in spite of increasing VR and SV through venoconstriction, will also induce significant arterial vasoconstriction, which could eventually lead to a decrease in CO (6). The negative impact of vasopressors on blood flow/CO can be suspected if a substantial increase in arterial pressure induced by these drugs is paralleled by clinically relevant bradycardia, which is probably caused by activation of the baroreceptor reflex.

WHAT IS FLUID RESPONSIVENESS AND HOW CAN IT BE ASSESSED?

In conscious patients with signs of acute circulatory failure (e.g., hypotension, increased blood lactate levels), intravascular



volume expansion is beneficial only if it significantly increases SV and CO. Titration of intravenous fluids to maximize SV and CO, while avoiding hyper- or hypovolemia is an ongoing paradigm in the medical field. The Frank-Starling curve provides the physiological basis for understanding the concept of fluid

responsiveness. To test the fluid responsiveness status of an individual, a change in preload must be provoked and the observed response in SV or CO recorded (8). Responders to volume expansion, whose heart is operating in the ascending limb of the Frank-Starling curve, are defined as those individuals

where SV or CO increase at least 10–15% after an increase in preload induced by test dose of fluids (i.e., a fluid challenge) or by a passive leg raise test (9–11). The passive leg raise test in humans involves raising both legs to a 45° angle in relation to the trunk to temporarily increase cardiac preload by diverting part of the blood volume (~300 ml) from the legs to the trunk/central circulation. This test allows determining the fluid responsiveness status of an individual without the need to administer fluids (11). In veterinary medicine, determination of fluid responsiveness has been restricted to the evaluation of changes in SV or CO in response to a fluid challenge in anesthetized or conscious dogs (12–22).

Dynamic assessment of fluid responsiveness relies on changes in preload induced by mechanical ventilation and the resulting change in surrogates of SV (23–29). Differently from the fluid challenge approach, which relies on a test dose of fluids to determine responsiveness status, heart/lung interactions during mechanical ventilation allows identifying the relative position of an individual in the Frank-Starling curve (i.e., fluid responsiveness status) *a priori* to fluid administration (23–29). Because preload changes induced by volume-controlled ventilation cause larger SV variations in patients positioned in the ascending limb of the Frank-Starling curve, responders to volume expansion can be identified if respiratory induced variations in SV are increased above a certain threshold. Surrogates of SV used for dynamic assessment of fluid responsiveness include respiratory variation in peak aortic flow velocity (ΔV_{peak}), pulse pressure variation (PPV), systolic pressure variation (SPV), plethysmographic variability index (PVI) and stroke volume variation derived from pulse contour analysis (SVV_{PCA}) (29).

In contrast with dynamic preload indexes, static markers of preload that reflect cardiac filling pressures (central venous pressure and pulmonary artery occlusion pressure), or that reflect end-diastolic volume, are not reliable to predict fluid responsiveness and have limited usefulness to guide fluid administration (30–32). Accurate prediction of fluid responsiveness by PPV and other dynamic preload indexes demands that patients are under volume-controlled mechanical ventilation with tidal volumes ≥ 8 ml/kg, without heart rhythm irregularities and without spontaneous breathing efforts (33). According to a meta-analysis, PPV was superior to predict responsiveness than other dynamic preload indexes in human patients under mechanical ventilation with tidal volumes ranging from 8 to 12 ml/kg (31). Although, PPV values $>12.5\%$ accurately discriminate responders from non-responders to a fluid challenge (31), this index has limited clinical application in the ICU setting because of inaccurate prediction of responsiveness in patients ventilated with low tidal volumes (<8 ml/kg) (34, 35). The ability of ΔV_{peak} , PPV, SPV, PVI, and SVV_{PCA} to predict the response to a fluid challenge has been assessed in anesthetized mechanically ventilated dogs (12–16, 18, 21, 22). In canine studies PPV thresholds $>11\text{--}16\%$ were able to identify responders to volume expansion (13–16, 18, 21, 22). The large variation in PPV thresholds reported by the veterinary literature can be explained in part by differences in the fluid challenge protocol, in the methods used for assessing the response to volume expansion, and in mechanical ventilation adjustments.

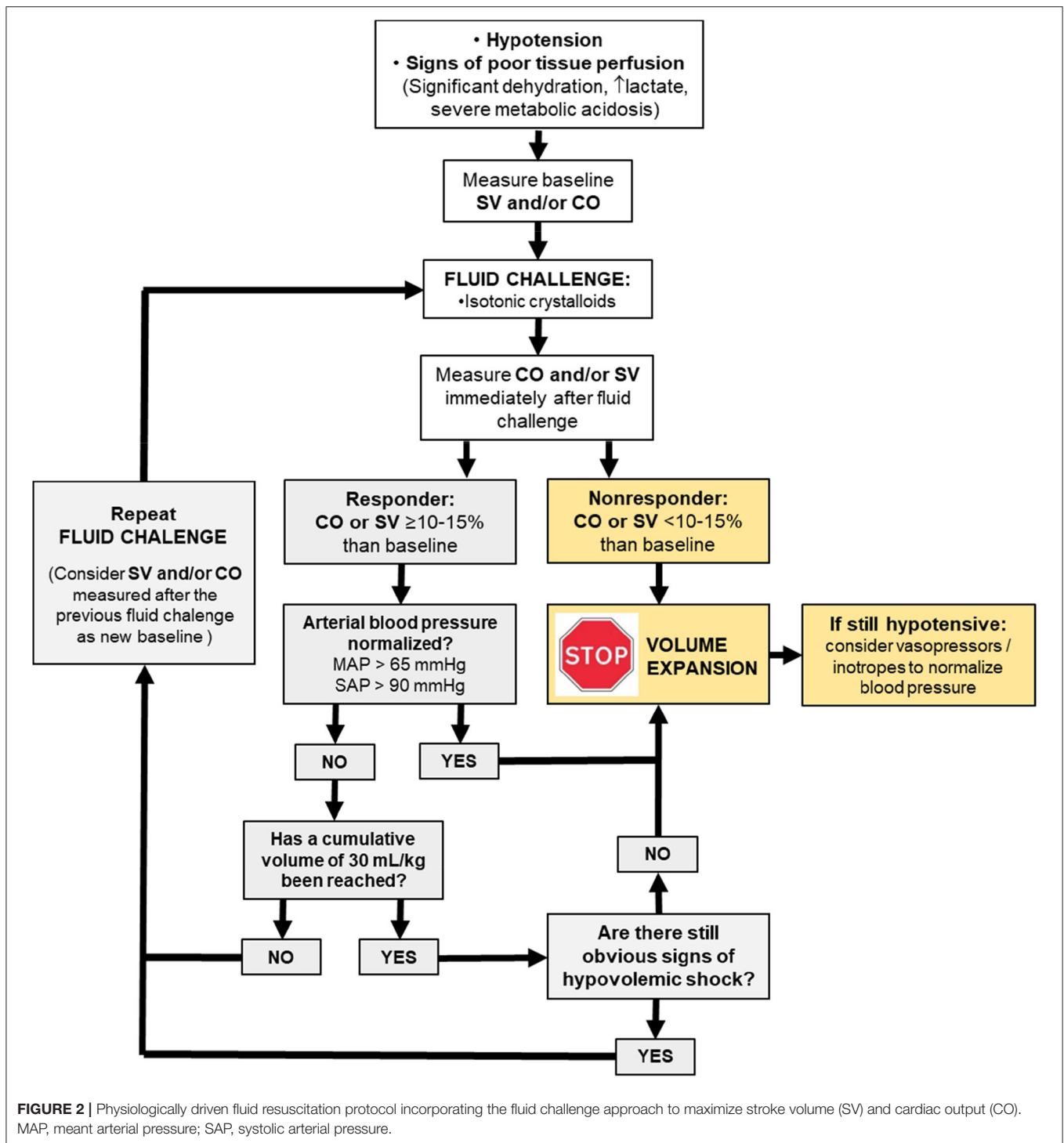
Although, dynamic preload indexes are effective tools to predict fluid responsiveness, the necessity for patients to be under mechanical ventilation without cardiac arrhythmias and spontaneous breathing efforts is a major limiting factor to their use in clinical practice. In critically ill spontaneously breathing human patients, the response to volume expansion can be predicted by ultrasound assessment of respiratory induced variations in inferior vena cava diameter (i.e., inferior vena cava collapsibility index) (36, 37). In a heterogeneous population of hospitalized dogs, ultrasonographic indexes showed different results, the “caudal” vena cava collapsibility index could not predict fluid responsiveness; while the “caudal” vena cava to aortic diameter ratio (CVC/Ao ratio), showed reasonable ability to discriminate responsiveness status *a priori* to volume expansion (19). The CVC/Ao ratio appears useful to detect early stages of volume depletion in dogs, but with variable results (38–41).

THE FLUID CHALLENGE APPROACH AND THE END-POINT OF FLUID RESSUSCITATION

A fluid challenge is the rapid administration of a relatively small volume of fluid to test if an individual has a cardiac preload reserve. Inasmuch as small amounts of fluids are titrated “to effect,” based on pre-established goals, the fluid challenge also provides volume replacement with lower risk of volume overload (9, 10). Percent changes in SV or CO are the target hemodynamic variables and individuals where SV or CO increased by more than 10–15% from values recorded before the fluid challenge are characterized as responders to volume expansion (i.e., are positioned in the ascending limb of the Frank-Starling Curve). With the fluid challenge traditionally used in adult humans (500 ml of artificial colloids or crystalloids), it has been recognized that 52% of patients in the ICU and 63% of patients in the operating room show preload dependency (i.e., are responders to volume expansion) (32). More recent a meta-analysis has confirmed that only 50% of critically ill human individuals positively respond to a fluid challenge (42).

In individuals with signs of poor tissue perfusion that are responders to the first fluid challenge (SV or CO increase $\geq 10\text{--}15\%$ above baseline), maximization of SV and CO can be achieved by administering additional fluid challenges (9, 10). Before a decision is made on whether fluid resuscitation should be continued, SV or CO values recorded after the previous fluid challenge is taken as the new baseline to determine percent changes in SV or CO. Stepwise fluid resuscitation can be interrupted once the individual becomes a non-responder to volume expansion (i.e., until increases in SV or CO are $<10\text{--}15\%$). Because the only excess fluid administered corresponds to the volume of one fluid challenge, the risk of volume overload can be minimized (9, 10, 42).

One question that remains opened is the end-point of fluid resuscitation in individuals that show preload dependence. Unless there is evidence of significant hypovolemia, it has been the suggested in humans admitted for emergency care that



the volume of intravenous fluids should be initially limited to 20–30 ml/kg before vasopressors are considered to treat hypotension (7). The updated guidelines of the surviving sepsis campaign recommends intravenous administration of 30 ml/kg of crystalloids during the first hour in septic human patients with hypotension and elevated plasma lactate (43, 44). Although, fluids are titrated to maximize SV and CO in GDFT (i.e.,

until the individual is in the transition between the ascending and the flat portion of the Frank-Starling curve), a maximum cumulative volume of fluids can be predefined in GDFT protocols to minimize the risk of fluid overload (45). In patients that are hypotensive from hypovolemia and sepsis, normalization of arterial pressure could be determinant for terminating fluid resuscitation, even if assessment of fluid responsiveness still

shows a state of preload dependence (45). Otherwise, vasopressor therapy should be initiated within the first hour if initial fluid administration is not sufficient to achieve the hemodynamic resuscitation goals (43–45) (**Figure 2**).

In individuals admitted for emergency care with signs of circulatory failure, hypotension is often caused by poor circulating volume that may be associated or not with sepsis-induced loss of vasomotor tone. Otherwise, hypotension during anesthesia is often caused by drug-induced decreases in systemic vascular resistance (SVR) and/or CO and does not imply that there is a circulating volume deficit (46). Although, it has been recognized that responders to volume expansion are not necessarily hypovolemic (28), hypotension-inducing hemorrhage in isoflurane anesthetized dogs can lead to a state of preload dependence, as suggested by increases in PPV and PVI from pre-hemorrhage values (47, 48). In case of intraoperative hypotension where the suspected cause is poor circulating volume, a fluid challenge approach may be attempted but cardiovascular support with sympathomimetics should not be delayed due to the dose-dependent depressant effects of inhalant anesthetics and/or neuraxial anesthesia on contractility and vasodilation (46). A drug with α -1 and β -1 effects is ideal to improve both arterial blood pressure and CO, respectively (46). Constant rate infusions of vasopressor drugs, such as norepinephrine and dexmedetomidine, should be carefully used as these drugs can mask hypotension and increases in PPV and SPV caused by poor circulating volume, probably by shifting blood from the unstressed to stressed volume *via* a venoconstrictive action (47, 49).

According to a systematic review of literature, the fluid challenge most commonly used in adult human patients with signs of poor tissue perfusion consisted of 500 ml of crystalloids or colloids (~ 7 ml/kg to an adult patient weighing 70 kg), administered during 20–30 min (42). The target variable most commonly monitored after the fluid challenge in humans was an increase in CO $\geq 15\%$ (42). Because traditionally used fluid challenges might result in some risk of volume overload, a mini-fluid challenge technique, based on the use of smaller volumes of fluids administered at faster rates has been used to predict if patients will respond to a “standard” fluid challenge (**Table 1**). Use of a mini-fluid challenge to test for a cardiac preload reserve can reduce the risk of fluid overload that would otherwise occur with the administration of a traditional fluid challenge. In critically ill adult humans, rapid administration of 50–150 ml of fluids during 10 s to 2 min reasonably predicts the response to larger volumes of fluids (250–500 ml) (50–55). In children undergoing elective surgery, however, a 3 ml/kg mini-fluid challenge administered during 2 min weakly predicted the effects of a 15 ml/kg volume of lactated Ringer’s solution (LRS) (56). Recent meta-analysis concluded that a mini-fluid challenge reliably predicts fluid responsiveness status in the operating room and in the ICU setting (57).

A summary of studies evaluating responsiveness using fluid challenges in small animals is presented in **Table 2**. Several reports in veterinary medicine have evaluated fluid responsiveness *via* a fluid challenge approach in

healthy/normovolemic dogs under anesthesia (12, 15, 16, 20–22). In other studies a fluid challenge has been administered in dogs anesthetized for orthopedic/oncologic surgery that presented intraoperative hypotension (mean arterial pressure < 65 mmHg) (13, 18), or in dogs anesthetized for abdominal surgeries potentially associated with hemodynamic instability that were predicted as responders to volume expansion based on PPV values $> 13\%$ (14).

The volume and duration of infusion of fluid challenges administered to small animal patients in the literature varies considerably. Fluid responsiveness status in dogs has been assessed *via* administration of LRS at doses ranging from 10 to 20 ml/kg administered over 5–15 min (13, 14, 16, 18, 20, 22). In one study, a 10 ml/kg bolus of 6% hydroxyethyl starch (HES) was administered during 13 min in anesthetized dogs (15). Smaller volumes of isotonic crystalloids (LRS), administered at faster (4–5 ml/kg during 1 min) (12, 17, 19) or slower rates (5 ml/kg during 5 min) (21) have been used to evaluate fluid responsiveness status in canine species. Although, one might define these smaller volumes of LRS as mini fluid challenges, such definition might not be appropriate because there have been no published studies evaluating the ability of these volumes to predict the response to fluid challenges traditionally used in canine species (15–20 ml/kg of LRS).

The criteria used to define responders to volume expansion in veterinary studies has been an increase in CO or SV ≥ 10 –15% (**Table 2**). Transthoracic echocardiography (12, 15, 17, 19), transesophageal echocardiography (13, 18), esophageal Doppler (14), transpulmonary thermodilution (16, 20, 22), and uncalibrated pulse contour analysis (21) have been used to monitor fluid responsiveness status in anesthetized dogs. While it has been recognized that only 50% of critically ill human individuals positively respond to a fluid challenge with substantial increases in CO or SV (32, 42), the percentage of responders to a single fluid challenge with crystalloids in canine studies has been reported to range from 38 to 100% (**Table 2**). This large variability could be partly related to the fact that fluid responsiveness was evaluated in animals presenting with varying clinical conditions, which may lead to an altered fluid responsiveness status due to varying degrees of systemic illness. The proportion of responders/non-responders to volume expansion in these studies could also have been influenced by the use of fluid challenges administered at different volumes and rates, and to the use of monitoring devices that differ in their ability accurately to detect CO and/or SV changes induced by volume expansion (58).

WHICH TARGET VARIABLE SHOULD BE USED TO ASSESS FLUID RESPONSIVENESS STATUS BY A FLUID CHALLENGE?

In spite of recommendations for monitoring CO or SV changes as the main response variable during GDFT, large scale clinical trials reported that arterial blood pressure was still the most commonly used target variable in humans (59). However, evaluation of

TABLE 1 | Clinical studies using a mini-fluid challenge to predict the response to a standard fluid challenge in humans.

Fluid type	Mini fluid challenge:			Fluid challenge (criterion of responder)	Population evaluated	Reference
	Volume (infusion time)	Best cutoff*	AUROC** (95% CI)			
6% HES	100 ml (1 min)	↑ VTI _{Aortic flow} ≥ 10%	0.92 (0.78–0.98)	500 ml/15 min (↑ VTI _{Aortic flow} ≥ 15%)	39 patients with acute circulatory failure under mechanical ventilation.	Muller et al. (50)
“Crystalloid”	50 ml (10 s)	↑ VTI _{Aortic flow} > 9%	0.91 (NR)	500 ml/15 min (↑ CO _{Echo} ≥ 15%)	55 mechanically ventilated patients with inadequate perfusion.	Wu et al. (51)
“Crystalloid”	50 ml (10 s)	↑ CO _{Echo} > 6%	0.95 (NR)	500 ml/15 min (↑ CO _{Echo} ≥ 15%)	Same as above.	Wu et al. (51)
0.9% NaCl	100 ml (2 min)	↑ SVI _{PCA} > 6%	0.95 (0.90–0.99)	250 ml/10 min (↑ SVI _{PCA} ≥ 10%)	44 mechanically ventilated patients undergoing neurosurgery.	Biais et al. (52)
5% Albumin	150 ml (1 min)	↑ SV _{Echo} > 10%	0.86 (0.6–0.9)	500 ml/16 min (↑ SV _{Echo} ≥ 15%)	14 Child A cirrhosis patients receiving liver transplant***.	Mukhtar et al. (53)
0.9% NaCl	100 ml (1 min)	↑ SVI _{PCA} > 5.8%	0.97 (0.84–0.99)	500 ml/11 min (↑ SVI _{PCA**} > 15%)	33 mechanically ventilated obese patients undergoing neurosurgery.	Ali et al. (54)
6% HES	100 ml (1 min)	↑ SV _{PCA} > 5%	0.90 (0.82–0.99)	500 ml/11 min (↑ SV _{PCA**} ≥ 15%)	50 patients undergoing spine surgery in prone position.	Lee et al. (55)
LRS	3 ml/kg (2 min)	↑ VTI _{Aortic flow} > 1.5%	0.77 (0.63–0.87)	15 ml/kg (10 min)	55 children under general anesthesia for elective surgery with high risk of bleeding.	Zorio et al. (56)

*Best cutoff threshold to predict responders to the conventional fluid challenge.

**AUROC: Area under the receiver operating characteristics curve (values ≥ 0.75 and ≥ 0.90 indicate good and excellent ability to discriminate responders from non-responders to volume expansion, respectively).

***For individuals with child B and C cirrhosis the mini fluid challenge did not have discriminative ability (AUROC not different from 0.5).

CI, confidence intervals; HES, hydroxyethyl starch; ↑, increase in variable; LRS, lactated Ringer's solution; VTI_{Aortic flow}, velocity-time integral of aortic flow measured by echocardiography; CO_{Echo}, cardiac output measured by echocardiography; SVI_{PCA}, stroke volume index measured by uncalibrated pulse contour analysis; SV_{Echo}, stroke volume measured by echocardiography; SV_{PCA}, stroke volume measured by uncalibrated pulse contour analysis.

changes in arterial pressure as a surrogate of CO changes could be misleading even in individuals presenting with hypotension from hypovolemia because arterial elastance/resistance can be significantly altered (20, 59, 60). Data in veterinary medicine is lacking, but it appears that arterial blood pressure is commonly used as the main target variable in dogs and cats admitted with signs of shock. Despite its limitations, arterial pressure is the preferred method to assess the response to a fluid challenge if measurement of SV and CO or its surrogates are not available. In veterinary medicine, systolic arterial pressure (SAP) measured by a Doppler ultrasound device has the advantage of allowing a subjective assessment of the quality of the peripheral perfusion. The pulsatile arterial blood flow detected by the Doppler ultrasound may be inaudible or muffled in dogs and cats with severe circulatory failure, but it often improves after a first fluid challenge, allowing measurement of SAP. In the presence of signs of shock (SAP < 90 mmHg), an increase of at least 5–10 mmHg in SAP induced by a fluid challenge can be used to define a responder volume expansion. In a similar way as for SV and CO, as long as the response remains

positive, fluid challenges are repeated until the target SAP is achieved. If an animal does not respond to a fluid challenge with increases in SAP, fluid resuscitation should be stopped and other alternatives to stabilize blood pressure considered. In a retrospective study of dogs admitted to a veterinary care facility with signs of circulatory failure (SAP < 90 mmHg), when bolus fluid administration resulted in normalization of SAP within the first hour of fluid resuscitation (Doppler SAP ≥ 90 mmHg) there was lower probability of death compared to animals that remained hypotensive in response to rapid volume resuscitation (61).

The lack of implementation of CO or SV changes to guide fluid administration in patients with circulatory failure could be attributed to difficulties in monitoring CO and SV in a practical and reliable way. A clinically useful method of CO and SV measurement should be accurate (i.e., provide values that are close to a reference value), precise (i.e., provide values in close proximity when repeated measurements are performed during steady state conditions), and provide good ability to track changes in the target variable (62, 63). According to

TABLE 2 | Fluid challenge techniques with crystalloids used to evaluate fluid responsiveness in dogs.

Type of fluid	Volume infused (duration of infusion)	Criterion used to define responders to the fluid challenge	Percentage of responders to the first fluid challenge	Population evaluated	Reference
LRS	5 ml/kg (1 min)	↑ VTI _{Aortic flow} ≥ 15%	38%	24 healthy dogs undergoing elective surgeries.	Bucci et al. (12)
LRS	15 ml/kg (15 min)	↑ CO _{Echo} ≥ 15%	76%	33 dogs with hypotension during anesthesia under mechanical ventilation for orthopedic surgery.	Fantoni et al. (13)
LRS	10 ml/kg (10–15 min)	↑ SV _{EDM} ≥ 10%	82%	35 dogs anesthetized under mechanical ventilation for abdominal surgeries with pulse pressure variation > 13%.	Drozdynska et al. (14)
LRS	20 ml/kg (15 min)	↑ SVI _{TPTD} > 15%	100%	39 healthy bitches anesthetized under mechanical ventilation undergoing ovariohysterectomy.	Celeita-Rodríguez et al. (16)
LRS	4 ml/kg over (1 min)	↑ VTI _{Aortic flow} ≥ 15%	50%	26 conscious dogs referred for various clinical conditions.	Oricco et al. (17)
LRS	15 ml/kg (15 min)	↑ SV _{Echo} ≥ 15%	70%	50 dogs anesthetized under mechanical ventilation for orthopedic or oncologic surgery.	Gonçalves et al. (18)
LRS	4 ml/kg over (1 min)	↑ VTI _{Aortic flow} ≥ 15%	46%	22 dogs hospitalized for a variety of medical conditions.	Rabozzi et al. (19)
LRS	5 ml/kg (5 min)	↑ CI _{PCA} ≥ 15%	62.5%	80 dogs anesthetized under mechanical ventilation for orthopedic or soft tissue surgery.	Skouropoulou et al. (21)
LRS	10 ml/kg (5 min)	↑ SV _{TPTD} > 15%	83%	48 healthy dogs anesthetized under mechanical ventilation for elective surgery.	de Oliveira et al. (20)

LRS, lactated Ringer's solution; ↑, increase in variable; VTI_{Aortic flow}, velocity-time integral of aortic flow measured by echocardiography; CO_{Echo}, cardiac output measured by echocardiography; SV_{EDM}, stroke volume measured by esophageal Doppler monitor; SVI_{TPTD}, stroke volume index measured by transpulmonary thermodilution; SV_{Echo}, stroke volume measured by echocardiography; CI_{PCA}, cardiac index measured by uncalibrated pulse contour analysis; SV_{TPTD}, stroke volume measured by transpulmonary thermodilution.

current standards, a new technique of CO measurement is interchangeable with a reference method if the alternative technique presents acceptable agreement and good trending ability with the reference standard (62, 63). Percentage error (PE), calculated as 2 times the standard deviation of the bias between methods divided by the average CO of the population, evaluates the precision of agreement between methods. It has been suggested that PE values <30% denote an acceptable agreement between the alternative method and the reference standard used to measure CO (62). Polar plot analysis evaluates ability of an alternative method to track changes in the reference standard based on directional changes (increase or decrease in CO) and on the magnitude of changes in CO, with mean polar angle ≤ ±5° and radial limits of agreement ≤ ±30° denoting good trending ability (63).

In addition to meeting the criteria of accuracy and precision, a device should also be operator independent and allow real time CO and SV monitoring *via* minimally invasive or non-invasive

procedures (64). The accuracy/precision, trending ability, degree of invasiveness, operator dependence, and ability to provide real time CO and SV estimations of hemodynamic monitors currently available, with emphasis on their clinical application in fluid therapy guided by hemodynamic goals is discussed below.

Indicator Dilution Cardiac Output Techniques

Indicator dilution techniques are relatively independent of the operator skill and are considered the most accurate and precise methods of CO measurement available for clinical use (65). However, due to varying degrees of invasiveness and some other technical difficulties, indicator dilution techniques have not been routinely implemented to evaluate fluid responsiveness during fluid resuscitation of patients with signs of circulatory failure. Indicator dilution techniques provide intermittent CO and SV monitoring that need to be updated by the generation of new

indicator dilution curves *via* injection of a thermal or a chemical indicator, which could make evaluation of fluid responsiveness less practical.

Pulmonary Artery Thermodilution

Among the indicator dilution methods available, the pulmonary artery thermodilution (PATD) technique has been the clinical gold standard method for CO monitoring since its introduction in the 1970's (65). Pulmonary artery thermodilution measures right ventricular blood flow after a known volume of thermal indicator (ice-cold or room temperature 5% dextrose) is injected into the vena cava/right atrium for recording the change in blood temperature over time (thermodilution curve) in the pulmonary artery, *via* a fast-response thermistor located in the tip of a pulmonary artery catheter (PAC) (65). Cardiac output measured by PATD (CO_{PATD}) was used to evaluate the response to a fluid challenge in mechanically ventilated human individuals with acute circulatory failure related to sepsis (23, 26, 30) or during anesthesia for major surgery (66). However, questionable improvement in patient outcome in face of the higher degree of invasiveness and the inherent risks involved with placement of a PAC, including intra-cardiac knotting of the catheter and pulmonary artery rupture/thrombosis, has fueled a debate on whether the PAC should still be used (67, 68). For these reasons, advanced hemodynamic monitoring by means of a PAC in human ICUs has declined in favor of other less invasive/non-invasive methods of CO monitoring (67–69). In veterinary medicine, insertion of PACs for hemodynamic monitoring has been largely restricted to experimental studies.

Transpulmonary Thermodilution

Introduced during the 1990's in the medical field, transpulmonary thermodilution (TPTD) is a less invasive indicator dilution technique than PATD because changes in blood temperature induced by the thermal indicator are measured by a thermistor tipped catheter inserted into a central artery of the systemic circulation (e.g., femoral artery) (65, 69). Experimental studies have shown that the TPTD technique shows good ability to track changes in CO. A strong correlation (correlation coefficient = 0.95) between TPTD and the gold standard reference method (perivascular flow probe around the pulmonary artery) has been reported during CO changes induced by hemorrhage and volume replacement (70).

A summary of studies in small animals evaluating the ability of CO measured by TPTD (CO_{TPTD}) to track changes in CO measured by the reference standard (CO_{PATD}) using polar plot analysis is presented in **Table 3** (71–73). Based on experimental studies in dogs, where a range of CO values was obtained by increasing depth of anesthesia and inotropic (dobutamine) administration, it has been suggested that CO_{TPTD} can be used in replacement of CO_{PATD} because of an acceptable precision of agreement and good trending ability between these two techniques (73). Another report showed a marginal trending ability between CO_{TPTD} and CO_{PATD} in healthy anesthetized dogs (72). However, results were limited by the fact that the anesthetic protocol was designed for another purpose and no specific procedures were made to induce changes in CO (72).

In cats, limited data from a small number of animals ($n = 3$) showed that CO_{TPTD} overestimated CO_{PATD} . However, there was an acceptable precision of agreement and trending ability based on polar plot analysis (71).

Investigations have used the TPTD technique as a reference method to determine “true” fluid responsiveness status in humans (58, 77–79) and, more recently, in veterinary medicine (16, 20, 22). Averaging triplicate CO_{TPTD} measurements results in adequate precision (i.e., variability of repeated measurements <10%) to evaluate fluid responsiveness. The minimum percent change in CO that can be trusted as significant and not related to the imprecision of the method [i.e. the least significant change (LSC)] was reported decrease from 20% with single CO_{TPTD} measurements to 12% with triplicate CO_{TPTD} measurements in humans, which is adequate to detect responders to volume expansion (CO increases $\geq 15\%$) (80). Averaging the three closest sequential CO_{TPTD} values from a series of five measurements in anesthetized dogs, resulted in a higher level of precision (LSC = 5.1%) than previously reported in humans (LSC = 12%), which could allow reliable detection of changes in CO $\geq 10\%$ (16).

In spite of its acceptable accuracy/precision, CO_{TPTD} monitoring during the fluid resuscitation phase is limited by the fact that it requires not only a central venous catheter for injection of the thermal indicator (ideally ice-cold physiological saline), but also a thermistor tipped catheter placed in a central artery (e.g., femoral artery) (65, 69). Although, placing the thermistor tipped catheter in a peripheral artery seems an attractive alternative, this procedure is not recommended because loss of thermal signal in the periphery will lead to errors in CO measurement (overestimation of CO due to a decrease in the area under the thermodilution curve). Placement of the thermistor tipped catheter in a peripheral (metatarsal) artery in dogs failed to generate thermodilution curves necessary to measure CO_{TPTD} (81). Another disadvantage is the fact that CO_{TPTD} monitoring does not provide real time CO assessment and the need for rapid injection of ice-cold thermal signal to generate 3 thermodilution curves can result in an additional intravascular volume load. For use in small animals, the TPTD technique could be further limited by the high cost of the thermodilution catheter, which was designed for single use. Also the risk of displacement of the catheter from its insertion site (femoral artery) and hematoma formation should be considered as potential complications (72).

Lithium Dilution

Lithium dilution is a less invasive technique compared to PATD and TPTD because it does not demand catheterization of a central vein or a central artery. Injection of the chemical indicator (lithium chloride) can be performed through a peripheral venous catheter in humans and dogs (82, 83). The lithium dilution curve (plot of the lithium concentration over time) is measured in arterial blood withdrawn from a peripheral artery catheter into a lithium sensor located outside the patient (84). Although, PE (precision of agreement) calculations have not been reported in earlier studies, subjective assessment of Bland Altman analysis results has led authors to conclude that this technique provides reasonably good agreement with CO_{PATD}

TABLE 3 | Ability of several cardiac output monitors to track changes in cardiac output measured by a reference method induced by in dogs and cats.

Test method	Reference method	Concordance rate*	Mean polar angle (radial LOA)**	Trending ability	Species (number of animals) procedures/interventions	Reference
CO _{TPTD}	CO _{PATD}	94%	-5° (±33°)	Acceptable	Cats (n = 3) Inotropes, vasopressors, increased depth of anesthesia to manipulate CO	Kutter et al. (71)
CO _{TPTD}	CO _{PATD}	94%	-12° (±35°)	Marginal	Dogs (n = 6) Anesthesia for pharmacokinetic study (no procedures aiming to change CO).	Kutter et al. (72)
CO _{TPTD}	CO _{PATD}	100%	2° (±12°)	Good	Dogs (n = 8) Inotropes/increased depth of anesthesia to manipulate CO (Thermal signal: 5 ml of ice-cold 0.9% NaCl).	Garofalo et al. (73)
CO _{TPTD}	CO _{PATD}	100%	-1° (±8°)	Good	Dogs (n = 8) Inotropes/increased depth of anesthesia to manipulate CO (Thermal signal: 10 ml of ice-cold 0.9% NaCl).	Garofalo et al. (73)
Calibrated CO _{PCA} (PICCO ²)	CO _{PATD}	82%	-10° (±46°)	Poor	Cats (n = 3) Inotropes, vasopressors, increased depth of anesthesia to manipulate CO.	Kutter et al. (71)
Calibrated CO _{PCA} (PICCO ²)	CO _{PATD}	77%	-11° (±57°)	Poor	Dogs (n = 6) Anesthesia for pharmacokinetic study (no procedures aiming to change CO).	Kutter et al. (72)
Calibrated CO _{PCA} (PICCO ²)	CO _{PATD}	63%	38° (±33°)	Poor	Dogs (n = 8) Vasodilation (nitroprusside) and vasoconstriction (phenylephrine).	Garofalo et al. (73)
Calibrated CO _{PCA} (PulseCO)	CO _{PATD}	74%	2° (±60°)	Poor	Dogs (n = 6) Anesthesia for pharmacokinetic study (no procedures aiming to change CO).	Kutter et al. (72)
Uncalibrated CO _{PCA} (PRAM)	CO _{PATD}	93%	3.9° (±12.1°)	Good	Dogs (n = 6) Anesthesia for abdominal surgery. (Dogs with arrhythmias or that received sympathomimetics excluded).	Briganti et al. (74)
Electrical velocimetry	CO _{PATD}	88%	-5.9° (±46°)	Poor	Beagle dogs (n = 7) Anesthesia with sevoflurane under mechanical ventilation for experimental open-chest cardiovascular surgery.	Sasaki et al. (75)
Pulsed wave transit time	SV _{PATD}	95%	NR	Acceptable	Dogs (n = 8) Anesthesia with isoflurane under mechanical ventilation. Vasopressors, inotropes, and increased depth of anesthesia to manipulate CO.	Sano and Chambers (76)

*Concordance rates based on four-quadrant plot analysis: >95, between 90 and 95%, and <90%, indicate good, acceptable (or marginal), and poor trending ability, respectively (63).

**Mean polar angles and radial limits of agreement based on polar plot analysis: mean polar angle ≤5° and radial limits of agreement ≤30° indicate good trending ability (63).

CO_{TPTD}, cardiac output measured by transpulmonary thermodilution; CO_{PATD}, cardiac output measured by pulmonary artery thermodilution; CO_{PCA}, cardiac output measured by pulse contour analysis, SV_{PATD}, stroke volume measured by pulmonary artery thermodilution; NR, not reported.

in humans and animals, including dogs and cats (82–87). However, in addition to the fact that this technique demands catheterization of a peripheral artery (which may carry greater difficulty in hypovolemic/hypotensive patients), repeated lithium chloride injections for measuring CO in hemodynamically unstable patients may lead to inaccurate results due to lithium accumulation/recirculation (86). The lithium dilution technique does not seem a suitable technique for repeatedly assessing fluid responsiveness status in smaller veterinary patients, such as cats and small dogs, because the amount of arterial blood withdrawn into the lithium sensor (~4.6 ml per measurement) can become significant if several measurements are performed over time (87).

Pulse Contour Analysis Cardiac Output Techniques

While indicator dilution techniques provide intermittent CO values that need to be updated by the generation of new indicator dilution curves *via* injection of additional amounts of thermal (e.g., ice-cold 5% dextrose) or chemical (lithium chloride) indicators, the pulse contour analysis (PCA) method provides continuous, real time estimation of CO and SV.

Real time estimation of CO and SV could be particularly convenient to evaluate the response to a fluid challenge during volume resuscitation (88). However, PCA methods with potential application in animals demand catheterization of a central or a

peripheral artery, which may carry greater difficulty in animals with signs of shock. The major limitation of PCA devices is the poor ability to track changes in CO during conditions of hemodynamic instability associated with changes in SVR in humans (89, 90) and animals (72, 73, 91). Studies evaluating the ability of calibrated and uncalibrated PCA monitors to track changes in CO_{PATD} in small animals are summarized in **Table 3**. Interpretation of these studies should consider if their design incorporated or not manipulations aiming to induce changes in SVR, since the performance of PCA methods can be altered by hemodynamic instability associated with vasoconstriction/vasodilation.

Calibrated Contour Analysis Methods

The same monitors that measure CO intermittently by indicator dilution techniques (TPTD and lithium dilution) also provide real time CO and SV estimations by the calibrated PCA method. This technique is based on analysis of the arterial pressure waveform to estimate real time CO and SV using proprietary algorithms, after calibration of the system with CO_{TPTD} (PiCCO² system and VolumeView/EV1000 system) or with CO measured by lithium dilution (LIDCOplus and PulseCO systems). Studies have suggested that the calibrated PCA method could be useful to evaluate the response to a fluid challenge in humans (77, 79, 92). Cardiac output measured by a calibrated PCA system (PiCCO²) showed good correlation with changes in CO_{PATD} and CO_{TPTD} induced by volume expansion (correlation coefficient ≥ 0.70) (77, 92).

The ability of less invasive and non-invasive methods of CO monitoring to discriminate fluid responsiveness status is presented in **Table 4**. In septic human patients, receiver operating characteristics (ROC) curve analysis showed that continuous CO measured by calibrated PCA (PiCCO² system) could discriminate responders (CO_{TPTD} increases $\geq 15\%$) from non-responders (CO_{TPTD} increases $< 15\%$) to volume expansion (77, 79). However, CO and SV estimations by calibrated PCA devices may become unreliable in case of significant changes in SVR (73, 89) and the ability of calibrated PCA devices to track changes in CO_{TPTD} induced by a fluid challenge has been reported as poor (58). Although, the drift in CO estimations can be corrected by frequent recalibration of calibrated PCA systems with the indicator dilution method (94), these devices may not meet minimum criteria of accuracy, precision, and trending ability to detect changes in CO_{TPTD} induced by a fluid challenge (58).

Uncalibrated Pulse Contour Analysis Methods

Real time CO estimations can be provided by analysis of the arterial pressure waveform without requiring previous calibration of the system with a reference technique [FloTrac/Vigileo, LiDCOrapid, pulse recording analytical method (PRAM), ProAQT/Pulsioflex]. Real time SV monitoring with an uncalibrated PCA device (ProAQT/Pulsioflex) was used to evaluate the ability of a mini fluid challenge (50 and 100 ml of physiological saline) to predict the response to 250 ml of physiological saline in mechanically ventilated human patients undergoing neurosurgery (52). However, uncalibrated PCA

devices may not discriminate fluid responsiveness status based on ROC curve analysis (77, 78) (**Table 4**), and have shown poor ability to track changes in CO induced by a fluid challenge (58, 78, 95, 96) (**Table 5**).

In spite of continuous changes in the algorithm of one uncalibrated PCA device (FloTrac/Vigileo) over the recent years, studies have shown a poor agreement and limited ability to track phenylephrine-induced changes in CO measured by echocardiography (97) and by PATD (98). Studies point out that this uncalibrated PCA device overestimates CO measured by indicator dilution methods (PATD and Lithium dilution) and is unreliable to monitor CO in dogs (99, 100).

For another uncalibrated PCA device (PRAM), there are conflicting results regarding its ability to track changes in CO measured by a reference method. Earlier studies in pigs, where a range of CO values were induced by hemorrhage and inotropic administration (dobutamine), reported an acceptable agreement ($PE < 30\%$) between PRAM and CO measured by an aortic flow probe and between PRAM and PATD (101). However, this uncalibrated PCA device has also shown an unacceptable agreement/poor ability to track changes in CO measured by thermodilution techniques in humans and in animals (90, 92). Other studies have reported that this device was unable to track changes in CO induced by volume expansion in humans (95, 96). In veterinary medicine, a preliminary study performed in anesthetized dogs reported that the PRAM method showed good precision, acceptable concordance, and good trending ability with CO_{PATD} (74). However, results were limited by the fact that its reliability was not determined during conditions of hemodynamic instability/changes in SVR.

Echocardiography

Point of care echocardiography, in addition to its role in guiding fluid challenge administration, has the unique advantage of allowing to rule out other causes of shock, such as circulatory failure caused by pericardial effusion or by decreased myocardial contractility/systolic dysfunction, where fluid resuscitation is contraindicated. Cardiac output and SV measured by echocardiography (CO_{Echo} and SV_{Echo} , respectively) can be used to evaluate the response to a fluid challenge. While transthoracic echocardiography is useful in conscious individuals with signs of circulatory failure, transesophageal echocardiography is a practical means of monitoring the response to a fluid challenge in anesthetized patients during surgery or in unconscious/sedated individuals under mechanical ventilation. According to this technique SV_{Echo} is firstly measured by multiplying the area of the left ventricular outflow tract (LVOT) during mid systole (the point of maximal opening of aortic valve leaflets) by the velocity time integral (VTI) of the LVOT. Because the LVOT area during mid systole does not change over the respiratory and cardiac cycle, one single measurement of the LVOT area is usually performed for a patient as SV will vary exclusively as function of changes in aortic flow VTI (102–104). Parallel alignment between the Doppler beam and the aortic outflow, with an angle between the Doppler and LVOT as close to 0° as possible (ideally $< 20^\circ$) is critical for obtaining reliable aortic outflow measurements by

TABLE 4 | Ability of less invasive/non-invasive methods of cardiac output and stroke volume monitoring to discriminate responders from non-responders to volume expansion induced by a fluid challenge.

Less invasive/non-invasive monitor	Type of fluid (volume/infusion time)	Best cutoff*	AUROC** (95% CI)	Reference method (% change that defined responders)	Population evaluated	Reference
Calibrated CO _{PCA} (PiCCO ²)	0.9% NaCl (500 ml/30 min)	≥12%	0.878 (0.736–0.960)	Transpulmonary thermodilution (↑ CO _{TPTD} ≥ 15%)	80 human patients with septic circulatory failure.	Monnet et al. (77)
Calibrated CO _{PCA} (PiCCO ²)	6% HES (500 ml/15 min)	≥9%	0.85 (0.76–0.92)	Transpulmonary thermodilution (↑ CO _{TPTD} ≥ 15%)	78 human patients (after elective cardiac surgery).	Fischer et al. (79)
Non-calibrated CO _{PCA} (FloTrac/Vigileo)	NaCl 0.9% (500 ml/30 min)	≥12%	0.564*** (0.398–0.720)	Transpulmonary thermodilution (↑ CO _{TPTD} ≥ 15%)	80 human patients with septic circulatory failure.	Monnet et al. (77)
Non-calibrated CO _{PCA} (FloTrac/Vigileo)	NaCl 0.9% (500 ml/30 min)	NR	***	Transpulmonary thermodilution (↑ CO _{TPTD} ≥ 12%)	20 human patients with circulatory failure.	Monnet et al. (78)
Pulsed wave transit time	Crystalloid solution (500 ml/20 min)	≥11%	0.84 (0.69–0.99)	Transthoracic echocardiography (↑ CO _{Echo} ≥ 15%)	25 human patients in the early phase of septic shock.	Feissel et al. (93)
VTI _{aortic flow}	LRS (10 ml/kg/5 min)	≥14.7%	0.901 (0.812–0.990)	Transpulmonary thermodilution (↑ SV _{TPTD} > 15%)	48 healthy dogs anesthetized for elective surgery.	de Oliveira et al. (20)

*Best cutoff threshold to discriminate responders to the fluid challenge.

**AUROC: Area under the receiver operating characteristics curve (values ≥0.75 and ≥0.90 indicate good and excellent ability to discriminate responders from non-responders to volume expansion, respectively).

***AUROC not different from 0.5 (no discriminatory ability).

CI, confidence intervals; NR, not reported; ↑, increase in reference method; CO_{PCA}, cardiac output measured by pulse contour analysis; CO_{TPTD}, cardiac output measured by transpulmonary thermodilution; CO_{Echo}, cardiac output measured by echocardiography; VTI_{aortic flow}, velocity-time integral of aortic flow measured by echocardiography; SV_{TPTD}, stroke volume measured by transpulmonary thermodilution.

echocardiography (105). The left parasternal five-chamber view has been used to evaluate aortic flow VTI in dogs and cats (106). However, in canine species, a subcostal (or subxiphoid) view may be preferable in point-of-care settings because it does not demand the use of a echocardiography examination table and more accurately measures peak aortic velocities, resulting in higher VTI values than the five-chamber view (106) (**Figure 3**).

Velocity time integral measurements are sensitive to operator experience, cardiac arrhythmias and heart valve defects. Given the fact that echocardiographic measurements are highly operator dependent, a question frequently raised is the need for a certified specialist to reliably monitor CO_{Echo}. Studies have shown that CO_{Echo} measured by physicians with basic training in critical care echocardiography present good reproducibility and acceptable precision of agreement (PE = 17%) with CO_{PATD} (107). Providing that correct LVOT area and aortic flow VTI measurements are performed, transthoracic echocardiography has been considered an accurate and precise technique (PE <30%) to measure CO when compared with CO_{PATD} in critically ill humans (105). Polar plot analysis has also shown that CO measured by transthoracic echocardiography presents a good ability to track changes in CO_{PATD} (105), which is an important prerequisite for a technique used to assess the response to a fluid challenge. Beat by beat irregularities of left ventricular SV caused by arrhythmias will lead to a substantial error if CO_{Echo} and

SV_{Echo} is calculated from one single VTI measurement. Accuracy of measurements can be improved by averaging as many VTIs as possible in the presence of heart rhythm irregularities (108). Cardiac output measured by trans-esophageal echocardiography has been shown to present a good precision of agreement with CO_{PATD} (PE < 30%) in dogs that were normotensive and hypotensive during anesthesia (109). The ability of transthoracic and transesophageal echocardiography to track changes in CO_{PATD} has not been reported in small animals.

Cardiac output and SV values derived from transthoracic or transesophageal echocardiography have been used to discriminate responders from non-responders to volume expansion in the human medical field (25, 51, 53, 95, 110) and in dogs (13, 18). Because SV will change only as a function of changes in aortic flow, percent changes in aortic flow VTI have been used as a surrogate of SV to evaluate fluid responsiveness status in humans (36, 50, 56, 111) and dogs (12, 17, 19). More recently, in addition to the use of aortic flow VTI to track changes in SV, use of the “minute distance,” calculated as the VTI times the heart rate, has been proposed as a surrogate of CO in point-of-care settings (104).

Although, percent changes in aortic flow VTI have been used as a surrogate of SV changes in GDFT protocols, there have been no studies evaluating the ability of VTI to track changes in SV determined by a reference method

TABLE 5 | Ability of several monitors to track changes in cardiac output induced by a fluid challenge in humans.

Test method	Reference method	Type of fluid (volume/duration of infusion)	Concordance rate*	Mean polar angle (radial LOA)**	Trending ability	Reference
Uncalibrated CO _{PCA} (PRAM)	CO _{Echo}	0.9% NaCl (500 ml/15 min)	60%	NR	Poor	Blais et al. (95)
Uncalibrated CO _{PCA} (FloTrac/Vigileo)	CO _{TPTD}	0.9% NaCl (500 ml/15 min)	73%	NR	Poor	Monnet et al. (78)
Uncalibrated CO _{PCA} (FloTrac/Vigileo)	CO _{TPTD}	6% HES (500 ml/20 min)	80.5%	7.4° (±43.5°)	Poor	Geisen et al. (58)
Uncalibrated CO _{PCA} (LiDCOrapid)	CO _{TPTD}	Same as before	79.2%	10.5 (±41.7°)	Poor	Geisen et al. (58)
Calibrated CO _{PCA} (PICCO ²)	CO _{TPTD}	Same as before	78.3%	-6.4° (±41.2°)	Poor	Geisen et al. (58)
Uncalibrated CO _{PCA} (PRAM)	CO _{EDM}	"Crystalloid" (250–500 ml <10 min)	74%	7.8° (±41.7°)	Poor	Barthélémy et al. (96)

*Concordance rates based on 4-quadrant plot analysis: >95, between 90 and 95%, and <90%, indicate good, acceptable (or marginal), and poor trending ability, respectively (63).

**Mean polar angles and radial limits of agreement based on polar plot analysis: mean polar angle ≤5° and radial limits of agreement ≤30° indicate good trending ability (63).

LOA, limits of agreement; NR, not reported; CO_{PCA}, cardiac output measured by pulse contour analysis; CO_{Echo}, cardiac output measured by echocardiography; CO_{TPTD}, cardiac output measured by transpulmonary thermodilution; CO_{EDM}, cardiac output measured by esophageal Doppler monitor.

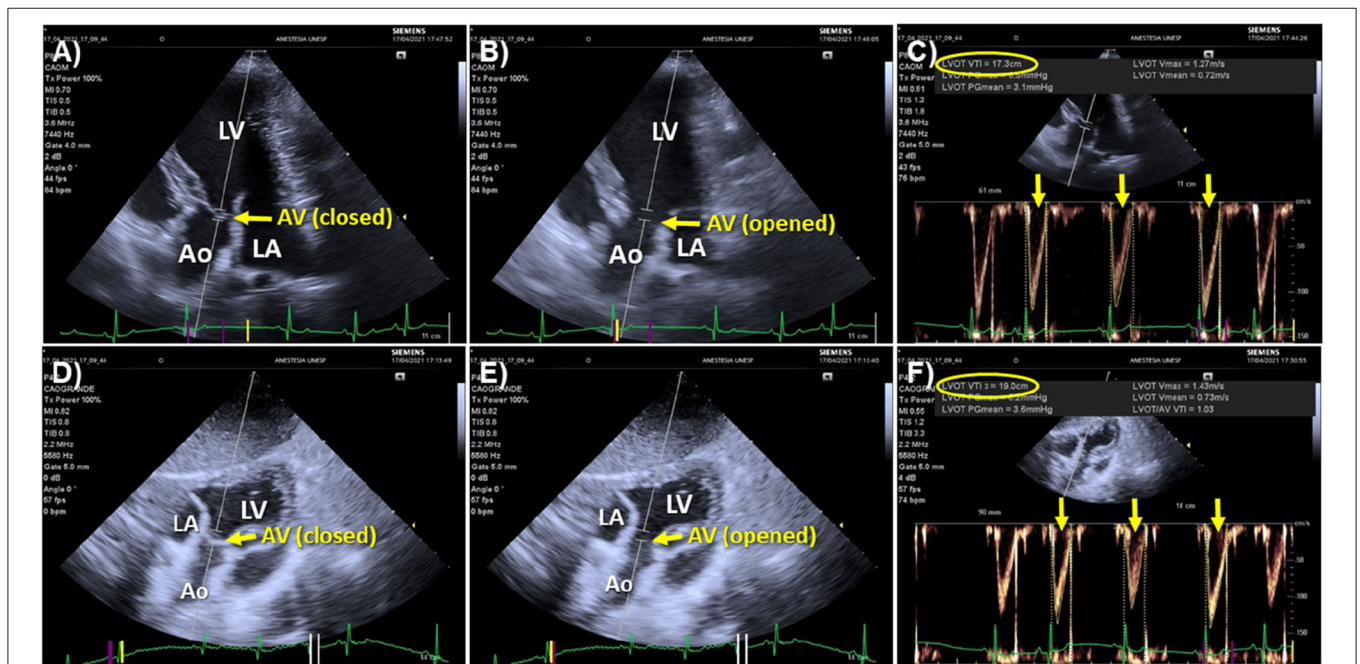


FIGURE 3 | Echocardiographic windows used to measure aortic flow velocity-time integral (VTI) in dogs. **(A)** Left parasternal, apical five-chamber view optimized for visualizing the left ventricular outflow tract (LVOT) with the aortic valve closed during diastole. The Doppler beam is aligned as parallel as possible with the aortic outflow and the Doppler sampler is positioned just below the mitral annulus (point of insertion of aortic valve leaflets). **(B)** The same image with the aortic valve (AV) opened during systole. **(C)** Acceleration of aortic flow over time measured by positioning the Doppler cursor as shown in **(A,B)**. The aortic flow VTI averaged of 3 sequential heartbeats (yellow arrows) using an automated algorithm was 17.3 cm (yellow oval). **(D)** Subxiphoid view of the LVOT showing alignment of the Doppler beam with the aortic outflow and the placement of the Doppler sampler with the AV closed during diastole. **(E)** The same image with the AV opened during systole. **(F)** Measurement of aortic flow VTI according to the subxiphoid view. The VTI averaged from 3 sequential heartbeats (yellow arrows) was 19.0 cm (yellow oval). Comparison between the five-chamber **(A,B)** and subxiphoid views **(D,E)** shows that the latter allowed better alignment of the Doppler beam with the aortic outflow, which contributed to a higher VTI measured from the subxiphoid view. Ao, aorta; AV, aortic valve; LV, left ventricle; LA, left atrium.

(e.g., thermodilution CO). It must be borne in mind that the reliability of VTI measurements is highly operator dependent. To account for operator related errors, studies evaluating fluid responsiveness with echocardiography should ideally report intra and inter-operator agreement (112). The reliability of repeated measures performed by one single observer (repeatability) and between observers (reproducibility) can be assessed by intraclass correlation coefficients. Values between 0.6–0.74 and 0.75–1 suggest good and excellent correlation, respectively (112).

When VTI is used to evaluate fluid responsiveness, one important question that arises is the level of precision (i.e., the proximity of repeated measurements) of aortic flow measurements obtained during stable hemodynamic conditions. If the precision of the method is poor, it may not be able to correctly identify responders to volume expansion (80). In human patients with a regular heart rhythm, averaging the VTI from 3 sequential heartbeats is recommended for achieving an adequate precision (108). In the presence of a regular heart rhythm, the minimum percent change in VTI between two successive measurements that can be trusted as significant (i.e., the least significant change) was 11%, which would be adequate to detect increases in VTI \geq 15% induced by a fluid challenge (108). Otherwise, in individuals with an irregular heart rhythm, evaluation of fluid responsiveness by VTI carries greater difficulty because of beat-by-beat variations on SV and aortic flow. Under these circumstances, averaging VTI from 5 sequential heartbeats or more may be necessary to achieve an adequate level of precision of the method (108).

The ability of a method to detect changes in SV induced by a fluid challenge can be inadequate during conditions of hemodynamic instability/irregular heart rhythm because the method's variance is composed not only by the precision of the method but also by the method's general variability about the true values (defined as "trueness") (113). Therefore, relatively small physiologic variations in CO and SV values can worsen the precision of the method and impair the ability of VTI to detect smaller changes in CO and SV induced by a fluid challenge (113). Fear, anxiety and discomfort caused by physical restraining, which is often necessary performing transthoracic echocardiography in conscious animals, can result in changes in sympathetic tone and interfere with the level of precision of VTI measurements. In anesthetized dogs, percent changes in aortic flow VTI induced by a fluid challenge $>$ 14.7% showed good ability to discriminate responders to volume expansion, defined as dogs where SV measured by TPTD increased $>$ 15% after the fluid challenge (20) (Table 4). The close proximity between the optimal cutoff threshold determined from the ROC curve (percent change in VTI $>$ 14.7%) and the percent change in SV used to define "true" responders to volume expansion, suggest that changes in aortic flow VTI can be used as a surrogate of SV to evaluate fluid responsiveness in dogs (20). However, percent changes in VTI associated with a high probability of false negative and/or false positive results (zone of diagnostic uncertainty) was reported to range from 11.8 to 17.6%, which could be related to errors in obtaining proper alignment of the pulsatile Doppler with the aortic flow (20). In conscious dogs with a variety of clinical conditions, baseline aortic flow VTI

(measurements obtained prior to a fluid challenge) \leq 10.3 cm predicted responders to volume expansion with high sensitivity (84.9%) and specificity (100%) (17).

Measuring the VTI demands several keystrokes and could be time-consuming, which may be less practical in the emergency setting. However, with the recent development of algorithms incorporated into ultrasound machines, it has become possible to perform automated VTI measurements. Use of tools that allow automated VTI measurements has the potential for optimizing evaluation of fluid responsiveness in the emergency settings (Figure 4).

Velocity time integral measurements are overestimated in the presence of moderate-to-severe aortic regurgitation and sub-aortic obstruction (aortic stenosis) (104). Dynamic LVOT obstruction may be observed during severe hypovolemia/inotropic stimulation, in dogs with sub-aortic stenosis, and cats with hypertrophic cardiomyopathy. In the presence of these conditions, it is not possible to determine if an increase in aortic flow VTI results from increased SV or from increased regurgitant volume (aortic regurgitation) or from subaortic/LVOT stenosis (104) (Figure 5).

Esophageal Doppler

The esophageal Doppler technique measures blood flow velocity in the descending aorta (or caudal aorta in quadrupeds) *via* a Doppler transducer inserted into the thoracic esophagus. The velocity of blood flow in the descending aorta plotted over time is used to determine the stroke distance (distance of the envelope that contains blood flow velocity vs. time curve measured in centimeters) (114–116). The SV measured by the esophageal Doppler method (SV_{EDM}) is calculated by stroke distance times the cross sectional area of the aorta. A nomogram developed for human patients (based on body weight, height and body surface area) estimates the cross sectional area of the aorta, assuming a 45° angle between the aorta and the esophageal probe (114–116). The algorithm for SV determination also assumes that the proportion of the blood flow/SV generated by the left ventricle at each heartbeat to the descending aorta remains fixed at 70% and CO measured by the esophageal Doppler method (CO_{EDM}) is calculated by the multiplying SV/stroke distance by the heart rate (114–116).

The esophageal Doppler monitor showed poor precision of agreement with the reference standard (PATD) in pediatric patients with congenital heart defects and in patients undergoing coronary artery bypass surgery (PE = 54 and 70%, respectively) (114, 115). Although, CO_{EDM} cannot be considered interchangeable with CO_{PATD}, this device can show an acceptable/marginal trending ability with CO_{PATD}, suggesting that this method could be used to guide volume expansion in goal directed fluid therapy (115). The use of esophageal Doppler monitoring to guide fluid administration reduced the rate of postoperative complications in patients undergoing major abdominal surgery compared to fluid therapy guided by conventional parameters (e.g., central venous pressure and arterial pressure) (116).

Similarly to human studies, it has been reported that CO_{EDM} does not present an acceptable agreement with CO_{PATD} in

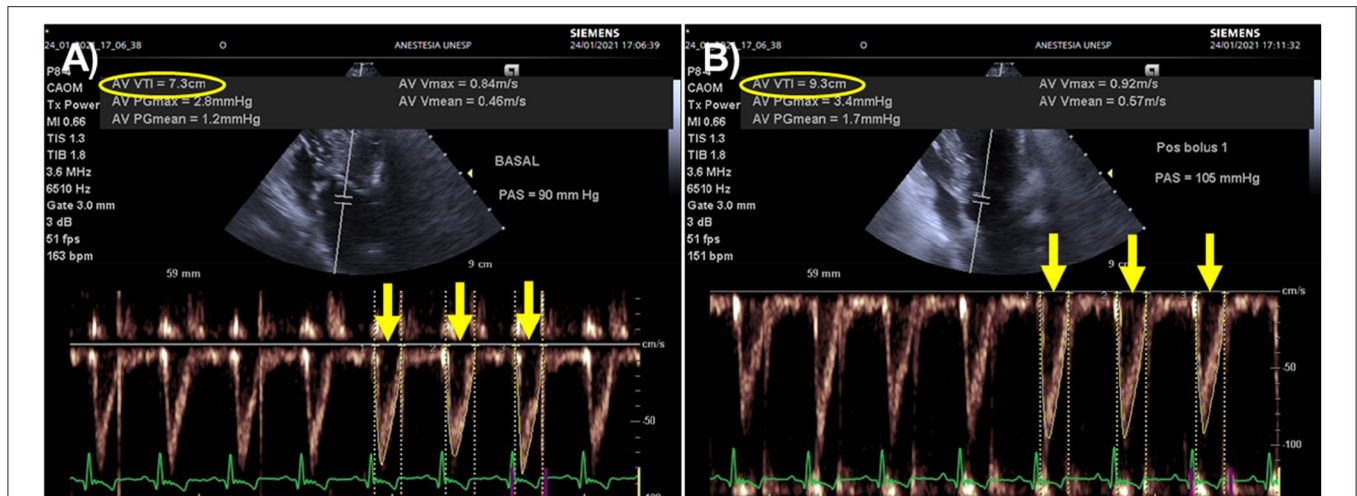


FIGURE 4 | Effects of a fluid challenge with 10 ml/kg of lactated Ringer's solution administered over 5 min on aortic flow velocity time integral (VTI) recorded from an apical five-chamber view in a dog with blunt trauma. An automated algorithm was used to measure aortic flow VTI as the average of 3 sequential heartbeats (yellow arrows). **(A)** Heart rate (HR), Doppler systolic arterial pressure (SAP), and aortic flow VTI before the fluid challenge were 163 beats/min, 90 mmHg and 7.3 cm (yellow oval), respectively. **(B)** After the fluid challenge, HR, Doppler SAP and aortic flow VTI were 161 beats/min, 105 mmHg and 9.3 cm (yellow oval). This animal was a responder to volume expansion because aortic flow VTI increased 27% (from 7.3 to 9.3 cm). The minute distance (HR times VTI), a surrogate index used to track changes in cardiac output, increased 17% after the fluid challenge (from 1197 to 1404 cm).

dogs (PE = 39%) (117). Otherwise, an abstract reported a close relationship between stroke distance measured by the esophageal Doppler and SV measured by thermodilution in dogs undergoing hemorrhage and re-transfusion of shed blood (correlation coefficient = 0.9), suggesting that this monitoring device might be a useful surrogate marker of SV changes induced by a fluid challenge (118). Additional studies are necessary to establish the clinical usefulness of the esophageal Doppler as a tool to monitor fluid responsiveness in dogs and cats.

Electrical Velocimetry

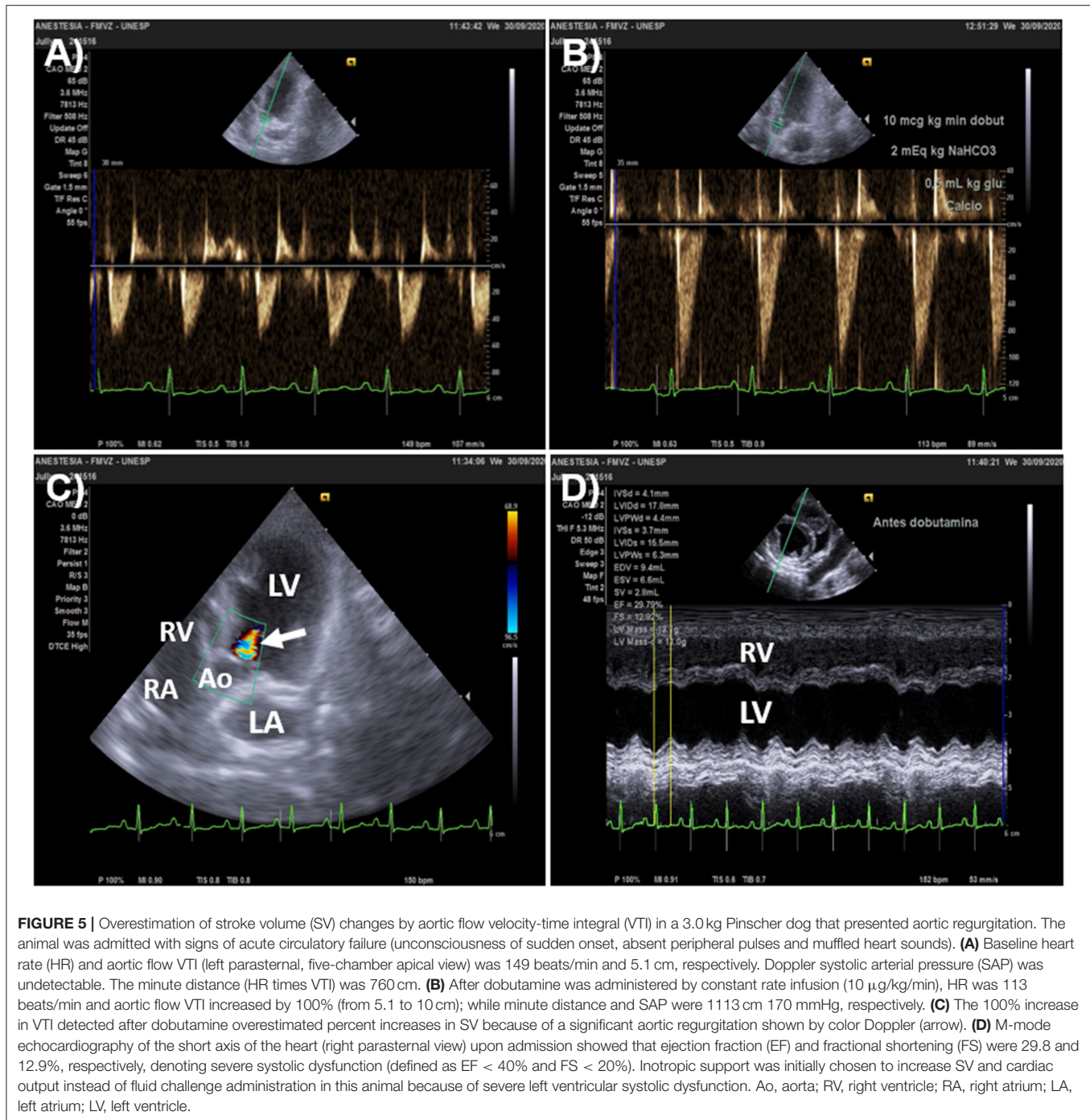
Electrical velocimetry (or transthoracic electrical bioimpedance) is a non-invasive method of continuous CO monitoring based on impedance cardiography. Measurement of left ventricular SV and CO is based on a transcutaneous electrical AC voltage applied to the chest to calculate changes in resistance during the cardiac cycle (119–125). Studies in humans have compared electrical velocimetry with PATD, TPTD, transthoracic, and transesophageal echocardiography with conflicting results (119–125). A recent meta-analysis concluded that electrical velocimetry cannot replace thermodilution or transthoracic echocardiography to measure CO because of an unacceptable precision of agreement (mean PE > 30%) with these methods (126). The clinical utility of electrical velocimetry is also limited in veterinary medicine. In sevoflurane-anesthetized dogs, an electrical velocimetry device showed a marginally acceptable agreement (PE = 30.4%) and a poor ability to track changes in CO_{PATD} (75), which could limit the usefulness of this method to evaluate the response to a fluid challenge in dogs (Table 3).

Pulse Wave Transit Time

Pulse wave transit time (PWTT) is another recently developed technique that provides continuous, non-invasive CO estimations. This method measures the time elapsed between the R wave of the electrocardiogram, which corresponds to the beginning of ventricular systole, and the appearance of the corresponding pulse wave on a pulse oximeter. Measurement of CO by PWTT is based on the principle that the transit time of pulsatile blood flow, detected by a pulse oximeter, is inversely proportional to CO (76, 93, 127, 128). However, studies have shown that PWTT has an unacceptable agreement with CO_{PATD} in dogs (PE = 61–63%) and humans (PE = 69%) (93, 127). Cardiac output measured by PWTT has also shown a poor agreement (PE = 47%) and poor trending ability (concordance rate = 74%) with CO_{TPTD} (128). In spite of its poor agreement and poor trending ability with reference methods, percent changes in CO measured by PWTT ≥ 11% showed reasonable ability to discriminate the response to a 500 ml fluid challenge (area under the ROC curve = 0.84) during the early phase septic shock humans (93). This observation, and the good ability of PWTT to detect a 15% increase in CO_{PATD} in dogs (76), raises the possibility that this monitoring tool might be useful evaluate fluid responsiveness (Tables 3, 4).

CONTROVERSIES OF GDFT AND THE RISK OF FLUID OVERLOAD

The benefits of volume expansion in hypovolemic individuals cannot be achieved without risks. Although, the physiological principles of GDFT make good sense, evidence of benefit on major outcomes/mortality has been considered inconsistent



in the human medical field (6). Otherwise, meta-analysis of 13 clinical trials enrolling 1642 patients, concluded that application of the concept of fluid responsiveness to patients that require acute volume resuscitation appeared to reduce mortality, duration of ICU stay, and duration of mechanical ventilation (3). However, conclusions of this study may be restricted to high-risk surgery, which comprised 12 of 13 trials analyzed (3). While it appears that GDFT in patients undergoing major surgery is beneficial, evidence of an improved outcome of GDFT in septic

individuals is lacking (129). In human patients with septic shock there is an association between the volume of fluids administered during resuscitation and the degree of damage to the endothelial glycocalyx, a carbohydrate-rich layer lining vascular endothelial cells that prevents leakage of fluids from the intravascular to the extravascular compartment (130). Theoretically, administering fluids until individuals are at the flat portion of the Frank-Starling curve might further damage the endothelial glycocalyx in septic patients. More recently, dynamic assessment of fluid

responsiveness to guide fluid or vasopressor administration in patients with septic shock decreased the total amount of intravenous fluids, lowered the risk of renal and respiratory failure when compared to usual care (45).

Damage to the Endothelial Glycocalyx and Lung Edema Secondary to Volume Expansion

Repeated fluid challenge administration until the heart is operating on the flat portion of the Frank-Starling curve may potentially lead to tissue/lung edema. Increases in cardiac filling pressures induced by fluid administration stimulates the release of atrial natriuretic peptide by myocardial cells (131), which is a physiological mechanism whereby the organism promotes elimination of excess fluid. However, it has been demonstrated that increased plasma atrial natriuretic peptide also promotes shedding of the endothelial glycocalyx, which may lead to tissue edema (132).

Pulmonary edema is a major complication of fluid overload that can be objectively evaluated in human critical care settings by measuring extra-vascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI) in patients monitored with TPTD technology (133, 134). In human subjects EVLWI > 10 ml/kg and PVPI < 2 are suggestive of cardiogenic pulmonary edema; whereas, EVLWI > 10 ml/kg and PVPI > 3 suggests that pulmonary edema is likely caused by increased pulmonary vascular permeability, such as in acute respiratory distress syndrome (133, 134). The superimposition of the Marik-Phillips curve and the Frank-Starling curve, which depict the relationship between EVLWI and SV with preload, respectively, allows understanding why there is an increased the risk of pulmonary edema if the heart is operating near the flat portion of the Frank-Starling curve (135) (**Figure 6**).

Based on experimental studies healthy anesthetized dogs, it appears that reference values of EVLWI in humans cannot be extrapolated to canine species, as mean EVLWI values of 12 ml/kg have been reported in healthy anesthetized dogs receiving a standard fluid rate of 2 ml/kg/hour of LRS (136). In normovolemic dogs undergoing elective surgery, mean EVLWI values were in the range of 9 to 10 ml/kg and were not significantly increased by one or two fluid challenges with 20 ml/kg of LRS administered over 15 min (16). Although, EVLWI did not increase after volume expansion, an increased incidence of peripheral edema in the form of chemosis and edema of the tongue was recorded the group of animals that were positioned at the flat portion of the Frank-Starling curve after receiving two 20 ml/kg crystalloid boluses (16).

Use of Point of Care Echocardiography to Evaluate the Risk of Pulmonary Edema Secondary to Volume Expansion

Hydrostatic pulmonary edema may occur if a fluid challenge is administered to individuals presenting a restrictive left ventricular filling pattern. Features of diastolic dysfunction leading to a restrictive filling pattern include an excessive acceleration of early transmitral flow (E wave), and a decreased

longitudinal myocardial fiber lengthening at the level of the mitral annulus during early diastole (e' wave), measured by pulse wave Doppler and by tissue Doppler imaging, respectively (137). The E/e' ratio has been in humans used as an estimate of left ventricular filling pressures (LVFP), with values > 14 (e' averaged from the septal and lateral mitral annulus) identifying elevated LVFP with high specificity (low false positive rate) (137).

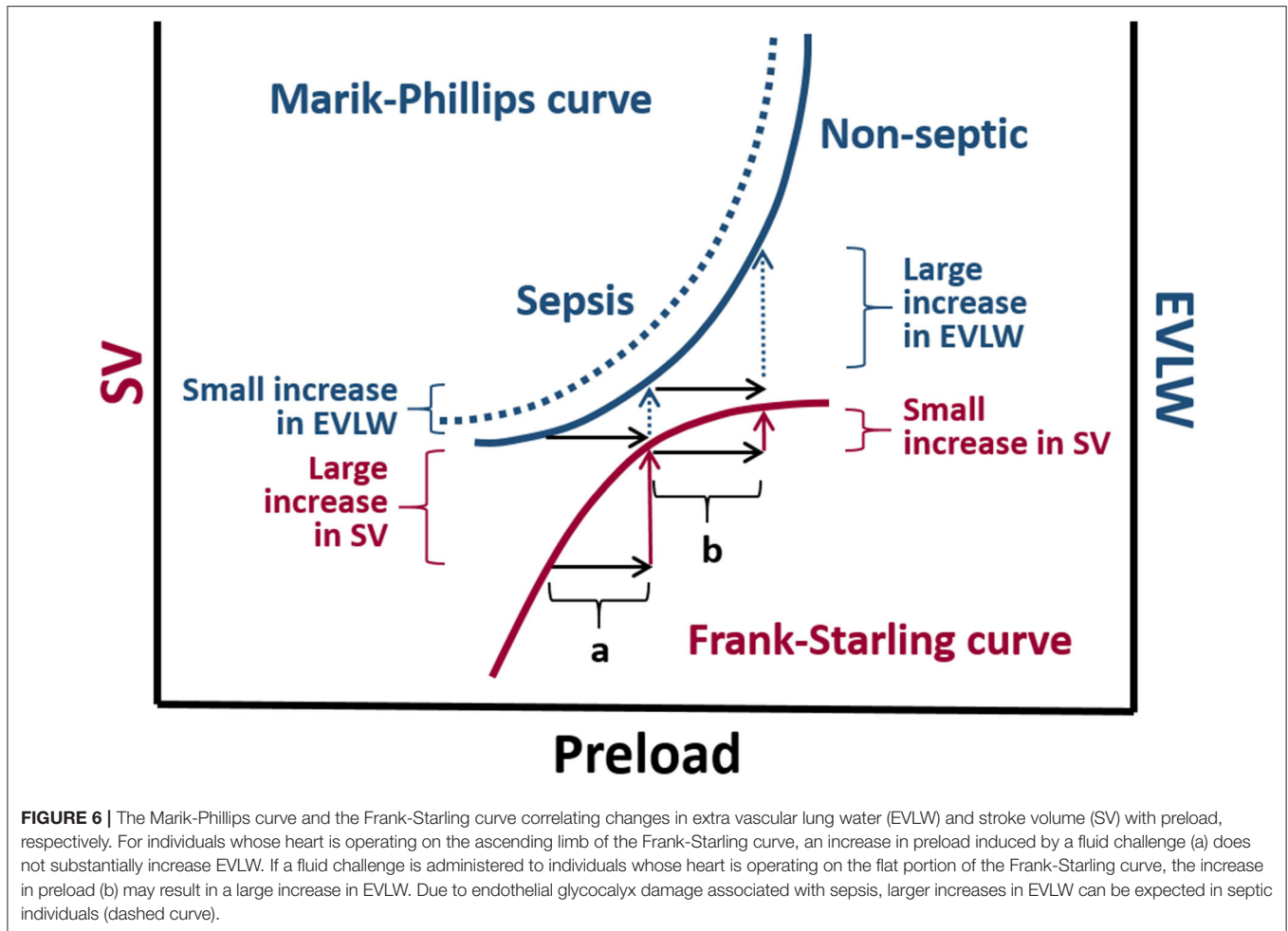
Myxomatous mitral valve disease and dilated cardiomyopathy are among the heart diseases that lead to elevated LVFP and increased risk of pulmonary edema from bolus fluid administration in canine species (138). In cats, hypertrophic, restrictive, and dilated cardiomyopathy may be associated with elevated LVFP and pulmonary edema (139). The E/e' ratio (e' averaged from the septal and lateral mitral annulus) > 12.4 shows a reasonably good ability to discriminate dogs with congestive heart failure (area under the ROC curve = 0.79) (138). However, compared to the E/e' ratio, the ratio between the E wave and the isovolumic relaxation time (IRVT) showed higher accuracy (area under the ROC curve = 0.97) to identify congestive heart failure in canine species (138). In dogs with experimentally induced fluid overload, $E/IVRT$ ratio values > 2.2 are able to identify left atrial pressure values > 15 mmHg with high sensitivity (90%) and specificity (100%) (140). Excessive increases in LVFP due to congestive heart failure in dogs are associated with $E/IVRT$ ratio > values 2.5 and excessively accelerated E waves (>120 cm/s) (138, 141).

Although, data are lacking in veterinary medicine, left ventricular diastolic dysfunction has been recognized as a common feature in humans with sepsis or septic shock (142). Systolic dysfunction (defined as a decrease in left ventricular ejection fraction to <50%) may not be associated with mortality in sepsis. Otherwise, diastolic dysfunction, characterized by a decrease in longitudinal fiber lengthening during early diastole (e') and an increase in E/e' ratio, has been reported to occur more frequently than systolic dysfunction (50 vs. 30% of patients) and has been associated with higher mortality in septic human patients (142, 143). The prevalence of diastolic dysfunction dogs and cats with sepsis/septic shock deserves further investigation as it can impact the prognosis and fluid resuscitation strategies in the emergency setting.

In the presence of echocardiographic changes suggestive of elevated LVFP a restrictive fluid therapy strategy should be considered (**Figure 7**). Otherwise, recognition of elevated LVFP does not rule out the need for volume replacement. Under these circumstances, the clinician should consider that range of optimal left ventricular filling pressure is relatively narrow and the left ventricle can be easily overfilled (103).

WHAT IS THE IDEAL FLUID CHALLENGE?

An ideal fluid challenge should reliably discriminate responders from non-responders to volume expansion by means of the smallest volume possible to minimize this risk of fluid overload. An excessively large volume of IV fluids used to test the preload dependency increases the risk of tissue edema. Otherwise, if the volume of fluid used as a “challenge” is excessively



small, the resultant increase preload might not be enough to identify responders to volume expansion, yielding false negative results. In hemodynamically stable post-cardiac surgery human patients the administration of progressively increasing volumes of isotonic crystalloids (1 to 4 ml/kg over 5 min) increased the proportion of responders from 20% (1 ml/kg) to 65% (4 ml/kg) (144). Therefore, the ideal fluid challenge is the minimal volume of fluid that still allows identification of all “true” responders to volume expansion.

Not only the volume of fluid, but also the duration of the infusion influences the recognition of responders to volume expansion. Meta-analysis studies in humans have shown that more prolonged infusion times (>30 min) decreases the proportion of responders to volume expansion (145). A third factor that can influence the identification of responders to volume expansion is the timing of the assessment of the change in CO and/or SV. In septic humans, the number of responders to a fluid challenge recorded upon conclusion of a 500 ml crystalloid fluid challenge (individuals where aortic flow VTI increased > 15% from baseline) was decreased by 44% when fluid responsiveness was reassessed 20 min later (111). The increase in preload induced by crystalloid solutions is transient as they

rapidly redistribute from the intravascular to the extravascular compartment (146). Persistence of isotonic crystalloids within the intravascular space is likely to be poorer in septic patients because of endothelial glycocalyx damage and low colloid oncotic pressure associated with hypoalbuminemia (130). Meta-analysis studies have not detected an influence of the type of fluid (colloids vs. crystalloids) on the proportion of responders to volume expansion (145). However, fluid challenges with artificial colloids have the potential to induce longer lasting increases in intravascular volume and cardiac preload than similar volumes of isotonic crystalloids.

Experimental evidence suggests that administration of 25% of the “shock dose” of crystalloids in dogs (20 ml/kg) can increase the risk of tissue edema because a larger cumulative volume of fluids may be administered until animals are recognized as non-responders to volume expansion (16). Lower volumes of crystalloids (10 ml/kg over 5 min) may be favored as standard fluid challenge because smaller cumulative volume of fluid is likely to be administered until dogs become non-responders (20). Because longer infusion times of crystalloids result in rapid redistribution of fluid from the intravascular compartment to other compartments (111, 146), infusion times should be kept

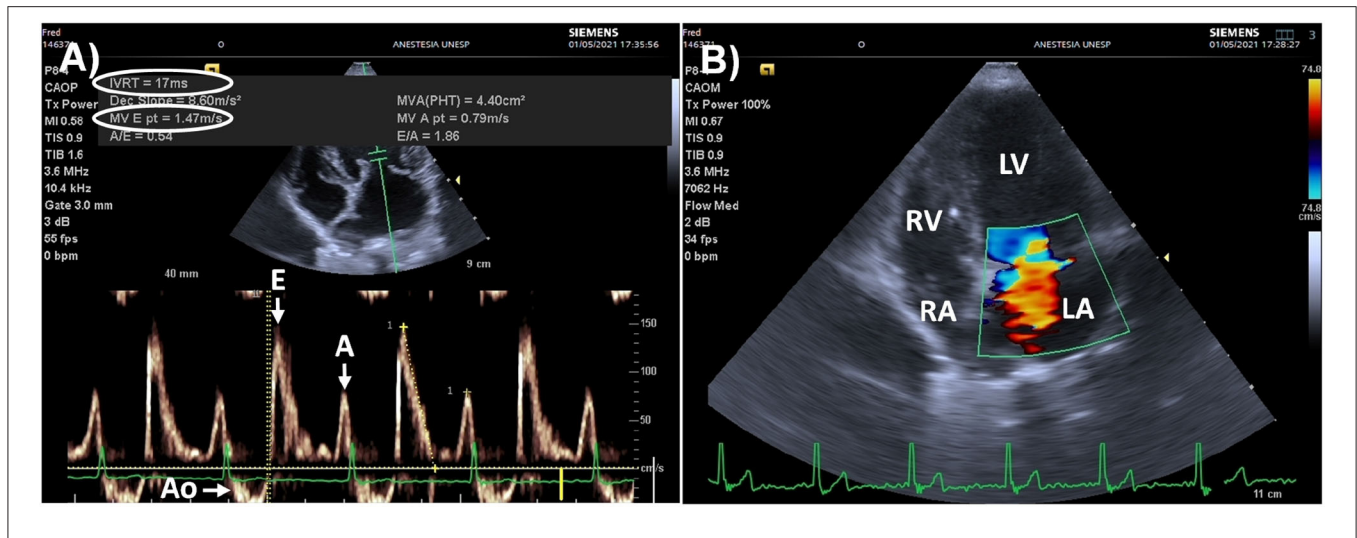


FIGURE 7 | Point of care echocardiography in an 8 kg Schnauzer dog presented for surgery due to a bleeding mass located in the upper lip that presented elevated left ventricular filling pressures (LVFP), secondary to myxomatous mitral valve disease. **(A)** Pulsed wave Doppler of mitral inflow (left apical, four/five-chamber view) showing marked acceleration of the early passive diastolic filling wave (E wave = 147 cm/s, normal range: 53–108 cm/s). The isovolumic relaxation time (IVRT) was low (17 ms, normal range: 43–63 ms), and the E/IVRT ratio was markedly increased (8.64, upper reference value: 2.5), indicating high LVFP due to congestive heart failure. **(B)** Color Doppler (left apical, four-chamber view) showing mitral regurgitation during mid systole. This animal was anesthetized as an emergency procedure with the recommendation for a restrictive fluid therapy strategy. Inotropes/vasopressors instead of fluid boluses were recommended to manage intraoperative hypotension. The congestive heart failure was later managed by a cardiologist. Ao, aorta; E, early passive diastolic filling wave, A, late diastolic filling wave induced by atrial contraction; RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

as short as possible (e.g., 5 to 10 min). The standard crystalloid bolus in cats with signs of shock has traditionally been limited to 10 ml/kg over 15 min because of this species present a smaller circulating blood volume (60 ml/kg of body weight) in comparison to dogs (80 ml/kg of body weight) and because of a perceived higher risk of volume overload in this species. However, clinical data on the use fluid challenges is lacking in cats and crystalloid volumes lower than 10 ml/kg are probably adequate in this species.

CONCLUSIONS

Knowledge on the assessment of fluid responsiveness has experienced a significant development during the past two decades in the human medical field. In patients admitted with signs of circulatory failure, fluid resuscitation guided by a fluid challenge approach has the potential to improve patient outcome. Considering the principle of “less is more,” to minimize the risk of fluid overload, it has been recognized that smaller volumes of fluids, or mini-fluid challenges, may allow identification of responders to volume expansion induced by a standard fluid challenge. To reduce the risk of edema from fluid overload, recommendations for the use of 25% of the “shock dose” should be revised in favor of smaller volumes of crystalloids as standard fluid challenge (up to 10 ml/kg over 5–10 min in dogs and < 10 ml/kg over 10–15 min in cats). When using the fluid challenge approach, it should be recognized that the response variable measured before and after the fluid challenge (i.e., the method of CO and SV measurement or its surrogates) will significantly impact the identification of responders to volume expansion. In veterinary medicine, goal-directed fluid therapy aiming to maximize CO and SV is in

its infancy. Among the CO and SV measurement technologies that could be used to assess the response to a fluid challenge, aortic flow VTI obtained by transesophageal and transthoracic echocardiography appears to be a promising tool to evaluate fluid responsiveness in animals. Esophageal Doppler monitoring might be particularly useful to guide fluid administration in anesthetized dogs and cats or in animals under mechanical ventilation in the ICU. Future studies are needed to assess fluid responsiveness status in dogs and cats with signs of circulatory failure and the potential benefits that could be achieved by maximizing CO and SV *via* fluid administration in high-risk small animal patients.

AUTHOR CONTRIBUTIONS

FT-N: manuscript conception and writing (~70% of manuscript text). AV: Manuscript preparation, writing (~30% of manuscript text), and critical review. Both authors contributed to the article and approved the submitted version.

FUNDING

Partial funding for this article was provided by PROAP-CAPES, Ministry of Education, Brazil (Grant number: AUXPE 1088/2020).

ACKNOWLEDGMENTS

Images reproduced in **Figure 5** were obtained in collaboration with Angelica Alfonso and Maria Lucia Gomes Lourenço from the Cardiology Section of Faculdade de Medicina Veterinária e Zootecnia–UNESP, Brazil.

REFERENCES

- Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg.* (2012) 114:640–51. doi: 10.1213/ANE.0b013e318240d6eb
- Davis H, Jensen T, Johnson A, Knowles P, Meyer R, Rucinsky R, et al. 2013 AAHA/AAFP fluid therapy guidelines for dogs and cats. *J Am Anim Hosp Assoc.* (2013) 49:149–59. doi: 10.5326/JAAHA-MS-5868
- Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med.* (2017) 45:1538–45. doi: 10.1097/CCM.0000000000002554
- Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology.* (2008) 108:735–48. doi: 10.1097/ALN.0b013e3181672607
- Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care.* (2016) 20:271. doi: 10.1186/s13054-016-1438-7
- Gelman S, Bigatello L. The physiologic basis for goal-directed hemodynamic and fluid therapy: the pivotal role of the venous circulation. *Can J Anaesth.* (2018) 65:294–308. doi: 10.1007/s12630-017-1045-3
- Spiegel R. Stressed vs. unstressed volume and its relevance to critical care practitioners. *Clin Exp Emerg Med.* (2016) 3:52–4. doi: 10.15441/ceem.16.128
- Cherpanath TG, Geerts BF, Lagrand WK, Schultz MJ, Groeneveld AB. Basic concepts of fluid responsiveness. *Neth Heart J.* (2013) 21:530–6. doi: 10.1007/s12471-013-0487-7
- Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? *Curr Opin Crit Care.* (2011) 17:290–5. doi: 10.1097/MCC.0b013e32834699cd
- Carsetti A, Cecconi M, Rhodes A. Fluid bolus therapy: monitoring and predicting fluid responsiveness. *Curr Opin Crit Care.* (2015) 21:388–94. doi: 10.1097/MCC.0000000000000240
- Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! *Crit Care.* (2015) 19:18. doi: 10.1186/s13054-014-0708-5
- Bucci M, Rabozzi R, Guglielmini C, Franci P. Respiratory variation in aortic blood peak velocity and caudal vena cava diameter can predict fluid responsiveness in anaesthetised and mechanically ventilated dogs. *Vet J.* (2017) 227:30–5. doi: 10.1016/j.tvjl.2017.08.004
- Fantoni DT, Ida KK, Gimenes AM, Mantovani MM, Castro JR, Patrício GCF, et al. Pulse pressure variation as a guide for volume expansion in dogs undergoing orthopedic surgery. *Vet Anaesth Analg.* (2017) 44:710–8. doi: 10.1016/j.vaa.2016.11.011
- Drozdzyńska MJ, Chang YM, Stanzani G, Pelligand L. Evaluation of the dynamic predictors of fluid responsiveness in dogs receiving goal-directed fluid therapy. *Vet Anaesth Analg.* (2018) 45:22–30. doi: 10.1016/j.vaa.2017.06.001
- Sano H, Seo J, Wightman P, Cave NJ, Gieseg MA, Johnson CB, et al. Evaluation of pulse pressure variation and pleth variability index to predict fluid responsiveness in mechanically ventilated isoflurane-anesthetized dogs. *J Vet Emerg Crit Care.* (2018) 28:301–9. doi: 10.1111/vec.12728
- Celeita-Rodríguez N, Teixeira-Neto FJ, Garofalo NA, Dalmagro TL, Giroto CH, Oliveira GCV, et al. Comparison of the diagnostic accuracy of dynamic and static preload indexes to predict fluid responsiveness in mechanically ventilated, isoflurane anesthetized dogs. *Vet Anaesth Analg.* (2019) 46:276–88. doi: 10.1016/j.vaa.2018.12.004
- Oricco S, Rabozzi R, Meneghini C, Franci P. Usefulness of focused cardiac ultrasonography for predicting fluid responsiveness in conscious, spontaneously breathing dogs. *Am J Vet Res.* (2019) 80:369–77. doi: 10.2460/ajvr.80.4.369
- Gonçalves LA, Otsuki DA, Pereira MA, Nagashima JK, Ambrosio AM, Fantoni DT. Comparison of pulse pressure variation versus echocardiography-derived stroke volume variation for prediction of fluid responsiveness in mechanically ventilated anesthetized dogs. *Vet Anaesth Analg.* (2020) 47:28–37. doi: 10.1016/j.vaa.2019.08.047
- Rabozzi R, Oricco S, Meneghini C, Bucci M, Franci P. Evaluation of the caudal vena cava diameter to abdominal aortic diameter ratio and the caudal vena cava respiratory collapsibility for predicting fluid responsiveness in a heterogeneous population of hospitalized conscious dogs. *J Vet Med Sci.* (2020) 82:337–44. doi: 10.1292/jvms.19-0028
- de Oliveira GCV, Teixeira-Neto FJ, Dalmagro TL, Alfonso A, Celeita-Rodríguez N, Lobo CPC, et al. Use of aortic flow indexes derived from transthoracic echocardiography to evaluate response to a fluid challenge in anesthetized dogs. *Vet Anaesth Analg.* (2021) 48:187–97. doi: 10.1016/j.vaa.2020.12.006
- Skouropoulou D, Lacitignola L, Di Bella C, Stabile M, Acquafredda C, Brienza N, et al. Intraoperative assessment of fluid responsiveness in normotensive dogs under isoflurane anaesthesia. *Vet Sci.* (2021) 8:26. doi: 10.3390/vetsci8020026
- Dalmagro TL, Teixeira-Neto FJ, Celeita-Rodríguez N, Garofalo NA, López-Castañeda B, Nascimento-Junior PD. 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.* (2021) 48:501–8. doi: 10.1016/j.vaa.2021.01.009
- Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med.* (2000) 162:134–8. doi: 10.1164/ajrccm.162.1.9903035
- Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care.* (2000) 4:282–9. doi: 10.1186/cc710
- Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest.* (2001) 119:867–73. doi: 10.1378/chest.119.3.867
- Kramer A, Zygun D, Hawes H, Easton P, Ferland A. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest.* (2004) 126:1563–8. doi: 10.1378/chest.126.5.1563
- Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology.* (2005) 103:419–28. doi: 10.1097/0000542-200508000-00026
- Michard F, Lopes MR, Auler JO Jr. Pulse pressure variation: beyond the fluid management of patients with shock. *Crit Care.* (2007) 11:131. doi: 10.1186/cc5905
- Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care.* (2016) 6:111. doi: 10.1186/s13613-016-0216-7
- Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med.* (2007) 35:64–8. doi: 10.1097/01.CCM.0000249851.94101.4F
- Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med.* (2009) 37:2642–7. doi: 10.1097/CCM.0b013e3181a590da
- Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med.* (2013) 41:1774–81. doi: 10.1097/CCM.0b013e31828a25fd
- Michard F, Chemla D, Teboul JL. Applicability of pulse pressure variation: how many shades of grey? *Crit Care.* (2015) 19:144. doi: 10.1186/s13054-015-0869-x
- Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care.* (2014) 18:650. doi: 10.1186/s13054-014-0650-6
- Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, Ospina-Tascón GA, Cruz Martínez LE. Use of pulse pressure variation as predictor of fluid responsiveness in patients ventilated with low tidal volume: a systematic review and meta-analysis. *Clin Med Insights Circ Respir Pulm Med.* (2020) 14:1179548420901518. doi: 10.1177/1179548420901518
- Muller L, Bobbia X, Toumi M, Louart G, Molinari N, Ragonnet B, et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care.* (2012) 16:R188. doi: 10.1186/cc11672
- Corl KA, George NR, Romanoff J, Levinson AT, Chheng DB, Merchant RC, et al. Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically-ill patients. *J Crit Care.* (2017) 41:130–7. doi: 10.1016/j.jccr.2017.05.008
- Cambournac M, Goy-Thollot I, Violé A, Boisvineau C, Pouzot-Nevoret C, Barthélemy A. Sonographic assessment of volaemia: development and

- validation of a new method in dogs. *J Small Anim Pract.* (2018) 59:174–82. doi: 10.1111/jsap.12759
39. Kwak J, Yoon H, Kim J, Kim M, Eom K. Ultrasonographic measurement of caudal vena cava to aorta ratios for determination of volume depletion in normal beagle dogs. *Vet Radiol Ultrasound.* (2018) 59:203–11. doi: 10.1111/vru.12566
 40. Marshall KA, Thomovsky EJ, Brooks AC, Johnson PA, Lim CK, Heng HG. Ultrasound measurements of the caudal vena cava before and after blood donation in 9 greyhound dogs. *Can Vet J.* (2018) 59:973–80.
 41. Herreria-Bustillo VJ, Fitzgerald E, Humm KR. Caval-aortic ratio and caudal vena cava diameter in dogs before and after blood donation. *J Vet Emerg Crit Care.* (2019) 29:643–6. doi: 10.1111/vec.12900
 42. Messina A, Longhini F, Coppo C, Pagni A, Lungu R, Ronco C, et al. Use of the fluid challenge in critically ill adult patients: a systematic review. *Anesth Analg.* (2017) 125:1532–43. doi: 10.1213/ANE.0000000000002103
 43. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* (2017) 43:304–77. doi: 10.1007/s00134-017-4683-6
 44. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med.* (2018) 46:997–1000. doi: 10.1097/CCM.00000000000003119
 45. Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, et al. Fluid response evaluation in sepsis hypotension and shock: a randomized clinical trial. *Chest.* (2020) 158:1431–45. doi: 10.1016/j.chest.2020.04.025
 46. Valverde A. Fluid resuscitation for refractory hypotension. *Front Vet Sci.* (2021) 8:621696. doi: 10.3389/fvets.2021.621696
 47. Diniz MS, Teixeira-Neto FJ, Cândido TD, Zanuzo FS, Teixeira LR, Klein AV, et al. Effects of dexmedetomidine on pulse pressure variation changes induced by hemorrhage followed by volume replacement in isoflurane-anesthetized dogs. *J Vet Emerg Crit Care.* (2014) 24:681–92. doi: 10.1111/vec.12246
 48. Klein AV, Teixeira-Neto FJ, Garofalo NA, Lagos-Carvajal AP, Diniz MS, Becerra-Velásquez DR. Changes in pulse pressure variation and plethysmographic variability index caused by hypotension-inducing hemorrhage followed by volume replacement in isoflurane-anesthetized dogs. *Am J Vet Res.* (2016) 77:280–7. doi: 10.2460/ajvr.77.3.280
 49. Nouira S, Elatrous S, Dimassi S, Besbes L, Boukef R, Mohamed B, et al. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med.* (2005) 33:2339–43. doi: 10.1097/01.CCM.0000182801.48137.13
 50. Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology.* (2011) 115:541–7. doi: 10.1097/ALN.0b013e318229a500
 51. Wu Y, Zhou S, Zhou Z, Liu B. A 10-second fluid challenge guided by transthoracic echocardiography can predict fluid responsiveness. *Crit Care.* (2014) 18:R108. doi: 10.1186/cc13891
 52. Biais M, de Courson H, Lanchon R, Pereira B, Bardonneau G, Griton M, et al. Mini-fluid challenge of 100 ml of crystalloid predicts fluid responsiveness in the operating room. *Anesthesiology.* (2017) 127:450–6. doi: 10.1097/ALN.0000000000001753
 53. Mukhtar A, Awad M, Elayashy M, Hussein A, Obayah G, El Adawy A, et al. Validity of mini-fluid challenge for predicting fluid responsiveness following liver transplantation. *BMC Anesthesiol.* (2019) 19:56. doi: 10.1186/s12871-019-0728-4
 54. Ali A, Dorman Y, Abdullah T, Yasa C, Orhan-Sungur M, Akinci IO, et al. Ability of mini-fluid challenge to predict fluid responsiveness in obese patients undergoing surgery in the prone position. *Minerva Anesthesiol.* (2019) 85:981–8. doi: 10.23736/S0375-9393.19.13276-2
 55. Lee CT, Lee TS, Chiu CT, Teng HC, Cheng HL, Wu CY. Mini-fluid challenge test predicts stroke volume and arterial pressure fluid responsiveness during spine surgery in prone position: a STARD-compliant diagnostic accuracy study. *Medicine.* (2020) 99:e19031. doi: 10.1097/MD.00000000000019031
 56. Zorio V, Lebreton T, Desgranges FP, Bochaton T, Desebbe O, Chassard D, et al. Does a two-minute mini-fluid challenge predict fluid responsiveness in pediatric patients under general anesthesia? *Paediatr Anaesth.* (2020) 30:161–7. doi: 10.1111/pan.13793
 57. Messina A, Dell'Anna A, Baggiani M, Torrini F, Maresca GM, Bennett V, et al. Functional hemodynamic tests: a systematic review and a meta-analysis on the reliability of the end-expiratory occlusion test and of the mini-fluid challenge in predicting fluid responsiveness. *Crit Care.* (2019) 23:264. doi: 10.1186/s13054-019-2545-z
 58. Geisen M, Ganter MT, Hartnack S, Dzemali O, Hofer CK, Zollinger A. Accuracy, precision, and trending of 4 pulse wave analysis techniques in the postoperative period. *J Cardiothorac Vasc Anesth.* (2018) 32:715–22. doi: 10.1053/j.jvca.2017.09.006
 59. Cecconi M, Hofer C, Teboul JL, Pettita V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med.* (2015) 41:1529–37. doi: 10.1007/s00134-015-3850-x
 60. Piarrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? *Intensive Care Med.* (2012) 38:422–8. doi: 10.1007/s00134-011-2457-0
 61. Silverstein DC, Kleiner J, Drobatz KJ. Effectiveness of intravenous fluid resuscitation in the emergency room for treatment of hypotension in dogs: 35 cases (2000–2010). *J Vet Emerg Crit Care.* (2012) 22:666–73. doi: 10.1111/j.1476-4431.2012.00822.x
 62. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput.* (1999) 15:85–91.
 63. Critchley LA, Critchley LA, Yang XX, Lee A. Assessment of trending ability of cardiac output monitors by polar plot methodology. *J Cardiothorac Vasc Anesth.* (2011) 25:536–46. doi: 10.1053/j.jvca.2011.01.003
 64. Geerts BF, Aarts LP, Jansen JR. Methods in pharmacology: measurement of cardiac output. *Br J Clin Pharmacol.* (2011) 71:316–30. doi: 10.1111/j.1365-2125.2010.03798.x
 65. Reuter DA, Huang C, Edrich T, Shernan SK, Eltzschig HK. Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. *Anesth Analg.* (2010) 110:799–811. doi: 10.1213/ANE.0b013e3181cc885a
 66. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a “gray zone” approach. *Anesthesiology.* (2011) 115:231–41. doi: 10.1097/ALN.0b013e318225b80a
 67. Vincent JL. The pulmonary artery catheter. *J Clin Monit Comput.* (2012) 26:341–5. doi: 10.1007/s10877-012-9389-2
 68. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. *Ann Intensive Care.* (2013) 28:38. doi: 10.1186/2110-5820-3-38
 69. Sakka SG, Reuter DA, Perel A. The transpulmonary thermodilution technique. *J Clin Monit Comput.* (2012) 26:347–53. doi: 10.1007/s10877-012-9378-5
 70. Lemson J, de Boode WP, Hopman JC, Singh SK, van der Hoeven JG. Validation of transpulmonary thermodilution cardiac output measurement in a pediatric animal model. *Pediatr Crit Care Med.* (2008) 9:313–9. doi: 10.1097/PCC.0b013e31816c66fa1
 71. Kutter AP, Bektas RN, Hofer CK, Larenza Menzies MP, Bettschart-Wolfensberger R. 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.* (2015) 29:377–83. doi: 10.1007/s10877-014-9615-1
 72. Kutter AP, Bettschart-Wolfensberger R, Romagnoli N, Bektas RN. Evaluation of agreement and trending ability between transpulmonary thermodilution and calibrated pulse contour and pulse power cardiac output monitoring methods against pulmonary artery thermodilution in anesthetized dogs. *J Vet Emerg Crit Care.* (2016) 26:531–40. doi: 10.1111/vec.12439
 73. Garofalo NA, Teixeira-Neto FJ, Rodrigues JC, Cerejo SA, Aguiar AJ, Becerra-Velásquez DR. Comparison of transpulmonary thermodilution and calibrated pulse contour analysis with pulmonary artery thermodilution cardiac output measurements in anesthetized dogs. *J Vet Intern Med.* (2016) 30:941–50. doi: 10.1111/jvim.13984
 74. Briganti A, Evangelista F, Centonze P, Rizzo A, Bentivegna F, Crovace A, et al. A preliminary study evaluating cardiac output measurement using Pressure Recording Analytical Method (PRAM) in anaesthetized dogs. *BMC Vet Res.* (2018) 14:72. doi: 10.1186/s12917-018-1392-5

75. Sasaki K, Mutoh T, Mutoh T, Kawashima R, Tsubone H. Electrical velocimetry for non-invasive cardiac output and stroke volume variation measurements in dogs undergoing cardiovascular surgery. *Vet Anaesth Analg.* (2017) 44:7–16. doi: 10.1111/vaa.12380
76. Sano H, Chambers JP. Ability of pulse wave transit time to detect changes in stroke volume and to estimate cardiac output compared to thermodilution technique in isoflurane-anesthetized dogs. *Vet Anaesth Analg.* (2017) 44:1057–67. doi: 10.1016/j.vaa.2016.11.014
77. Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul JL. Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care.* (2010) 14:R109. doi: 10.1186/cc9058
78. Monnet X, Anguel N, Jozwiak M, Richard C, Teboul JL. Third-generation FloTrac/Vigileo does not reliably track changes in cardiac output induced by norepinephrine in critically ill patients. *Br J Anaesth.* (2012) 108:615–22. doi: 10.1093/bja/aer491
79. Fischer MO, Rebet O, Guinot PG, Lemétayer C, Saplacan V, Gérard JL, et al. Assessment of changes in cardiac index with calibrated pulse contour analysis in cardiac surgery: a prospective observational study. *Anaesth Crit Care Pain Med.* (2016) 35:261–7. doi: 10.1016/j.accpm.2015.12.010
80. Monnet X, Persichini R, Ktari M, Jozwiak M, Richard C, Teboul JL. Precision of the transpulmonary thermodilution measurements. *Crit Care.* (2011) 15:R204. doi: 10.1186/cc10421
81. Shih A, Maisenbacher HW, Bandt C, Ricco C, Bailey J, Rivera J, et al. Assessment of cardiac output measurement in dogs by transpulmonary pulse contour analysis. *J Vet Emerg Crit Care.* (2011) 21:321–7. doi: 10.1111/j.1476-4431.2011.00651.x
82. Kurita T, Morita K, Kato S, Kawasaki H, Kikura M, Kazama T, et al. Lithium dilution cardiac output measurements using a peripheral injection site comparison with central injection technique and thermodilution. *J Clin Monit Comput.* (1999) 15:279–85. doi: 10.1023/A:1009918904525
83. Mason DJ, O'Grady M, Woods JP, McDonell W. Comparison of a central and a peripheral (cephalic vein) injection site for the measurement of cardiac output using the lithium-dilution cardiac output technique in anesthetized dogs. *Can J Vet Res.* (2002) 66:207–10.
84. Linton R, Band D, O'Brien T, Jonas M, Leach R. Lithium dilution cardiac output measurement: a comparison with thermodilution. *Crit Care Med.* (1997) 25:1796–800. doi: 10.1097/00003246-199711000-00015
85. Mason DJ, O'Grady M, Woods JP, McDonell W. Assessment of lithium dilution cardiac output as a technique for measurement of cardiac output in dogs. *Am J Vet Res.* (2001) 62:1255–61. doi: 10.2460/ajvr.2001.62.1255
86. Mason DJ, O'Grady M, Woods JP, McDonell WN. Effect of background serum lithium concentrations on the accuracy of lithium dilution cardiac output determination in dogs. *Am J Vet Res.* (2002) 63:1048–52. doi: 10.2460/ajvr.2002.63.1048
87. Beaulieu KE, Kerr CL, McDonell WN. Evaluation of a lithium dilution cardiac output technique as a method for measurement of cardiac output in anesthetized cats. *Am J Vet Res.* (2005) 66:1639–45. doi: 10.2460/ajvr.2005.66.1639
88. Monnet X, Teboul JL. Minimally invasive monitoring. *Crit Care Clin.* (2015) 31:25–42. doi: 10.1016/j.ccc.2014.08.002
89. Yamashita K, Nishiyama T, Yokoyama T, Abe H, Manabe M. The effects of vasodilation on cardiac output measured by PiCCO. *J Cardiothorac Vasc Anesth.* (2008) 22:688–92. doi: 10.1053/j.jvca.2008.04.007
90. Paarmann H, Groesdonk HV, Sedemund-Adib B, Hanke H, Heinze H, Heringlake M, et al. Lack of agreement between pulmonary arterial thermodilution cardiac output and the pressure recording analytical method in postoperative cardiac surgery patients. *Br J Anaesth.* (2011) 106:475–81. doi: 10.1093/bja/aeq372
91. Urbano J, López J, González R, Fernández SN, Solana MJ, Toledo B, et al. Comparison between pressure-recording analytical method (PRAM) and femoral arterial thermodilution method (FATD) cardiac output monitoring in an infant animal model of cardiac arrest. *Intensive Care Med Exp.* (2016) 4:13. doi: 10.1186/s40635-016-0087-0
92. Felbinger TW, Reuter DA, Eltzschig HK, Bayerlein J, Goetz AE. Cardiac index measurements during rapid preload changes: a comparison of pulmonary artery thermodilution with arterial pulse contour analysis. *J Clin Anesth.* (2005) 17:241–8. doi: 10.1016/j.jclinane.2004.06.013
93. Feissel M, Aho LS, Georgiev S, Taponnier R, Badie J, Bruyère R, et al. Pulse wave transit time measurements of cardiac output in septic shock patients: a comparison of the estimated continuous cardiac output system with transthoracic echocardiography. *PLoS ONE.* (2015) 10:e0130489. doi: 10.1371/journal.pone.0130489
94. Hamzaoui O, Monnet X, Richard C, Osman D, Chemla D, Teboul JL. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. *Crit Care Med.* (2008) 36:434–40. doi: 10.1097/01.CCM.0B013E318161FEC4
95. Biais M, Cottenceau V, Stecken L, Jean M, Ottolenghi L, Rouillet S, et al. Evaluation of stroke volume variations obtained with the pressure recording analytic method. *Crit Care Med.* (2012) 40:1186–91. doi: 10.1097/CCM.0b013e31823bc632
96. Barthélémy R, Neuschwander A, Dramé F, Redouté M, Ditchi D, Stern J, et al. Monitoring haemodynamic response to fluid-challenge in ICU: comparison of pressure recording analytical method and oesophageal Doppler: a prospective observational study. *Eur J Anaesthesiol.* (2019) 36:135–43. doi: 10.1097/EJA.0000000000000924
97. Hattori K, Maeda T, Masubuchi T, Yoshikawa A, Ebuchi K, Morishima K, et al. Accuracy and trending ability of the fourth-generation FloTrac/Vigileo system in patients with low cardiac index. *J Cardiothorac Vasc Anesth.* (2017) 31:99–104. doi: 10.1053/j.jvca.2016.06.016
98. Maeda T, Hamaguchi E, Kubo N, Shimokawa A, Kanazawa H, Ohnishi Y. The accuracy and trending ability of cardiac index measured by the fourth-generation FloTrac/Vigileo system™ and the Fick method in cardiac surgery patients. *J Clin Monit Comput.* (2019) 33:767–76. doi: 10.1007/s10877-018-0217-1
99. Valverde A, Gianotti G, Rioja E, Hathway A. Comparison of cardiac output determined by arterial pulse pressure waveform analysis method (FloTrac/Vigileo) versus lithium dilution method in anesthetized dogs. *J Vet Emerg Crit Care.* (2011) 21:328–34. doi: 10.1111/j.1476-4431.2011.00650.x
100. Bektas RN, Kutter AP, Hartnack S, Jud RS, Schnyder M, Matos JM, et al. Evaluation of a minimally invasive non-calibrated pulse contour cardiac output monitor (FloTrac/Vigileo) in anesthetized dogs. *Vet Anaesth Analg.* (2012) 39:464–71. doi: 10.1111/j.1467-2995.2012.00741.x
101. Scolletta S, Romano SM, Biagioli B, Capannini G, Giomarelli P. Pressure recording analytical method (PRAM) for measurement of cardiac output during various haemodynamic states. *Br J Anaesth.* (2005) 95:159–65. doi: 10.1093/bja/aei154
102. Blanco P, Aguiar FM, Blaivas M. Rapid Ultrasound in Shock (RUSH) velocity-time integral: a proposal to expand the RUSH protocol. *J Ultrasound Med.* (2015) 34:1691–700. doi: 10.7863/ultra.15.14.08059
103. Miller A, Mandeville J. Predicting and measuring fluid responsiveness with echocardiography. *Echo Res Pract.* (2016) 3:G1–12. doi: 10.1530/ERP-16-0008
104. Blanco P. Rationale for using the velocity-time integral and the minute distance for assessing the stroke volume and cardiac output in point-of-care settings. *Ultrasound J.* (2020) 12:21. doi: 10.1186/s13089-020-00170-x
105. Mercado P, Maizel J, Beyls C, Titeca-Beauport D, Joris M, Kontar L, et al. Transthoracic echocardiography: an accurate and precise method for estimating cardiac output in the critically ill patient. *Crit Care.* (2017) 21:136. doi: 10.1186/s13054-017-1737-7
106. Riesen SC, Doherr MG, Lombard CW. Comparison of Doppler-derived aortic velocities obtained from various transducer sites in healthy dogs and cats. *Vet Radiol Ultrasound.* (2007) 48:570–3. doi: 10.1111/j.1740-8261.2007.00299.x
107. Villavicencio C, Leache J, Marin J, Oliva I, Rodriguez A, Bodí M, et al. Basic critical care echocardiography training of intensivists allows reproducible and reliable measurements of cardiac output. *Ultrasound J.* (2019) 11:5. doi: 10.1186/s13089-019-0120-0
108. Jozwiak M, Mercado P, Teboul JL, Benmalek A, Gimenez J, Dépret F, et al. What is the lowest change in cardiac output that transthoracic echocardiography can detect? *Crit Care.* (2019) 23:116. doi: 10.1186/s13054-019-2413-x
109. Mantovani MM, Fantoni DT, Gimenes AM, de Castro JR, Flor PB, Ida KK, et al. Clinical monitoring of cardiac output assessed by transoesophageal echocardiography in anesthetized dogs: a

- comparison with the thermodilution technique. *BMC Vet Res.* (2017) 13:325. doi: 10.1186/s12917-017-1227-9
110. Brun C, Zieleskiewicz L, Textoris J, Muller L, Bellefleur JP, Antonini F, et al. Prediction of fluid responsiveness in severe preclampic patients with oliguria. *Intensive Care Med.* (2013) 39:593–600. doi: 10.1007/s00134-012-2770-2
 111. Roger C, Zieleskiewicz L, Demattei C, Lakkhal K, Piton G, Louart B, et al. Time course of fluid responsiveness in sepsis: the fluid challenge revisiting (FCREV) study. *Crit Care.* (2019) 23:179. doi: 10.1186/s13054-019-2448-z
 112. Bunting KV, Steeds RP, Slater LT, Rogers JK, Gkoutos GV, Kotecha D. A practical guide to assess the reproducibility of echocardiographic measurements. *J Am Soc Echocardiogr.* (2019) 32:1505–15. doi: 10.1016/j.echo.2019.08.015
 113. Hapfelmeier A, Cecconi M, Saugel B. Cardiac output method comparison studies: the relation of the precision of agreement and the precision of method. *J Clin Monit Comput.* (2016) 30:149–55. doi: 10.1007/s10877-015-9711-x
 114. Knirsch W, Kretschmar O, Tomaske M, Stutz K, Nagdyman N, Balmer C, et al. Comparison of cardiac output measurement using the CardioQP oesophageal Doppler with cardiac output measurement using thermodilution technique in children during heart catheterisation. *Anaesthesia.* (2008) 63:851–5. doi: 10.1111/j.1365-2044.2008.05495.x
 115. Møller-Sørensen H, Cordtz J, Østergaard M, Nilsson JC, Hansen KL. Transesophageal Doppler reliably tracks changes in cardiac output in comparison with intermittent pulmonary artery thermodilution in cardiac surgery patients. *J Clin Monit Comput.* (2017) 31:135–42. doi: 10.1007/s10877-015-9806-4
 116. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia.* (2008) 63:44–51. doi: 10.1111/j.1365-2044.2007.05233.x
 117. Canfrán S, Cediel R, Sández I, Caro-Vadillo A, Gómez de Segura IA. Evaluation of an oesophageal Doppler device for monitoring cardiac output in anaesthetised healthy normotensive dogs. *J Small Anim Pract.* (2015) 56:450–5. doi: 10.1111/jsap.12362
 118. Chohan A, Pascoe P. Evaluation of transesophageal Doppler in Beagle dogs as an aid to provide goal directed fluid therapy (abstract). *Vet Anaesth Analg.* (2019) 46:831.e4. doi: 10.1016/j.vaa.2019.08.014
 119. Schmidt C, Theilmeier G, Van Aken H, Korsmeier P, Wirtz SP, Berendes E, et al. Comparison of electrical velocimetry and transoesophageal Doppler echocardiography for measuring stroke volume and cardiac output. *Br J Anaesth.* (2005) 95:603–10. doi: 10.1093/bja/aei224
 120. Zoremba N, Bickenbach J, Krauss B, Rossaint R, Kuhlen R, Schälte G. Comparison of electrical velocimetry and thermodilution techniques for the measurement of cardiac output. *Acta Anaesthesiol Scand.* (2007) 51:1314–9. doi: 10.1111/j.1399-6576.2007.01445.x
 121. Gujjar AR, Muralidhar K, Banakal S, Gupta R, Sathyaprabha TN, Jairaj PS. Non-invasive cardiac output by transthoracic electrical bioimpedance in post-cardiac surgery patients: comparison with thermodilution method. *J Clin Monit Comput.* (2008) 22:175–80. doi: 10.1007/s10877-008-9119-y
 122. Raue W, Swierzy M, Koplin G, Schwenk W. Comparison of electrical velocimetry and transthoracic thermodilution technique for cardiac output assessment in critically ill patients. *Eur J Anaesthesiol.* (2009) 26:1067–71. doi: 10.1097/EJA.0b013e32832bfd94
 123. Blohm ME, Obrecht D, Hartwich J, Mueller GC, Kersten JF, Weil J, et al. Impedance cardiography (electrical velocimetry) and transthoracic echocardiography for non-invasive cardiac output monitoring in pediatric intensive care patients: a prospective single-center observational study. *Crit Care.* (2014) 18:603. doi: 10.1186/s13054-014-0603-0
 124. Cox PBW, den Ouden AM, Theunissen M, Montenij LJ, Kessels AGH, Lancé MD, et al. Accuracy, precision, and trending ability of electrical cardiometry cardiac index versus continuous pulmonary artery thermodilution method: a prospective, observational study. *Biomed Res Int.* (2017) 2017:2635151. doi: 10.1155/2017/2635151
 125. Feng SM, Liu J. Electrical velocimetry has limited accuracy and precision and moderate trending ability compared with transthoracic echocardiography for cardiac output measurement during cesarean delivery: a prospective observational study. *Medicine.* (2020) 99:e21914. doi: 10.1097/MD.00000000000021914
 126. Sanders M, Servaas S, Slagt C. Accuracy and precision of non-invasive cardiac output monitoring by electrical cardiometry: a systematic review and meta-analysis. *J Clin Monit Comput.* (2020) 34:433–60. doi: 10.1007/s10877-019-00330-y
 127. Magliocca A, Rezoagli E, Anderson TA, Burns SM, Ichinose F, Chitilian HV. Cardiac output measurements based on the pulse wave transit time and thoracic impedance exhibit limited agreement with thermodilution method during orthotopic liver transplantation. *Anesth Analg.* (2018) 126:85–92. doi: 10.1213/ANE.0000000000002171
 128. Ehlers U, Erlebach R, Brandi G, Stretti F, Valek R, Klinzing S, et al. Continuous estimation of cardiac output in critical care: a noninvasive method based on pulse wave transit time compared with transpulmonary thermodilution. *Crit Care Res Pract.* (2020) 2020:8956372. doi: 10.1155/2020/8956372
 129. Richard JC, Bayle F, Bourdin G, Leray V, Debord S, Delannoy B, et al. Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. *Crit Care.* (2015) 19:5. doi: 10.1186/s13054-014-0734-3
 130. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care.* (2019) 23:16. doi: 10.1186/s13054-018-2292-6
 131. Omar S, Ali A, Atiya Y, Mathivha RL, Dulhunty JM. Changes in B-type natriuretic peptide and related hemodynamic parameters following a fluid challenge in critically ill patients with severe sepsis or septic shock. *Indian J Crit Care Med.* (2017) 21:117–21. doi: 10.4103/ijccm.IJCCM_318_16
 132. Chappell D, Bruegger D, Potzel J, Jacob M, Brettner F, Vogeser M, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. *Crit Care.* (2014) 18:538. doi: 10.1186/s13054-014-0538-5
 133. Jozwiak M, Teboul JL, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. *Ann Intensive Care.* (2015) 5:38. doi: 10.1186/s13613-015-0081-9
 134. Tagami T, Ong MEH. Extravascular lung water measurements in acute respiratory distress syndrome: why, how, and when? *Curr Opin Crit Care.* (2018) 24:209–15. doi: 10.1097/MCC.0000000000000503
 135. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. *Br J Anaesth.* (2014) 112:617–20. doi: 10.1093/bja/aet590
 136. Diniz MS, Teixeira-Neto FJ, Celeita-Rodríguez N, Giroto CH, Fonseca MW, Oliveira-Garcia AC, et al. Effects of 6% tetrastarch and lactated ringer's solution on extravascular lung water and markers of acute renal injury in hemorrhaged, isoflurane-anesthetized healthy dogs. *J Vet Intern Med.* (2018) 32:712–21. doi: 10.1111/jvim.14853
 137. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* (2016) 29:277–314. doi: 10.1016/j.echo.2016.01.011
 138. Schober KE, Hart TM, Stern JA, Li X, Samii VF, Zekas LJ, et al. Detection of congestive heart failure in dogs by Doppler echocardiography. *J Vet Intern Med.* (2010) 24:1358–68. doi: 10.1111/j.1939-1676.2010.0592.x
 139. Schober KE, Chetboul V. Echocardiographic evaluation of left ventricular diastolic function in cats: hemodynamic determinants and pattern recognition. *J Vet Cardiol.* (2015) 17(Suppl. 1):S102–33. doi: 10.1016/j.jvc.2015.02.002
 140. Schober KE, Bonagura JD, Scansen BA, Stern JA, Ponzio NM. Estimation of left ventricular filling pressure by use of Doppler echocardiography in healthy anesthetized dogs subjected to acute volume loading. *Am J Vet Res.* (2008) 69:1034–49. doi: 10.2460/ajvr.69.8.1034
 141. de Madron E. Echocardiographic evaluation of the left ventricle filling pressure. In: de Madron E, Chetboul V, Bussadori C, editors. *Clinical Echocardiographic of the Dog and Cat*. 1st ed. St. Louis, MO: Elsevier Masson (2016). p. 139–50. doi: 10.1016/B978-0-323-31650-7.00009-0
 142. Sanfilippo F, Corredor C, Fletcher N, Landesberg G, Benedetto U, Foex P, et al. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. *Intensive Care Med.* (2015) 41:1004–13. doi: 10.1007/s00134-015-3748-7

143. Sanfilippo F, Corredor C, Arcadipane A, Landesberg G, Vieillard-Baron A, Cecconi M, et al. Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis. *Br J Anaesth.* (2017) 119:583–94. doi: 10.1093/bja/aex254
144. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. *Crit Care Med.* (2017) 45:e161–8. doi: 10.1097/CCM.0000000000002067
145. Toscani L, Aya HD, Antonakaki D, Bastoni D, Watson X, Arulkumaran N, et al. What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis. *Crit Care.* (2017) 21:207. doi: 10.1186/s13054-017-1796-9
146. Barros JM, do Nascimento P Jr, Marinello JL, Braz LG, Carvalho LR, Vane LA, et al. The effects of 6% hydroxyethyl starch-hypertonic saline in resuscitation of dogs with hemorrhagic shock. *Anesth Analg.* (2011) 112:395–404. doi: 10.1213/ANE.0b013e3181f2e9b2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Teixeira-Neto and Valverde. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.