ESCOLA UNIVERSITÁRIA VASCO DA GAMA

MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

VOLEMIA ASSESSMENT AND FLUID THERAPY RESPONSIVENESS

THE STATE OF THE ART IN SMALL ANIMAL VETERINARY MEDICINE

Ana Sofia Neto Nunes

Coimbra, julho de 2021

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Aluna do Mestrado Integrado em Medicina Veterinária

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Dissertação de Estágio Curricular do Ciclo de Estudos Conducente ao Grau de Mestre em Medicina Veterinária da EUVG

Confia em ti mesmo. Cria o tipo de vida que te fará feliz para o resto dos teus dias. Aproveita as tuas capacidades ao máximo, transformando as pequeninas centelhas de possibilidade que tens dentro de ti em chamas de conquista.

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List of abbreviations

ANP – Atrial Natriuretic Peptide
CaO_2 - Arterial oxygen content
cm – centimeter
CO - Cardiac Output
CVC – Caudal Vena Cava
CVCCI – Caudal Vena Cava Collapsibility Index
CVP - Central Venous Pressure
DO_2 - Oxygen Delivery
EC – Endothelial Cell
EEO - End Expiratory Occlusion test
EG – Endothelial Glycocalyx
e.g. – exempli gratia (In latin, for example)
FCD - Functional Capillary Density
GB – Gall bladder
$GEDVI_{TPTD}$ – Global End-Diastolic Volume Index measured by Transpulmonary Thermodilution
Hb – Hemoglobin
HCO_3 - Bicarbonate
Hct – Hematocrit
HR – Heart Rate
H_2O - Water
IVC - Inferior Vena Cava
J_v – Transvascular fluid flow
kD - kilodalton
K_{fc} - Filtration coefficient
kg - kilogram
L – Liter
LVEDA – Left Ventricular End-Diastolic Area
MAP - Mean arterial blood pressure
mL - mililiters
mmHg - millimetre of mercury
mmol – milimole
NIRS - Near Infrared Spectroscopy
σ - Reflection coefficient
O_2 - Oxygen
O_2D - Oxygen debt
P – Hydrostatic pressure
P_c - Intravascular hydrostatic pressure
pCO_2 – Partial pressure of carbon dioxide
PCV – Packed Cell Volume
PEEP – Positive End-Expiratory Pressure
π – Oncotic pressure
$π_c$ - Plasma oncotic pressure
$π_i$ - Interstitial oncotic pressure
$π_{sg}$ - Subglycocalyx colloid osmotic pressure
PI – Peripherical perfusion index
P_i - Interstitial hydrostatic pressure
PLR – Passive Leg Raising
PO_2 - Partial pressure of oxygen
POCUS – Point-of-care Ultrasound
PPV – Pulse Pressure Variation
Pra - Right arterial pressure
PVI – Plethysmographic Variability Index
P50 - Partial pressure of oxygen to saturate 50% of hemoglobin
SaO2 – Hemoglobin oxygen saturation
$ScvO_2$ – Central venous oxygen saturation
$SmvO_2$ - Mixed venous oxygen saturation
SpO_2 – Peripheral oxygen saturation
StO_2 - Tissue oxygen tension
SV – Stroke Volume
SVR – Stroke Volume Ratio
SVV - Stroke Volume Variation
SVV_{PCA} – Stroke Volume Variation measured by Pulse Contour Analysis
VE – Volume Expansion
VO_2 – Total oxygen consumption
VPOCUS – Veterinary Point-of-Care Ultrasound
VTI – Velocity Time Integral

Volemia and fluid therapy responsiveness – the state of the art in veterinary medicine

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Resumo

A fluidoterapia faz parte do plano de tratamento de uma grande parte dos pacientes hospitalizados na prática clínica de animais de companhia. É de maior importânia o reconhecimento das necessidades hemodinâmicas dos pacientes, de modo a alcançar melhorias clínicas sem que haja efeitos nefastos devido a sobrecarga de fluidos ou a seleção inadequada do tipo de terapia implementada.

O conhecimento dos compartimentos corporais, da distribuição da água corporal, de como o fluxo de fluidos ocorre e o que influencia todo o processo é essencial para tomar medidas relativamente ao tipo de fluidoterapia. Com esse objetivo, existem alguns modelos disponíveis para explicar os eventos hemodinâmicos, dos quais esta revisão destaca o princípio de Starling e o glicocálix endotelial. Além disso, o médico veterinário deve estar apto a avaliar o estado de perfusão do animal, de modo a que a terapia possa ser ajustada. A oxigenação tecidual depende do débito cardíaco, o qual varia com a administração de fluidos. Esta interação pode ser explicada pela lei de Frank-Starling. Alguns parâmetros da avaliação da perfusão podem ser acedidos através do exame físico. Contudo, um estado inicial de hipovolémia oculta pode estar presente e não ser possível detetá-la. Ademais, parâmetros estáticos que têm sido tradicionalmente usados para avaliar a resposta a fluidos durante a ventilação mecânica demonstraram ser pouco sensíveis na deteção de hipovolémia, devido às interações cardio-pulmonares. Deste modo, o objetivo desta revisão é salientar algumas ferramentas recentes que possam ser úteis para avaliar o estado de volume do paciente, para que estados de hipo ou hipervolémia possam ser detectados numa fase precoce, e que a fluidoterapia possa ser monitorizada e ajustada, permitindo melhores resultados clínicos. Neste trabalho são abordados métodos de avaliação da perfusão tecidual - espectroscopia de infravermelho próximo-, de imagem - ultrassom *point-of-care*-, e outros de avaliação de índices hemodinâmicos, tais como a variação de pressão de pulso, o índice de variabilidade pletismográfica, o índice de perfusão periférica, o teste de oclusão expiratória final e o levantamento passivo das pernas.

Palavras-chave

Hemodinâmica; Fluxo de fluidos; Fluidoterapia; Resposta a fluidos; Hipovolémia; Débito cardíaco; Lei de Frank-Starling

Abstract

Fluid therapy is part of the treatment plan of a large percentage of the hospitalized patients in small animal clinical practice. It's of the utmost importance to recognize the dynamic needs of the patients, in order to achieve a clinical improvement, without any harmful effects by a fluid overload or an inadequate selection of the type of therapy implemented.

Knowledge of the the body compartments, the distribution of body water, how fluid flow occurs and what influences all the process is crucial to make fluid therapy decisions. For that purpose, there are some models available to explain hemodynamic events, of which, with this review, stands out the Starling's principle and endothelial glycocalix. Furthermore, the clinician should be able to evaluate the perfusion status of the animal, so that the therapy can be adjusted. The tissue oxygenation depends on cardiac output, which varies with fluids administration. Its interaction can be understood with Frank-Starling law. Some of the perfusion evaluation parameters can be acessed by physical examination. However, an initial state of occult hypovolemia may be present and not possible to detect. In addition, static parameters that have traditionally been used to evaluate fluids responsiveness during mechanical ventilation have shown to be insentitive to detect hypovolemia, due to heart-lung interactions. Thereby, the aim of this revision is to bring out some of recent tools that can be useful to evaluate the volume status of the patient, so that states of hypo or hypervolemia can be detected in an earlier phase, and fluid therapy can be monitored and adjusted, allowing better outcomes. This paper approaches methods of evaluation of tissue oximetry – near-infrared spectroscopy -, of imaging - point-of-care ultrasound -, and others hemodynamic indices evaluation, such as pulse pressure variation, plethysmographic variability index, peripheral perfusion index, end-expiratory occlusion test and passive leg raising.

Keywords

Hemodynamics; Fluid flow; Fluid therapy; Fluid responsiveness; Hypovolemia; Cardiac output; Frank-Starling law

1. INTRODUCTION

Fluids administration is a common part of the treatment plan in small animal practice (Byers, 2017). The decision about the type of fluidtherapy is often based on the clinician individual experience and preferences (Yiew *et al*., 2020), which takes to some general principles applicable to patients with different needs to achieve fluid balance, leading to poor outcomes (Gladden, 2018). In order to avoid these undesirable effects, it is crucial that an individualized fluid therapy plan be implemented, considering the main reason that leads a particular animal to go to the hospital and recquire fluids, besides comorbidities that may be present. In some pathological conditions, such as renal or cardiac diseases, or in some circumstances such as anesthetic procedures, the patients are more susceptible to hemodynamic changes, which means that they will be more predisposed to an overload or a insufficient fluid therapy (Kampmeier & Ertmer, 2019). Being aware of these particularities will help the clinician, when considering the purpose and limitations of the available fluid therapy options. The decision about the type of fluids, rate, volume and composition must be constantly re-evaluated, based on the type of disorder present – volume (e.g. hemorrhage), content (e.g. hyperkalaemia) or distribution (e.g. effusions) – and electrolytic, oncotic and acid-base changes (David, Jensen, & Johnson, 2013).

The fluid responsiveness varies in the same patient due to variations in hydratation status, underlying diseases, preload, afterload and cardiac contractility (Sano *et al*., 2018). Reaching an optimal fluid response can optimize oxygen delivery, avoiding tissue hypoxia and reperfusion damage. On the other hand, fluid overload is related with longer need of intensive care, organ dysfunction and increased mortality (Boysen, 2020).

In order to understand how fluids influence hemodynamic parameters, and how new tools can be reached to acess fluid responsiveness, it is essential to understand the changes in cardiac output, as well as other physiological aspects of volemia and fluid balance, and factors that influence the response to fluids.

This paper aims to describe some fluid responsiveness predictors and strategies to restore tissue perfusion, and also their limitations. For this purpose, recent fluid therapy guidelines for small animal clinical practice will be mentioned as well as the comparison between human and veterinary medicine, and the tools available in each area to evaluate fluid responsiveness and optimize the outcomes.

To this review several databases were used to gather the information intended to study, in which are included PubMed, ScienceDirect and VIN, using the following search terms: “fluid therapy”, “volemia”, tissue perfusion”, “fluid therapy guidelines”, “fluid responsiveness evaluation”, “near-infared spectroscopy”, “pulse pressure variation”, “plethysmographic variability index”, “peripherical perfusion

index", "end expiratory occlusion test", "passive leg raising" and "veterinary point-of-care ultrasound". The search covered mainly articles published since 2010 and included reviews and clinical trials both in human and veterinary medicine.

2. VOLEMIA

2.1. Physiology and hemodynamic indicators

To understand the consequences of fluids administration to a patient, the fluid balance whitin the body must be understood as well as its composition and distribution, and recognize its behaviour during health and disease conditions. About 60% of a dog´s or cat´s total body weight is water, being able to vary with age, gender, lean body mass and body condition, and in healthy animals it has been estimated as approximately 534 mL/kg to 660 mL/kg (Mazzaferro & Powell, 2013). One third of this water is in the extracellular space, divided between interstitial space (75%) and intravascular space (25%), while the other two thirds are in the intracellular space (Mcbride & Mymms, 2017). Intravascular fluid corresponds to 8% to 10% of total body water, and consists of plasma fluid, cellular components, proteins, and electrolytes. Interstitial fluid corresponds to 24% of total body water, and there is still transcellular fluid, within the joints, cartilage, gastro-intestinal tract and cerebrospinal space (Mazzaferro & Powell, 2013). It has been estimated that dogs and cats have a total intravascular fluid volume of 80 mL/kg to 90 mL/kg, and that of this fluid component, intravascular plasma water volume is about 45 mL/kg to 50 mL/kg (DiBartola, 2006).

2.1.1. Starling's principle

The fluid flow occurs between the intravascular and the interstitial space, which can be explained by *Starling's principle*. This principle is useful to understand fluid balance, edema formation and plasma volume regulation (Reminga, 2015), and can be defined by the follow equation:

$$J_v = K_{fc} [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

(J_v = transvascular fluid flow; K_{fc} = filtration coefficient; P_c = intravascular hydrostatic pressure; P_i = interstitial hydrostatic pressure; σ = reflection coefficient; π_c = plasma oncotic pressure; π_i = interstitial oncotic pressure)

Thereby, oncotic (π) pressures of the intravascular and interstitial space are determined by the plasma protein concentration. These factors, as well as hydrostatic (P) pressures and capillary permeability influence the transvascular fluid flow (J_v) (Mcbride, 2014). There is a hydrostatic pressure gradient directed outwards of the capillaries between interstitial and intravascular compartments, opposed to an oncotic gradient. The capillary hydrostatic pressure (P_c) is dominant at the arteriolar

end, which leads to the fluid filtration from the arteriolar cappilaries into the interstitial space ($P_c > P_i$ and π_c), and the reapsortion takes place in the venular system due to a superior plasma oncotic pressure and a fall in intravascular hydrostatic pressure ($\pi_c > P_c$ and π_i) (Muir, 2016). The lymphatic drainage then removes excessive interstitial filtration (Reminga, 2015). The capillary wall permeability to water is defined by the filtration coefficient (K_{fc}), which is dependent on hydraulic conductance and capillary surface area (Mcbride & Mymms, 2017). The reflection coefficient (σ) is the fraction of total osmotic pressure that a solute exerts across a capillary membrane, corresponding to the protein permeability of the capillary wall (Muir, 2016).

2.1.2. Transcapillary fluid flow

In addition to pressure dynamics explained by Starling's forces, the integrity of endothelial glycocalyx (EG) (Figure 1) influences the movement of fluid out of the vascular space (Sharp, 2017). The glycocalyx is a layer that coats most of the blood vessels, which is composed by glycoproteins and proteoglycans that have negative charged glycosaminoglycan side chains, and separates plasma from a subglycocalyx, a space almost protein-free (Woodcock & Woodcock, 2012), by covering endothelial intercellular clefts (Muir, 2016). Due to endothelial adhesion molecules in its constitution, it prevents leukocyte and blood platelet adhesion, regulates hemostasis, vascular tone, fluid and solute exchange, coagulation and inflammation (Reminga, 2015).

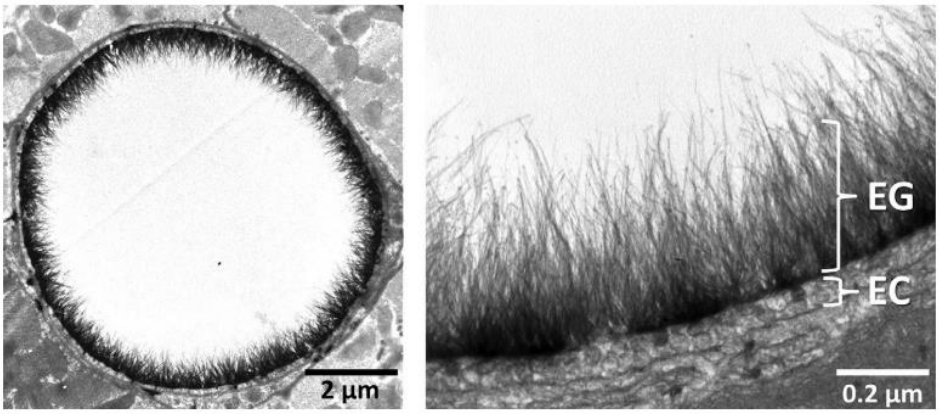


Figure 1 - Electron micrograph of a coronary capillary, evidencing the endothelial glycocalyx (EG) and endothelial cell (EC) (Gaudette *et al*., 2020).

The glycocalyx is semi-permeable to anionic macromolecules (albumin and other plasmatic proteins) (Vink, 2000) and acts like a barrier to larger molecules (e.g. colloids > 40-60 kD), but not to water flow, which means that it allows the passage of crystalloids (Muir, 2016). It is an interface between blood and the capillary wall (Woodcock & Woodcock, 2012) and divides the intravascular fluid compartment into three regions - the central volume (circulating plasma), the red blood cell volume and a non-circulating fluid volume that is within the glycocalyx (Muir, 2016). Between the

circulating plasma and the endothelial intercellular clefts, there is a protein concentration gradient (Woodcock & Woodcock, 2012). Intravascular hydrostatic pressure (P_c) is the main parameter that contributes to transvascular fluid flow (J_v). There is no reabsorption at the venular end of the capillary and the increase of plasma colloid osmotic pressure does not cause significant absorption of interstitial fluid (Muir, 2016). The Michelle-Winebaum explanation for transcapillary fluid flow brings some reconsiderations to the Starling's law:

$$\mathbf{J_v = K_{fc}\{ (P_c - P_i) - \sigma (\pi_p - \pi_{sg}) \},}$$

where interstitial oncotic pressure (π_i) is replaced by subglycocalyx colloid osmotic pressure (π_{sg}), which is the main determinant of transcapillary flow (J_v) (Adamson, 2004; Curry, 2005).

Lymph flow and low transcapillary flow in most of the tissues is due to the low protein concentration within the subglycocalyx intercellular spaces. In the early stages of inflammation, plasma proteins pass through pores to the interstitial space, which increases transcapillary fluid flow (Levick, 2010). Hypotension caused by acute blood loss can prompt fluid reabsorption through venous capillaries. Cases of hypotension without blood loss rarely happen and only occur until hydrostatic pressures (P_c and P_i) equilibrate (Muir, 2016).

According to Muir (2016), the administration of hypertonic and hyperoncotic fluids can produce volume expandind effects with approximately 85-95% efficiency and can last within circulation for long periods. These are even higher when hypovolemia from blood loss is treated with colloids. Nonetheless, if reached hypervolemia conditions or if normovolemic patients are treated with colloids, the intravascular volume expanding effect has an efficiency of only about 35–45%, which means that the effects are dependent on initial volume status and are superior after an acute blood loss.

The damage of glycocalyx can lead to fluid extravasation, and preceed interstitial edema and organ compromise (Sharp, 2017), leading to multiple organ dysfunction (Yozova *et al*., 2020). To preserve the physiologic functions of endothelial glycocalix, there are some aspects to consider when administering fluids. One of them is to avoid hypervolemia, by not infusing large volumes of intravenous fluids at the beginnig of the therapy when the patient is normovolemic, such as during elective surgical procedures (Sharp, 2017). Hypervolemia increases hydrostatic pressure (Thomovsk *et al*., 2016) and stretches the cardiac atria, leading to the release of atrial natriuretic peptide (ANP) from the atrial myocites (Gaudette *et al*., 2020). ANP stimulates natriuresis and promotes a fluid shift from the intravascular to the interstitial space, causes vasodilation of vascular beds (Gaudette *et al*., 2020), besides activating metalloproteinases (Palmer & Square, 2015), which damages endothelial glycocalyx (Yozova *et al*., 2020; Mcbride, 2014; Kampmeier & Ertmer, 2019). The consequences of this damage are the decrease in EG layer volume, exposure of the endothelium, changes in transvascular fluid dynamics (Mcbride, 2014), interstitial edema, increased vascular permeability and thus oxygen delivery to the tissues is compromised (Yozova *et al*., 2020). Coagulation is activated

locally, contributing to microcirculatory disturbances and biding of selectins and integrins, which activates inflammation (Yozova *et al*., 2020). On the other hand, situations of hypovolemia lead to low capillary pressures (Palmer & Square, 2015) and induce the reabsorption of fluid from the interstitial space into the intravascular compartment, which increases protein concentration in the subglycocalyx space, to a certain point of capillary pressure, where a greater increase in oncotic pressure reabsorption is reverted to net filtration (Mcbride, 2014).

Critically ill patients are predisposed to increased transvascular flow and, thereafter, to destruction of endothelial glycocalyx, so it is imperative to adequate the volume of fluids at any resuscitation stategy to avoid hypervolemia and hypovolemia, and mantain a functional and preserved endothelial surface layer (Reminga, 2015; Chawla *et al*., 2014).

3. TISSUE OXYGENATION

For a correct tissue oxygenation, there must be taken into account variables such as cardiac output (CO) and arterial oxygen content (CaO_2), that can help to understand how an effective oxygen delivery (DO_2) is achieved on tissues and how oxygen debt (O_2D) and anaerobic metabolism occur (Muir, 2006). CO is defined by the ammount (expressed in liters) of blood pumped from the heart per minute to supply the body metabolic recquirements and depends on the heart rate and stroke volume (Figure 2) (de Tombe & Tyberg, 2018). The stroke volume is the volume of blood ejected per beat by the left ventricle into the aorta, and results from heart contractility, preload (the stretching of the cardiac myocytes prior to contraction) and afterload (the load against which the heart has to contract to eject the blood) (DiBartola, 2006).

When packed cell volume (PCV) is below 15 to 20% and hemoglobin concentration decreases, the oxygen demand of tissues leads to an increase in CO and tissue oxygen extraction from the blood. Under physiologic conditions, the availability of oxygen exceeds oxygen consumption and DO_2 is not rate-limited (Nelson *et al*., 1987; Rivers *et al*., 2001). At low levels of DO_2, VO_2 is supply limited. At normal or high levels of DO_2, oxygen consumption and delivery are independent (Graphic 1) (Muir, 2006). There is an ability to increase the oxygen extraction to compensate a decreased DO_2 until a biological limit, a point called critical extraction ratio. This point varies according to metabolic demand and capillary density of the tissue. Below this value, there is supply-dependent oxygen consumption, and hypoxia and hypoperfusion leads to tissue oxygen debt and, thus, can lead to organ dysfunction (Walton & Hansen, 2018).

CaO_2 depends on the hemoglobin, oxygen saturation and the value of oxygen that each gram of hemoglobin can carry (Hüfner's constant), that corresponds to 1,34 mL in humans and varies between 1,34 and 1,39 in dogs (Shimizu *et al*., 1986). Oxygen saturation can be obtained directly by using a

pulse oxymeter, or it can be calculated by relating oxygen tension, blood temperature, hemoglobin saturation and blood pH (Kittleson & Kienle, 2005).

$$CO = SV \times HR = MAP/SVR$$

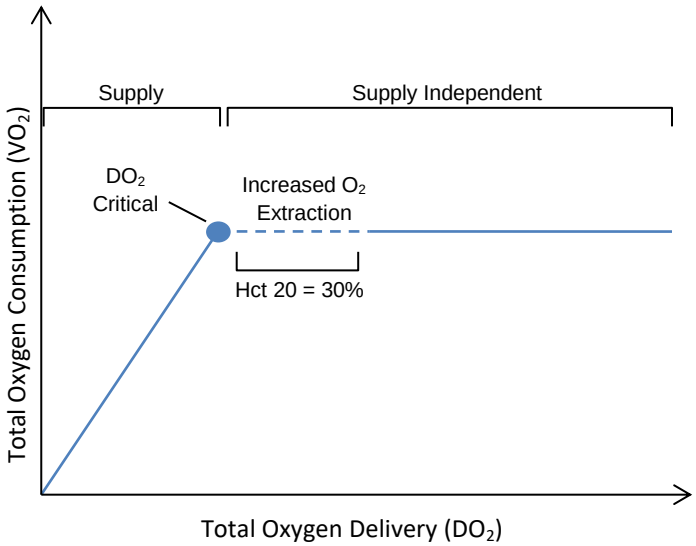
$$DO_2 = CO \times CaO_2$$
$$CaO_2 = (Hb \times 1.34 \times SaO_2) + (PO_2 \times 0.003)$$

$$DO_2 = SV \times HR \times (Hb \times 1.34 \times SaO_2) + (PO_2 \times 0.003)$$

(CO = cardiac output; SV = stroke volume; HR = heart rate; MAP = mean arterial pressure; SVR = stroke volume ratio; DO_2 = oxygen delivery; CaO_2 = arterial oxygen content; Hb = hemoglobin; SaO_2 = Hb oxygen saturation; PO_2 = partial pressure of O_2

Figure 2 – Determinants of cardiac output (Muir, 2016).

The tissue oxygenation depends on a minimal mean arterial blood pressure (MAP), as well as on the functional capillary density (FCD) and distribution of blood flow. FCD varies according to blood volume, viscosity and pH, partial pressure of oxygen (PO_2) and partial pressure of oxygen to saturate 50 % of hemoglobin (P50) (Muir, 2006)**.** The difference between inspired and expired oxygen content expresses the oxygen consumption, which varies between tissues according to metabolic needs (Curtis & Cain, 1992). The oxygen consumption determines the blood flow in the different organs, which is regulated to meet their demand (Walton & Hansen, 2018). The existing gradient between the capillaries and the mitochondrias is what determines oxygen delivery and its direction is defined by capillary oxygen pressure, since the mithocondrial PO_2 is about 1 mmHg (Kittleson & Kienle, 2005). When there is superior tissue demand, arterial blood is regulated to increase DO_2 and, therefore, CO increases to maintain systemic blood pressure. Oxygen extraction from the delivered blood also increases, allowing a greater oxygen consumption (Walton & Hansen, 2018). Tissue metabolic demand influences redistribution of blood flow, increasing oxygen extraction by increasing functional capillary density (Walton & Hansen, 2018). The value of capillary oxygen tension can be assessed by measuring the arterial blood pressure. Near the juction of cappilaries and venules, the oxygen pressure decreases until the venous oxygen pressure equals (Clemmer, 1981). When the venous oxygen tension is below 24 mmHg in skeletal muscle, the oxygen supply becomes compromised and the anaerobic metabolism starts to be used, this increases blood lactate concentration. Pulmonary artery blood is a mixture of venous blood from all vascular beds, and this is why a blood sample colleted from this vessel is called mixed venous blood, being the ideal to evaluate oxygenation status of a patient (Clemmer, 1981; Lee *et al*., 1972).



Graphic 1 - Relationship between oxygen delivery and oxygen consumption (adapted from Muir, 2016).

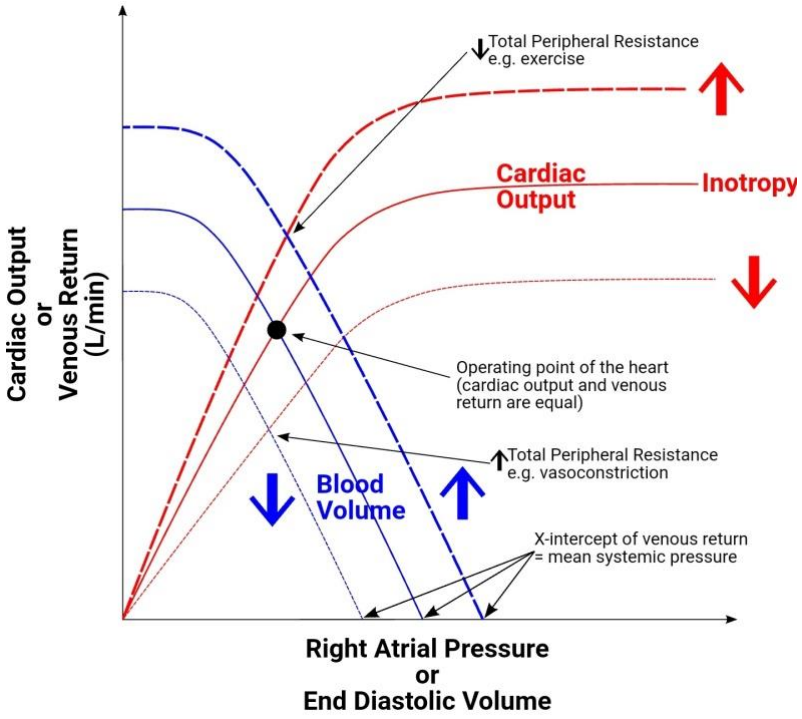
The central venous pressure (CVP) or the right arterial pressure (Pra) defines cardiac outputs for a certain preload (Magder, 2010), and the greater it is, the greater the output (Katz, 2002). The cardiac function can be annalysed according to Frank-Starling curves (Graphic 2), in which each is represented by constant values of afterload, contractility and heart rate (Magder, 2010), and it is an approach of the end-diastolic ventricular volume and its correlation with systolic ventricular performance (Schwarzwald *et al*. , 2009).

When preload increases, the ventricular output also increases, since the rise of ventricular diastolic volume increases the myocardial fibers stretch and, therefore, the ventricule force of contraction (Delicce & Makaryus, 2018). This is possible because of the inotropy, which is the capacity of myosin and actin (cardiac contractile proteins), to adapt contractile forces according to calcium availability. Myocardial relaxation requires recapture of calcium from the cytoplasm and it is afected by hypoxia, acidosis and decreased perfusion (Schwarzwald *et al*., 2009).

A decrease in afterload or an increase in heart rate or contractility leads to a curve alteration, moving to the left and upward, meaning that there is a higher cardiac output (Magder, 2010). In the same way, decreased left ventricular contractility (for example, by systolic heart failure) decreases cardiac performance and shifts the curve downward (Delicce & Makaryus, 2018). Thus, stroke volume will be decreased, and there will be incomplete left ventricular emptying and, during diastole, there will be a greater volume of blood accumulated, resulting in a greater residual volume. The myocardial fibers will stretch and, therefore, increase stroke volume so that the left ventricle can be deflated and cardiac output preserved (Delicce & Makaryus, 2018). This is explained because when the plateau is achieved, the cardiac output does not suffer changes, even if there are additional increases in preload. At this point the heart is overdistended and the left heart filling is compromised, as well as myocardial

perfusion, which can lead to peripheral edema. This plateau is determined by the limits of cardiac chambers filling, by stiff pericardium and cardiac cytoskeleton, which occurs at lower pressures on the right side of the heart, protecting the lungs. The plateau can be reached if sufficient volume is infused. Cardiac filling can also be limited by hyperinflated lungs, swelling or blood in the mediastinum and pleural space (Magder, 2010).

Frank-Starling`s law of the heart acts like a mechanism to compensate systolic heart failure, regulating cardiac output to guarantee blood pressure to vital organs perfusion (Delicce & Makaryus, 2018). Two common causes of a decrease of cardiac output are subnormal venous filling presures and hypovolemia (Schwarzwald *et al*., 2009). Hypotension due to vasodilation can reduce ventricular afterload. A raise in afterload reduces cardiac output by limiting ventricular systolic performance and decreasing stroke volume (Schwarzwald *et al*., 2009).



Graphic 2 - Physiological relationship between the Frank–Starling Law of the heart and venous return pressure and volume (Delicce & Makaryus, 2018).

Fluid administration should improve clinical indicators, but it is only proven benefit if volume infusion increases cardiac output (Magder, 2010). Thus, it is essential to understand the changes in cardiac output to manage fluid therapy.

4. FLUID THERAPY GOALS

There are some aspects to consider when formulating a fluid therapy plan. First of all, determine if fluids administration is indicated. If it is, then the clinician should decide the type of fluid, route, rate and volume to be administrated, when to discontinue the fluid therapy (DiBartola, 2012) and in which compartment the fluid is needed – interstitial or intravascular (Davis *et al*., 2013). The decision should always be individualised considering each patient, being aware of underlying diseases (Mazzaferro & Powell, 2013) and often re-evaluated according to changes in status and, if necessary, reformulated (Davis *et al*., 2013). For this reason, it should be assessed the animal's hydration, intravascular volume status and its capacity to retain fluid within the intravascular space, type of fluid lost, acid-base and electrolyte disturbances and when treating dehydration or hypovolemia the determinants of resuscitation endpoints (Mazzaferro & Powell, 2013).

In general, the main goals are based on restablishing fluid deficits (interstitial, intracellular and intravascular), correcting electrolyte, acid-base or oncotic disturbances and maintaining total body water in its normal values (Mazzaferro & Powell, 2013; David *et al*., 2013).

5. EVALUATION AND MONITORING FLUID RESPONSIVENESS

To evaluate the requirement of fluids, there has to be a complete physical examination and a study of the medical history as thorough as possible to identify any loss of fluids, of any body compartment, duration of illness; if there is any vomiting or diarrhoea and its frequency, water and food intake and any haemorrhage (O'Dwyer, 2018). The physical examination should allow the clinician to evaluate the tissue perfusion and if the patient is dehydrated (David *et al*., 2013). It is important to differenciate hypovolaemia from dehydration and the clinical signs associated with each of them, so that different types of fluids and rates can be administered. Hypovolaemia refers to a decrease of intravascular volume, which reduces the tissue perfusion, whereas dehydration is when there is a reduction of the fluids of the whole body, mainly intracellular and interstitial (O'Dwyer, 2018). When an animal is in shock, which means that there is not an adequate delivery of oxygen to the tissues, leading to a decrease of tissue perfusion. This can be evaluated by the mucous membrane colour, capillary refill time, pulse quality, heart rate and urine output. Clinical indices such as pale mucous membranes, increased capillary repletion time, decreased peripheral temperature and decreased urinary output due to vasoconstriction, tachycardia (cats can be bradycardic), decreased pulse quality (hypotension), decreased oxygen saturation, lactate greater than 2 mmol/L and metabolic acidosis indicate that the patient needs to receive therapy with fluids and restore perfusion, by restoring intravascular volume and flow (DiBartola, 2006). Combination of mucous membranes, skin turgor and retraction of the globe can indicate the hydration status (O'Dwyer, 2018).

When receiving fluid therapy, all the parameters mentioned before should be monitored to confirme if there is a return to normal values and, therefore, an adequate restore of tissue perfusion. In addition to those previously mentioned, some indices may be used to evaluate fluid responsiveness, such as mental status, digits color and temperature (DiBartola, 2006), respiratory effort, urine specific gravity, blood urea nitrogen, creatinine, electrolytes, blood pressure, venous or arterial blood gases, packed cell volume, total protein, lung sounds, skin turgor, body weight (Davis *et al*., 2013), mean arterial pressure, arterial pH, electrolyte balance and HCO_3, mixed venous oxygen saturation SmvO2 ($ScvO_2$), mixed venous pCO_2 and tissue pCO_2 (Mark, 2010).

In addition to the information obtained by the clinical evaluation and physical exam of the patient, there are some new strategies that are being studied in human medicine to evaluate and predict the fluid responsiveness. Some of them are mentioned below and compared with their applicability in veterinary medicine.

6. NEW STRATEGIES TO MONITOR FLUID RESPONSIVENESS

The search of new strategies arose with the difficulty of determining intravascular volume only with clinical examination (Mark, 2010). Its determination is essential to evaluate fluid responsiveness and, therefore, to guide fluid management. Traditionally it has been used central venous pressure and pulmonary artery occlusion pressure, although it has been demonstrated that cardiac filling pressures are not sufficient to help the clinician to predict fluid responsiveness (Mark, 2010), since preload also depends on the venous tone and compliance of the heart (Sano *et al*., 2018).

By giving fluids it is expected that there is an increase in intravascular volume, in order to increase cardiac output and stroke volume (Marik *et al*., 2009), and thus improve oxygenation and tissue perfusion (Sano *et al*., 2018; Paranjape *et al*., 2019). However, it does not always happen because of the Frank-Starling curve principle, in which the preload increase leads to a left ventricular stroke volume increase to a point that stroke volume remains constant (Figure 3) (Mark, 2010). If there is preload reserve – ascending part of the Frank-Starling curve – a cardiac preload growth will increase stroke volume, which means that there is a positive response to fluid administration (Drozdzynska *et al*., 2018). Although, if there is no preload reserve – distal and flat part of the curve – fluid loading will not increase stroke volume significantly, and there will be no benefits from fluid administration, as it can lead to an increase of tissue edema, promote tissue dysoxia, lung inflation and worse gas exchange if there is pulmonary injury (Marik *et al*., 2009; Monnet & Teboul, 2008; Sano *et al*., 2018). One of the strategies that allows identifying the patients in which fluid administration improves hemodynamic parameters is called “fluid challenge”. After an administration of fluid bolus, it can be evaluated if there is a preload reserve and if there would be profit from an intravenous volume increase (Cecconi *et al*., 2011).

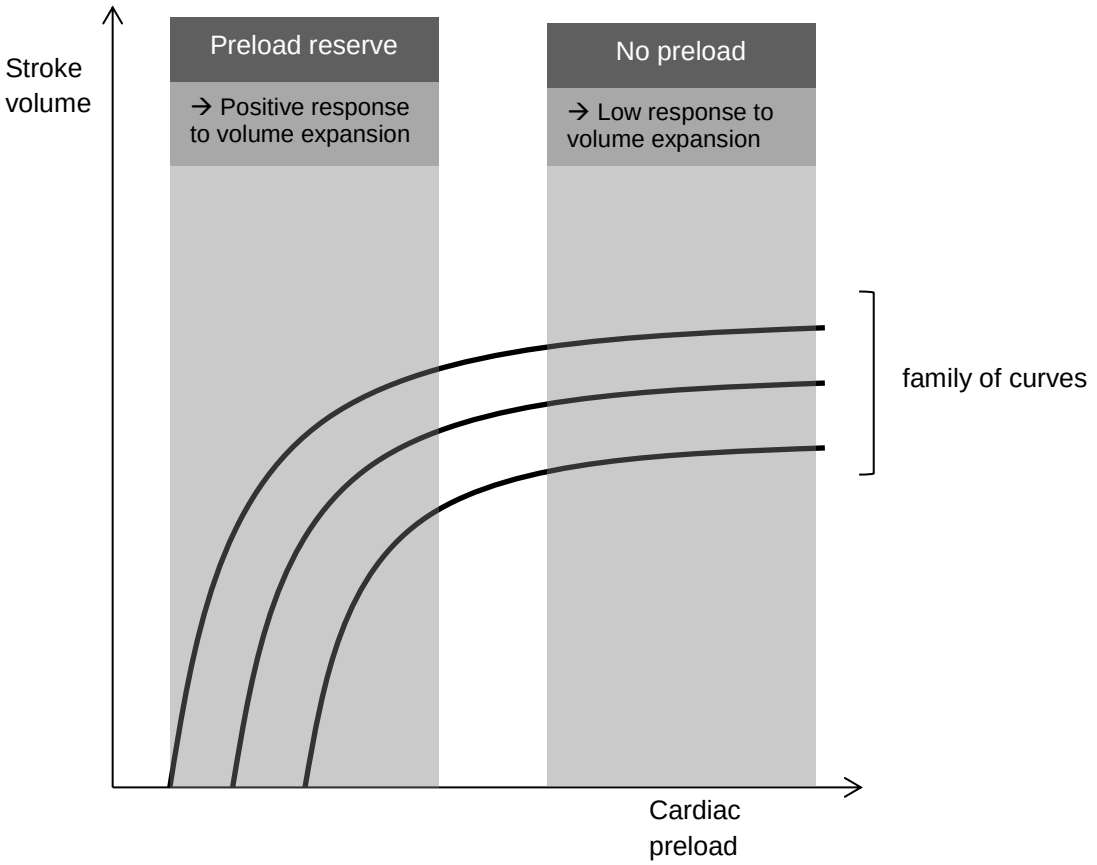


Figure 3 – Frank-Starling relationship (adapted from Mark, 2010).

6.1. Non-invasive tissue oximetry

Near-infrared spectroscopy (NIRS) provides a continuous non invasive tissue oxygen tension (StO_2) measurement and has been studied in human and veterinary medicine for detection of changes in microvascular circulation and occult shock (Gray *et al*., 2018).

NIRS emits infrared light and measures its absorption by tissues, to determine the oxygen hemoglobin saturation of microcirculation, which comprises vessels with diameter less than 100 microns (De Backer *et al*., 2010). The chromophores within the tissue are what define the absorption, mainly cytochrome aa3, myoglobin, oxyhemoglobin and deoxyhemoglobin, having each one a different spectrum of absorption (Pellicer & Bravo, 2011). Hematomas, fat and bone under the probe can alter the measurement, as well as excessive movement and fluctuations in body temperature or the skin pigmentation (Salcedo, Tart, & Hall, 2016).

Usually skin probes are made of adhesive disks, that are placed over the skin area to be measured, allowing the measurement of oxygen saturation (Hall *et al*., 2008) and, therefore, the detection of microvascular perfusion abnormalities (Salcedo *et al*., 2016). In human medicine, the most reliable StO_2 values are from the thenar eminence, while on dogs they are from the sartorius, epaxial, digital extensors and biceps femoris (Figure 4) (Salcedo *et al*., 2016; Hall *et al*., 2008). The sartorius is the ideal monitoring area in canine species, because of the easier positioning, less skin pigment and limited hair (Hall *et al*., 2008).

Besides the StO_2 value (Figure 5), the devices also read tissue hemoglobin index, which represents the amount of hemoglobin present in the monitored tissue, indicating the signal strenght and, therefore, the accuracy of StO_2 value (Hall *et al*., 2008).

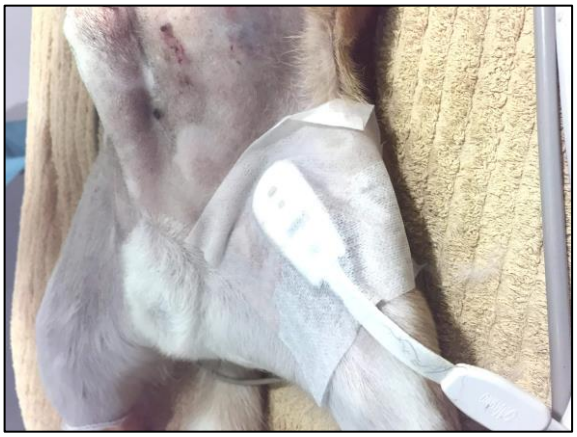


Figure 4 - Near-infrared spectroscope (NIRS) probe (Image kindly provided by Dr. Lénio Ribeiro, CHV).

Figure 5 - Portable near-infrared spectroscope (NIRS) and pleth variability index (PVI) with continuous data readings (Image kindly provided by Dr. Lénio Ribeiro, CHV).

The main utility described in human literature is the identification of hypoperfusion following trauma, surgery or states of sepsis, in order to predict organ dysfunction when the StO_2 level is lower than 75% (Cohn *et al*., 2007). This allows to find a strategy that optimizes cardiac output and hematocrit, in order to correct deficits in oxygen consuption and tissue oxygen delivery (Putnam *et al*., 2007). NIRS also helps to guide fluid ressuscitation, allowing lower volumes of intravenous fluids administered, and decide about transfusion with the identification of tissue hypoxia (Salcedo *et al*., 2016). Inadequate oxygen delivery can be accessed by high values of base deficit and plasma lactate concentration, since it indicates that there is a shift towards anaerobic metabolism within tissues (Putnam *et al*., 2007). StO_2 has shown to be an early predictor of hemodynamic status rather than plasma lactate concentration and base deficit (Santora & Moore, 2009). It is reported that during a study of hypovolemic patients undergoing anesthesia, after intravenous fluid administration, StO_2 improved earlier than other hemodynamic parameters such as arterial blood pressure. Less than 70%

of StO_2 revelead to be related to increased hospitalization and longer need of intensive care (Salcedo *et al*., 2016).

In the veterinary field, this tool is not completely described and there were few studies performed in dogs (Hall *et al*., 2008). However a parallelism with human medicine applications can be established, being able to be applied for tissue oxygen monitoring and to detect occult shock, guide management of trauma, sepsis and other critical illnesses in dogs (Hall *et al*., 2008). Therefore, it could be profitable to acess hemodynamic status, since it is a non invasive, continuous, portable, easy and quickly performed technique (Salcedo *et al*., 2016). Hall *et al*. (2008) performed a study with healthy dogs in order to establish reference values for StO_2. For this purpose, all the patients had uniform weights and were subjected to physical examination, cell blood count and biochemistry, evaluation of perfusion (by systolic blood pressure) and of oxygenation of arterial blood (by peripheral oxygen saturation - SpO_2 - or PO_2). Further investigation should be done, in order to fill the lack existing in standardized variables among machines and measurement sites (Salcedo *et al*., 2016).

6.2. Pulse pressure variation, plethysmographic variability index and peripherical perfusion index

Due to heart-lung interactions during mechanical ventilation, traditional hemodynamic markers such as heart rate or arterial blood pressure have shown to be insensitive to detect hypovolaemia (Drozdzynska *et al*., 2018). However, pulse pressure variation (PPV), plethysmographic variability index (PVI) and perfusion index (PI) have demonstrated to be predictive of fluid responsiveness (Marik *et al*., 2009). These interactions are complex and there is a need of an understanding of the relationship between positive pressure ventilation and right and left ventricular function so that dynamic indices can be interpretated (Araos *et al*., 2020). Mechanical ventilation induces inspiratory increase in pleural pressure, resulting in a decrease of a venous return pressure gradient and thus in a decrease of preload. It also induces an inspiratory increase in transpulmonary pressure, resulting in an increase of the right ventricle afterload. These events lead to a decrease in right ventricle stroke volume, which reaches its minimum at the end of the inspiratory period, leading to a reduction of left ventricule filling and thus, to a decrease in left ventricule stroke volume, that reaches its minimum during the expiratory period. Taking into account the Frank-Starling curve, the changes in stroke volume are greater when the ventricules operate on the steep portion of the curve, rather than the flat part (Marik *et al*., 2009). Volume responsiveness is related with the variation of the magnitude of the respiratory changes in left ventricule stroke volume and hence arterial blood pressure (Sano *et al*., 2018; Marik *et al*., 2009; Mark, 2010).

The pulse oximeter plethysmographic waveform measures volume in arterial vessels. The PVI measures dynamic ventilation-induced changes in the PI during a respiratory cycle (Drozdzynska *et*

al., 2018), which provides a measurement of the variation in the amplitude of the pletysmographic waveform (Figure 6) (Paranjape *et al*., 2019; Mark, 2010), and represents the strength of the infrared signal returning from the monitoring site (Drozdzynska *et al*., 2018; Sano *et al*., 2018). PI allows the acess to peripheral perfusion (van Genderen *et al*., 2012) and is a reliable tool for detecting hypoperfusion (Lima *et al*., 2002; He *et al*., 2015). In humans, values inferior to 1.4% indicate hypoperfusion (Lima *et al*., 2002). In dogs, the relationship between peripheral PI and peripheral perfusion is unknown (Teixeira *et al*., 2018). PVI is measured by the pulse oxymeter probe attached to the animal`s tongue (Sano *et al*., 2018). Pulse pressure and stroke volume variations vary according to the tidal volume for any preload condition, but may not be reliable in cases of arrhythmias and spontaneous breathing activity (Mark, 2010).

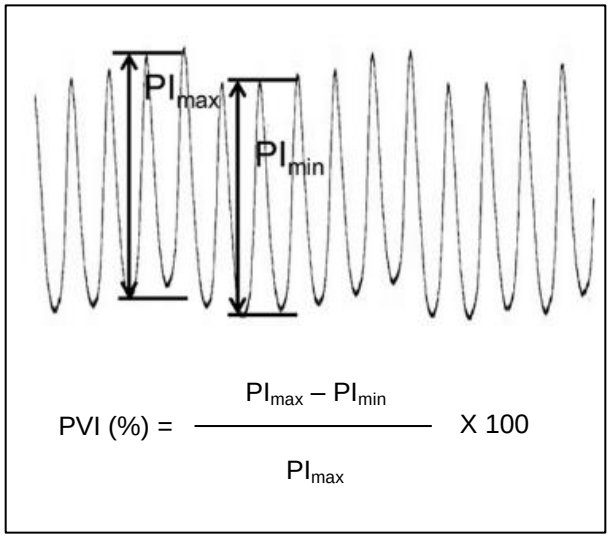


Figure 6 – Plethysmography waveform (adapted from Sano *et al*., 2018).

PPV and PVI are measurable in veterinary practice and refer to arterial blood pressure variation and plethysmography waveforms of the pulse oximeter, that derives from respiratory changes and beat-to-beat oscillations in stroke volume, due to intrathoracic pressure changes caused by positive pressure ventilation (Sano *et al*., 2018; Paranjape *et al*., 2019; Celeita-Rodríguez *et al*., 2019). PPV is obtained directly by the bedside monitor linked to the artherial line (Sano *et al*., 2018; Paranjape *et al*., 2019) and is considered to be the most sensitive an speficic of these dynamic predictors, by detecting hypovolaemia and predicting cardiovascular changes after fluid administration (Drozdzynska *et al*., 2018). PPV expresses the difference between maximum and minimum pulse pressure that occurs within one respiratory cycle, divided by the mean of these values and is expressed as a percentage (Figure 7) (Drozdzynska *et al*., 2018).

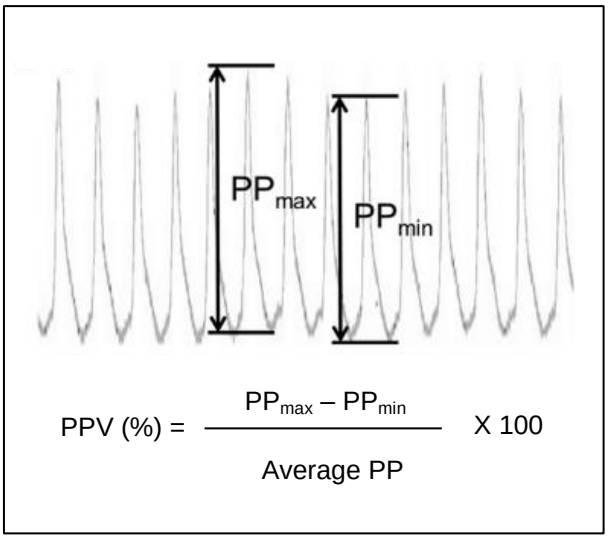


Figure 7 – Arterial blood pressure waveform (adapted from Sano *et al*., 2018).

Macrocirculation can be evaluated by certain parameters - mentation, mucous membrane color, capillary refill time, heart rate, blood pressure and plasma lactate concentration – and should be assessed and normalized in first place (Salcedo *et al*., 2016). However, these routine parameters may not be enough to detect occult hypoperfusion (Putnam *et al*., 2007). Microcirculation can vary according to tissue oxygen comsuption or delivery and distribution of blood flow to the capillaries (De Backer *et al*., 2010).

In human medicine, the access to PPV and PVI is associated to lower fluid administration, and it is thought that the same happens in veterinary medicine, being reported that these variables decreased with volume expansion and increased with decreased blood volume in mechanically ventilated anesthetized dogs. Hypovolemia and hemorrhage increase intrathoracic pressure, compressing intrathoracic veins, oscillating stroke volume and arterial pressure, therefore increasing PPV and PVI. Nevertheless, in small animal practice the volume acessment throught PPV and PVI has not been reported in nonhemorragic conditions (Sano *et al*., 2018). This study, conducted by Sano *et al*. (2018), showed that in responders, PPV and PVI were higher before the fluid challenge, and stroke volume and cardiac index were lower. After the fluid challenge, variations in heart rate, systolic arterial pressure, diastolic arterial pressure, arterial pressure mean, stroke volume, cardiac index, PPV and PVI were superior in responders, but the CVP were greater in nonresponders. PVI showed to be more executable in veterinary practice since it does not require arterial catheter, being a noninvasive tool. In anesthetized euvolemic hypotensive dogs, rapid high volume administration of isotonic crystalloids or colloids did not improve arterial blood pressure, meaning that blood pressure is not the best predictor of the hemodynamic response to fluids administration. Some limitations of this

study are related to the impact on the values dynamic parameters because of irregular pleural pressure caused by spontaneous respiratory effort during mechanical ventilation (Sano *et al*., 2018).

A study conducted by Drozdzynska *et al*. (2018) in small animal was the first in the veterinary field that established success rate of PPV and suggested PVI cut-off value. It was possible to predict a cardiovascular fluid responsiveness in 82.8% of the dogs undergoing abdominal surgery, with a PPV of ≥ 13%. After the bolus administration, the majority of responders were normotensive, suggesting that PPV is able to an ealier optimization of intravascular volume, since it allows the detection of hypovolaemia before hypotension occurs and, therefore prevent cardiovascular decompensation. It was suggested the value for PVI ≥ 13% to differentiate responders from non responders.

Endo and colleagues (2017) reported threshold values of 16% to PPV, with 71% of sensitivity and 82% of specificity, and 12% to PVI, with 78% of sensitivity and 72% of specificity, being a reliable index to predicted fluid responsiveness in mechanically ventilated sevoflurane-anaesthetized hypovolemic dogs. Therefore, increases in 16% of PPV and in 12% of PVI are associated with CO decrease during hypotension or haemorrhage. These values can be used to predict fluid responsiveness in dogs. However, further clinical trials are needed to confirm these threshold values.

In a study conducted by Celeita-Rodríguez and colleagues (2019) in anesthetized mechanically ventilated dogs, PPV demonstrated to be more accurate in discriminating responders from nonresponders to volume expansion than PVI. In this investigation, there were compared several dynamic and static preload indexes, in order to evaluate their ability as fluid responsiveness predictors (Figure 8).

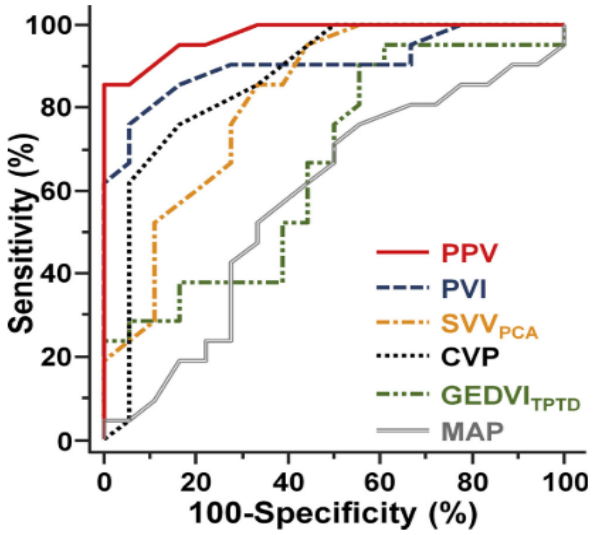


Figure 8 - Comparison of dynamic and static preload indexes used to predict fluid responsiveness in anesthetized mechanically ventilated dogs. MAP, mean arterial pressure; PPV, pulse pressure variation; PVI, plethysmographic variability index; SVVPCA, stroke volume variation measured by pulse contour analysis; CVP, central venous pressure; GEDVITPTD, global end-diastolic volume index measured by transpulmonary thermodilution (Celeita-Rodríguez *et al*., 2019).

6.3. End expiratory occlusion test

Each insufflation during mechanical ventilation increases intrathoracic pressure and reduces the systemic venous return. The end expiratory occlusion (EEO) test is performed by interrupting mechanical ventilation during 15 seconds, at the end of expiration, which will suppress the cyclic decrease in cardiac preload (Figure 9). The consequent cardiac preload increase is used to predict fluid responsiveness (Mark, 2010; Silva *et al*., 2013; Monnet *et al*., 2012; Monnet *et al*., 2009). This test basically consists in comparing cardiac index before and during the expiratory occlusion (Silva *et al*., 2013). After a fluid challenge, responder patients have shown a cardiac output increase above 15%, an increase of arterial pulse pressure and pulse contour cardiac output, in response to EEO test. With non responders, the pulse pressure and cardiac output are not significantly affected, however just about 5% are enough to predict fluid responsiveness (Mark, 2010).

The effects of EEO test can be explained by some events. Before the expiratory hold insufflation, it will increase intrathoracic pressure, inducing cyclic decreases in venous return (Silva *et al*., 2013). It also compresses the pulmonary vasculature, compressing intraalveolar pulmonary vessels. Adding this to the venous return decline, the left cardiac preload will decrease (Monnet *et al*., 2009). This reduction is also influenced by the tidal change in alveolar pressure and the lung compliance. The higher these determinants are, the higher the changes in intrathoracic pressure and thus the higher the impediment to venous return before EEO test, which allows a wide increase in venous return (Silva *et al*., 2013; Monnet *et al*., 2009). After the occlusion of the ventilation, at the level of positive end-expiratory pressure (PEEP), the cyclic venous return impediment is interrupted, leading to the maximum of the right cardiac preload (Gavelli *et al*., 2019). If there is preload dependence, this evolution will affect cardiac index (Silva *et al*., 2013), since this increase will be transmited to the left side of the heart, leading to an intensification in stroke volume and cardiac output (Gavelli *et al*., 2019).

One advantage of the EEO test is that it can be apllied in situations where dynamic tests, such as PPV and stroke volume variation (SVV), can be doubtful, such as cardiac arrhythmias and low tidal volume (Mark, 2010; Monnet *et al*., 2006), since its duration encompasses several cardiac cycles (Monnet *et al*., 2009). A study conducted by Silva *et al*. (2013) demonstrated the reliability of the EEO test in human patients with acute respiratory distress syndrome, a situation where PPV and SVV cannot be used, because of the low lung compliance and low tidal volume of mechanical ventilation, that limit its effects on the intramural pressure of the cardiac chambers.

It has been proposed to include EEO test as a predictor of fluid responsiveness at the bedside (Mark, 2010), however its limitations are not yet reported. Some studies reveal that the EEO test is valid even when the compliance of respiratory system is low. Although, it could limit the transmission of the airway pressure to the pleural spaces and cardiac chambers (Silva *et al*., 2013).

In veterinary medicine, Bouchacourt and colleagues (2020) performed a study with rabbit model of hemorrhage, demonstrating the advantage of the EEO test as a predictor of fluid responsiveness during hypovolemia. However, further studies are necessary to include this method as a convencional monitor of the volume status.

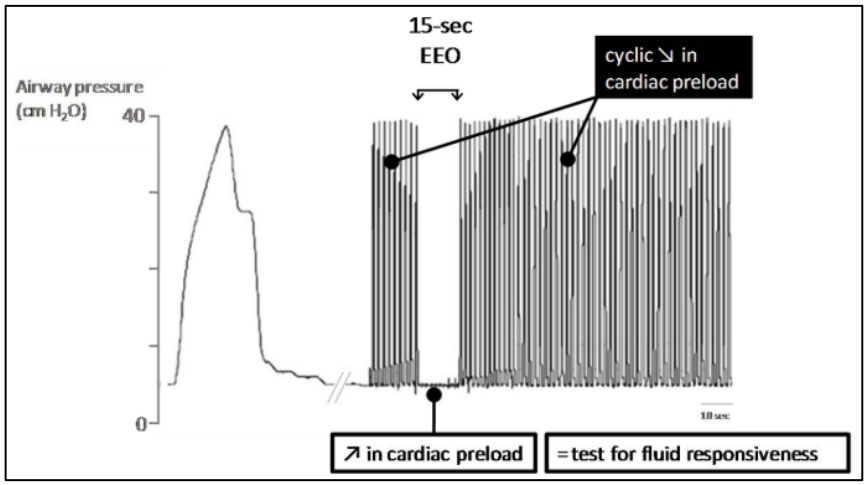


Figure 9 – End-expiratory occlusion test (Mark, 2010).

6.4. Passive leg raising

Passive leg raising (PLR) is a technique used for predicting volume responsiveness, when there is spontaneous breathing activity. It consists on mimetizing a rapid fluid loading (Lafanechère *et al*., 2006), by lifting the lower limbs, inducing a gravitational shift of blood to the intrathoracic compartment, which increases the left cardiac preload and, therefore, increases left ventricule ejection time, pulmonary artery occlusion pressure and venous return (Mark, 2010). The pulmonary artery occlusion pressure is obtained from a catheter in a large branch of the pulmonary artery, in which there is an inflated balloon, that creates a column between it and venous blood flow, reflecting the pressure in a large pulmonary vein and thereby the left atrial pressure (Teboul & Monnet, 2008). It was first demonstrated that after a fluid infusion there was an increase in thermodilution stroke volume, because of the increase in arterial pulse pressure induced by PLR (Mark, 2010).

The maneuver should start from semirecumbent position, in order to induce a sufficient increase in cardiac preload, and induce the transfer of blood from the legs and the abdominal compartment (Monnet & Teboul, 2010), when placing the lower limbs to 45° (Figure 10). One of the major advantages of this method is that by lowering the limbs to horizontal position, the effects are reversed (Mark, 2010). Another benefit is that it can be used in situations where PPV or PVI are not predictive tools, such as when there are cardiac arrhtythmias, spontaneous ventilator triggering, low tidal volume ventilation and low lung compliance (Monnet & Teboul, 2008; Paranjape *et al*., 2019).

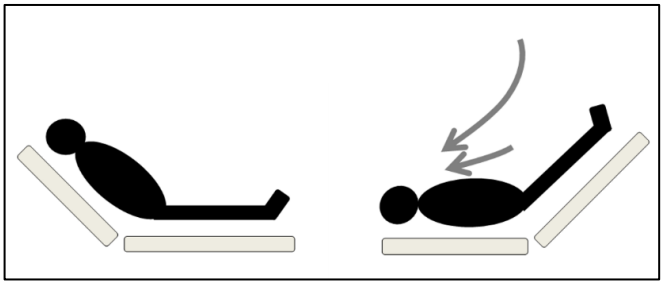


Figure 10 – Passive leg raising (Mark, 2010).

The first minute of leg elevation is when the hemodynamic effects of PLR are maximal, so the access to hemodynamic effects should be around 30-90 seconds after the onset of the test (Monnet & Teboul, 2008) and it is important that it is done in real-time (Mark, 2010). However, the echocardiographic methods used to predict responsiveness to volume administration - esophageal Doppler to measure aortic blood flow, transthoracic echocardiography to measure velocity-time integral and arterial Doppler to measure femoral artery flow – do not allow a real-time monitoring since it is operator-dependent (Lafanechère *et al*., 2006; Mark, 2010). Upon this, to acesss the cardiac output on a real-time basis, techniques such as thermodilution pulmonary artery catheter, transpulmonary thermodilution, pulse-contour analysis and bioreactance can be used. By using transpulmonary thermodilution to measure pulse-contour-derived stroke volume, it is possible to predict volume responsiveness in mechanically ventilated patients with spontaneous breathing activity when there is an increase of more than 10% in cardiac output after a PLR maneuver. Bioreactance cardiac output measurement comprises a high-frequency sine wave generator and electrodes to establish electrical contact with the patient. An oscillating current is generated that goes through the thoracic cavity, and it is analysed its relative phase shifts (Mark, 2010).

To evalute the PLR effects, there must be used direct measures of cardiac output or stroke volume. In spontaneously breathing patients, when it is only used arterial pulse pressure, it is not sensitive enough to detect changes in stroke volume (Mark, 2010).

The PLR challenges Frank-Starling relationship by inducing change in preload. If the cardiac preload increase results in a large growth of stroke volume (Figure 3), the patient is likely to be fluid responder. If there is a small amplitude in the increase of stroke volume, there may be no preload responsiveness and fluid administration should be avoided (Monnet & Teboul, 2008).

In veterinary, this method has been studied in isoflurane-anesthetized healthy pigs, in an attempt to predict fluid responsiveness. The choice of these animals has to do with the physiologic, anatomic and pathological similarities among them with human and canine species, particularly with regard to cardiovascular function (Paranjape *et al*., 2019). Paranjape *et al*. (2019) conducted an experimental study in which blood volume of mechanically ventilated pigs was manipulated to change the status from normovolemia to hypovolemia and hypervolemia. The hemodynamic variables measurement took place before and 3 minutes after a modified PLR, and 1 minute after the return of

the pelvic limbs to horizontal position, after raising them along with caudal portion to 15º inclination (Figure 11). Hypovolemic state was achieved by a controlled hemorrhage through a catheter placed in the left femoral artery, and the normovolemia was restablished by replacement of the total volume blood removed, through the left jugular vein. The hypervolemic state was reached with the administration of a 500 mL bolus of a colloid solution. It was considered as fluid responders, defined as a threshold of 15 % increase in cardiac output and a 15 % decrease in PVI between the moment before and 3 minutes after the modified PLR manouver. An increase of more than 30% in cardiac output was shown and a decrease in PPV and PVI, when the pigs were hypovolemic, whereas when they were normovolemic or hypervolemic there was no variation of hemodynamic parameters. When returning to the horizontal position, cardiac output and PPV immediately returned to the values before PLR, but the PVI was slower to respond. CVP did not vary significantly with the transitions between different volemia states. There are some limitations to be considered in this study, such as small sample size and the times of the data acquisition, that were arbitrary chosen since there was no pilot data to guide these decisions. It is necessary to further research to validate the PLR to predict fluid responsiveness in clinically ill animals, given the difficulty at the achievement of a standardization of the PLR technique to be applied in veterinary field, due to the wide variability in size, pelvic limb conformation and blood volume across species. However, this study suggests that it is a tool that can be useful for identification of hemodynamically unstable animals that are likely to respond to fluid therapy.

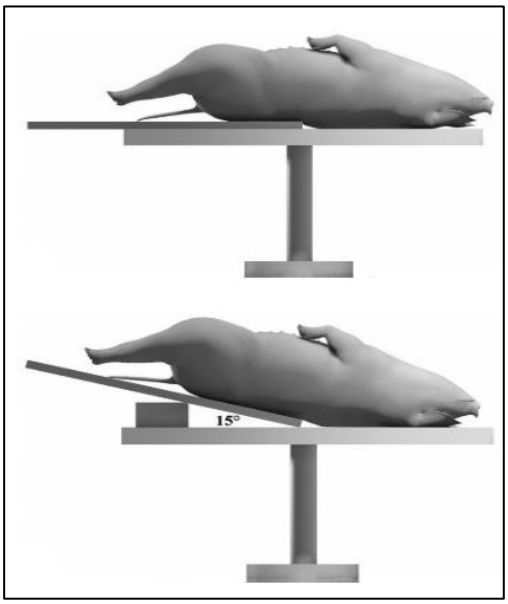


Figure 11 – Performance of modified PLR in pigs (adapted from Paranjape *et al*., 2019).

6.5. Veterinary Point-of-Care Ultrasound

Veterinary Point-of-Care Ultrasound (VPOCUS) is a tool that allows hemodynamic assessments to be performed through echocardiography, in order to evaluate the state of fluid volume and to contribute to a better adjustment of the fluids administered (Boysen, 2020). It has been aplied to monitor blood volume status by ultrasound markers, such as the thickness of the wall of the auricles and ventricles, the diameter of the caudal vena cava (CVC) (Boysen, 2020; Gommeren & Boysen, 2019) or the ventricular filling pressures (Ramsingh & Gatling, 2018). These ultrasound techniques have shown a high degree of correlation with PPV and CVP when acessing preload and volume responsiveness (Ramsingh & Gatling, 2018).

Caudal vena cava collapsibility index (CVCCI) can be used to predict fluid reponsiveness in spontaneous breathing human patients, and in mechanically ventilated humans and dogs (Donati *et al*., 2020). In human medicine, there are specific guidelines for inferior vena cava (IVC) diameter and collapsibility and corresponding atrial pressures (Ramsingh & Gatling, 2018). Measurement of IVC and the ratio between IVC and aorta are static index, thus having the same limitations as CVP when the purpose is to acess the volume status and fluid responsiveness. To acess a dynamic index, the IVC collapsibility has been studied, which evaluates the change in the diameter of IVC during the respiratory cycle, based on the impendance of the blood flow. In patients with positive pressure ventilation, inspiration leads to an increase of the extrathoracic vena cava diameter, while in spontaneously breathing patients, leads to its decrease (Boysen, 2020; Ramsingh & Gatling, 2018). Changes lower than 20% suggest hypervolemia while changes higher than 60% suggest hypovolemia (Boysen, 2020).

In human medicine, using Point-of-care Ultrasound (POCUS) to acess IVC diameter has shown a sensitivity and specificity of 90% in differentiating responders to no responders, following a fluid bolus. It is considered fluid responder when there is an increase in stroke volume by 10% following a fluid bolus (steep portion of the Frank- Starling curve) (Ramsingh & Gatling, 2018).

By measuring the left ventricular end-diastolic area (LVEDA) from a parasternal short axis view, it can also be determined the cardiosvascular filling pressures, and thus, predict preload status in ventilated patients (Ramsingh & Gatling, 2018).

In dogs, the normal ratio between the left atrium and the aorta should be between 1 and 1,5. Lower than 1 is suggestive of hypovolemia, and higher than 1,5 is an indicator of hypervolemia or left-sided congestive heart failure. In dyspnoic cats, a left atrial size superior to 16,5 mm is also suggestive of hypervolemia or left-sided congestive heart failure. In hypervolemic state the left ventricle will stretch, its lumen diameter will increase and its wall thickness will be decreased in end-diastole. Hypovolemic patients will have a collapse of the left ventricule, such as its lumen diameter decreased and wall thickness increased. This image of hypovolemic state is described as pseudohypertrophy,

and can be reversible with adequate fluid resuscitation (Boysen & Gommeren, 2019). Severe cases can result in an image described as “systolic obliteration”, which is when papillary muscles touch and the mitral valve enters the outflow tract (Gommeren & Boysen, 2019).

Through doppler echocardiography it is possible to estimate the stroke volume and, therefore, the cardiac output, by the calculation of velocity time integral (VTI) of the subaortic blood flow and by the area of the vessel crossed by the flow. It is reported both in human and veterinary medicine that VTI can be used as a monitor of fluid responsiveness (Donati *et al*., 2020).

In a study conducted by Donati and colleagues (2020), it was demonstrated that CVCCI could reliably predict fluid responsiveness in dogs with perfusion abnormalities. Aortic VTI was measured before and immediately after a fluid expansion. It was also measured the minimum and maximum diameter of vena cava during the respiratory cycle. The dogs included in the study had perfusion compromised. When the VTI obtained was equal or superior to 15%, the patients were considered fluid responders. Fluid administration was interrupted when there were observed 2 or more B lines in previously dry lungs, since this value is an end point of fluid ressustitation (Boysen, 2020). The concept of dry lung is related to the detection of B lines – white lines that extend vertically from the pleural line distally through the far field of the image, that move with respirations. B lines result from the fluid present in the lungs, and it is considered normal in dogs and cats if there are 1 to 3 per field (Boysen, 2020). Therefore, it suggests interstitial alveolar pathology (wet lung) (McMurray & Boysen, 2017). This information helps to understand the degree of extravascular lung water, that can help guide fluid therapy (Boysen, 2020). It was shown the greater the increase of CVC inspiratory collapse, the greater the VTI increase and thus the greater the CO after administration of fluids. It demonstrated the ability of CVCCI to quantify preload dependence. However, most of the dogs included in this study had hemorrhagic gastroenteritis, meaning that they may had hypovolemia associated due to intestinal fluid loss, and then, more likely, to respond to fluids.

Two thirds of the intravascular volume is contained in the venous capacitance system, being the CVC the largest capacitance vessel in animals, having an elastic wall that fluctuates in response to intravascular volume changes (Boysen, 2020). Negative pressure of spontaneous inspiration leads to the movement of blood from the abdominal CVC into the thoracic CVC, thus leading to a decrease of the abdominal CVC size. Positive pressure during expiration leads to the movement of blood from the thoracic CVC into the abdominal CVC (Boysen, 2020). When these changes are between 25 and 50%, they are considered normal (Figure 12, a). If they are superior to 50 %, the patient may be hypovolemic (Figure 12, b). If there are no fluctuation in the diameter of the CVC, it suggests an increase of the right atrial pressure, possible due to volume overload or right-sided heart failure (Figure 12, c) (McMurray & Boysen, 2017).

This hemodynamic acessment allows volume replacement or removal avoiding severe hypo or hypervolemic states (Boysen, 2020). Despite being poorly documented in veterinary literature, especially in cats (Boysen & Gommeren, 2019), it would easily be to put into practice as a routine in a animal clinic, as a bedside diagnostic tool to identify fluid responders and nonresponders (Donati *et al*., 2020), since the heart changes are easy to identify, it can be quickly acessed (Gommeren & Boysen, 2019)**,** is noninvasive, inexpensive, and widely available (Long *et al*., 2017).

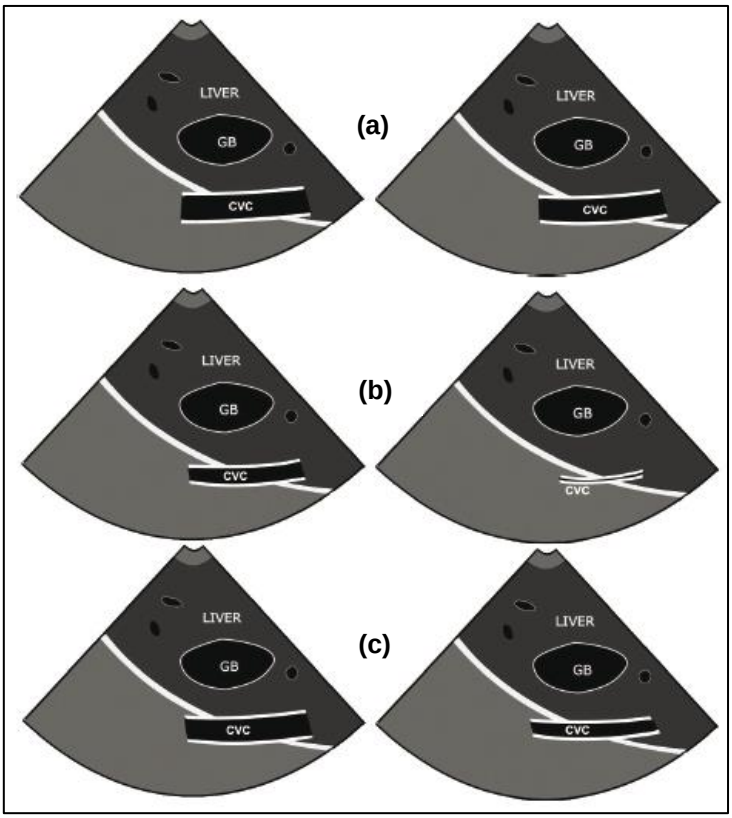


Figure 12 - Illustration of respiratory fluctuations in caudal vena cava diameter at the diaphragmaticohepatic (subxiphoid) site. (a) Normal respiratory fluctuations (25-50% change in diameter); (b) respiratory fluctuations >50%, suggesting hypovolemia; (c) absent respiratory fluctuations, suggesting volume overload or right-sided heart failure. GB, gall bladder; CVC, caudal vena cava (McMurray & Boysen, 2017).

7. FINAL CONSIDERATIONS

The knowledge of the volume status of the patient is the key to an adequate fluid management. Currently, there are still many clinicians that plan a protocol based on empirical experience. Even though there are guidelines and orientations about fluid therapy, some consensus are lacking, possibly leading to a void for the clinicians (Boysen & Gommeren, 2019).

Understanding the physiology of hemodynamic parameters that influence blood perfusion and thus cardiac output, as well as the composition of the vessel's walls, their permeability and how it influences the fluid flow is crucial to develop the clinical reasoning for a better adjustment of the therapy to be implemented.

Similarly to what is decribed in human patients, in veterinary medicine fluid overload is related to longer periods of hospitalization, longer need of mechanical ventilation, organ dysfunction and higher morbidity and mortality (Boysen & Gommeren, 2019; Paranjape *et al*., 2019). That's the reason why it is so important to stablish fluid therapy protocols, taking into mind timing, dose, rate, individual limitations, and methods to evaluate fluid responsiveness and the need of fluid removal, which can be very challeging (Boysen & Gommeren, 2019).

Some limitations of the evaluation of fluid responsiveness are related to the individual variations, which may lead to results different from the expected. It can be difficult to identify deficient tissue oxygenation due to decreased cardiac output by static parameters (Ramsingh & Gatling, 2018). NIRS, VPOCUS, PPV, PVI, PI, EEO and PLR are examples of dynamic flow predictors of hypovolemia that reveal a great utility when comparing to the parameters achieved by physical examination.

Despite the limited studies in small animal clinical practice, this review has demonstrated a generally positive result of the use of these new tools in the evaluation of fluid responsiveness in veterinary medicine, which can help guide both diagnostic and treatment methods, as well as the improvement of outcomes.

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