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Clinical investigation of plethysmographic variability index: A derivative index of pulse oximetry in anesthetized dogs

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CLINICAL INVESTIGATION OF PLETHYSMOGRAPHIC VARIABILITY INDEX:
A DERIVATIVE INDEX OF PULSE OXIMETRY IN ANESTHETIZED DOGS

For the degree of Master of Science

Is approved by the final examining committee:

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CLINICAL INVESTIGATION OF PLETHYSMOGRAPHIC VARIABILITY INDEX:
A DERIVATIVE INDEX OF PULSE OXIMETRY IN ANESTHETIZED DOGS

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of

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Vaidehi V. Paranjape

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of

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West Lafayette, Indiana

This work is dedicated to my parents. I thank them for bolstering my dreams and encouraging me to work hard towards fulfilling them. I am grateful to them for the love and care they bestowed upon me and supporting me financially, which helped me to take a step closer towards my goals.

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LIST OF ABBREVIATIONS

ΔV_{peak}	Aortic flow peak velocity
AB	Acepromazine-butorphanol
ADH	Acepromazine-dexmedetomidine-hydromorphone
AH	Acepromazine-hydromorphone
ASA	American Society of Anesthesiologists
BP	Blood pressure
CI	Cardiac index
CO	Cardiac output
CT	Computed tomography
CVP	Central venous pressure
DBP	Diastolic blood pressure
DH	Dexmedetomidine-hydromorphone
GA	General anesthesia
HR	Heart rate
ICU	Intensive care unit
IPLP	Intra-pleural pressure
IPP	Intra-pulmonary pressure
IQR	Inter-quartile range

LVSV	Left ventricular stroke volume
MBP	Mean blood pressure
Min	Minutes
MRI	Magnetic resonance imaging
NE	Norepinephrine
PCV	Packed cell volume
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end-expiratory pressure
PI	Perfusion Index
PlethV	Plethysmograph variation
PLR	Passive leg raise
PPV	Pulse pressure variation
PVI	Plethysmographic Variability Index
RR	Respiratory rate
RVSV	Right ventricular stroke volume
SBP	Systolic blood pressure
SET	Signal extraction technology
SpO ₂	Oxygen saturation of hemoglobin
SPV	Systolic pressure variation
SV	Stroke volume
SVI	Stroke volume index
SVV	Stroke volume variation
Temp	Temperature

TP	Total protein
TPP	Transpulmonary pressure
vs	Versus
V_T	Tidal Volume
VTI_{ao}	Aortic velocity-time integral

ABSTRACT

Paranjape, Vaidehi V. M.S., Purdue University, August 2014. Clinical Investigation of Plethysmographic Variability Index: A Derivative Index of Pulse Oximetry in Anesthetized Dogs. Major Professor: Jeff C. Ko.

Plethysmographic Variability Index (PVI) is a derivative index of pulse oximetry that allows evaluating an individual's intravascular volume status. Perfusion Index (PI) represents the strength of pulse signal at the anatomic site of measurement from which PVI is calculated using changes in PI over respiratory cycles. Plethysmographic Variability Index has been used to detect hypovolemia and predict fluid responsiveness in mechanically ventilated human patients however, fewer studies are available in spontaneously breathing patients. The use of PVI has not been explored extensively in dogs so far. The goals of this study were to establish a common range for PVI and assess relationship of the PVI, PI and various clinical variables in the anesthetized spontaneously breathing dogs. Values of PVI and PI derived from Masimo pulse oximetry were obtained at 5, 10, 15 and 20 minutes after anesthetic induction but before surgical stimulation together with cardiorespiratory variables that included heart rate, blood pressures (systolic, mean and diastolic blood pressures), respiratory rate and hemoglobin saturation of oxygen (SpO₂) in 73 dogs with ASA 1-3 status admitted to the Purdue Teaching Hospital.

Other clinical variables like body temperature, anesthetic protocol used, pre-induction packed cell volume (PCV) and total protein (TP) values, recumbency positions (sternal, lateral or dorsal recumbency) and rate of crystalloid fluids administration (5 vs 10 ml/kg/hr) were also obtained. Data were analysed using non-parametric Spearman's rho coefficient and Kruskal Wallis one-way ANOVA by ranks to assess temporal relationship of PVI with all the clinical variables and with significant level set at $P < 0.05$. A common range of PVI was 5-43% with a median 18%. There was no significant correlation found between PVI and PI. Plethysmographic Variability Index positively correlated with the systolic blood pressure ($r_s = 0.25$; $P < 0.001$), mean blood pressure ($r_s = 0.26$; $P < 0.001$), diastolic blood pressure ($r_s = 0.36$; $P < 0.001$) and body temperature ($r_s = 0.166$; $P = 0.004$). The other cardiorespiratory variables, recumbency positions, rate of crystalloid fluid administration, pre-operative PCV and TP values had no relationship with PVI. Premedication containing dexmedetomidine resulted in higher PVI (Kruskal-Wallis Test; $P = 0.001$) and lower PI values (Kruskal-Wallis Test; $P = 0.004$) and the opposite was true with protocols that contained acepromazine. It was concluded that while evaluating PVI for fluid response in the anesthetized dogs, various clinical factors should be taken into consideration.

CHAPTER 1. INTRODUCTION

1.1 Background and Significance

Vigilant monitoring of anesthetized and intensive care unit (ICU) patients plays a crucial role in any clinical practice. Different monitoring devices improve the quality of patient care by assessing the patient's clinical status, anticipating emergencies and formulating future diagnosis and treatment decisions. One such valuable monitoring tool is pulse oximetry. Although it has been used for many years in humans, it has gained immense popularity in veterinary practice ever since its use in dogs undergoing experimental trials in late 80's.

Pulse oximetry is a rapid, easily available and non-invasive monitoring tool to evaluate the cardiopulmonary function. It is favored due to its portability, easy handling and continuous bedside monitoring ability. It uses a two wavelength technique (infrared and red light) that estimates oxygen saturation of hemoglobin (SpO_2 ; functional hemoglobin) with infrared frequency and deoxyhemoglobin (dysfunctional part of hemoglobin) with red frequency. The absorbance of light measured at both these wavelengths has a pulsatile component which is the signal of interest and this comes from the arterial blood. Along with SpO_2 , the pulse rate which is detected by spectral analysis of plethysmographic waveform is also displayed on the screen.

The pulse oximeter technology functions efficiently under normal circumstances but it starts to demonstrate its limitations during motion artifacts, reduced pulse amplitude and ambient light, venous pulsations, poor signal-to-noise ratio, severe hypoxia or in presence of dyshemoglobins. By incorporating advanced engineering techniques, pulse oximeter analysis can be improved to overcome these limitations. The extended technology such as Masimo's Signal Extraction Technology (SET) includes morphological analysis of plethysmographic waveform to study the respiratory variations in ventricular preload which help measure Plethysmographic Variability Index (PVI).

The calculation of PVI involves Perfusion Index (PI) and is automatically and continuously calculated by the internal software inside the Masimo pulse oximeters like Radical 57, Radical 87 and Radical Rainbow 7. Perfusion Index depicts the status of peripheral perfusion and gives information about strength of pulse signal at the site of measurement. It has a wide range (0.02% to 20%) that helps to monitor the trend of circulatory perfusion in critical patients. The clinical implications of PVI include detection of hypovolemia and monitoring fluid responsiveness in mechanically ventilated patients that has helped clinicians improve fluid management by optimizing cardiac function and organ perfusion in humans.

This line of thought builds up the curiosity whether this index can be applied in assessing the fluid status in anesthetized veterinary patients. The two studies available in animals highlight the potential of PVI in identifying hypovolemia and detecting the response to fluid therapy in hypotensive patients.

However, there is a need to answer some of the basic preliminary questions regarding this index that can help us better understand its utility. Since most of the anesthetized patients in small animal practice are spontaneously breathing, there is a need to evaluate the performance of PVI in such conditions. This idea is postulated in the present study.

1.2 Specific Aims of Research and Hypotheses

- 1) To establish a common range of PVI values in spontaneously breathing dogs that are anesthetized for surgical or diagnostic procedures.
- 2) To study the relationship of PVI primarily with Perfusion Index and with other clinical variables that include heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, SpO₂ and temperature within 20 min of anesthetic induction and prior to surgical stimulation.

Hypothesis-Plethysmographic Variability Index values would be influenced by PI and other clinical variables.

- 3) To determine if the premedication drugs, acepromazine and dexmedetomidine with opioids can influence PVI values.

Hypothesis-The contrasting cardiovascular effects of acepromazine (vasodilation) and dexmedetomidine (vasoconstriction) would affect PVI values.

- 4) To determine whether pre-operative values of packed cell volume and total protein play a role in influencing the baseline PVI value which is recorded at 5 min after anesthetic induction.

Hypothesis- Pre-operative packed cell volume and total protein values would positively correlate with baseline PVI value measured at 5 min after anesthetic induction.

- 5) To observe whether different body positions (lateral recumbency vs dorsal recumbency vs sternal recumbency) cause changes in PVI values.

Hypothesis- Different body positions would affect the ventricular preload and thus lead to changes in PVI values.

CHAPTER 2. LITERATURE REVIEW

2.1 Physiology behind PVI

Fluid therapy is considered as the first step in stabilizing hemodynamically compromised patients. “How much to give?” and “When to give?” are the most commonly encountered questions in critical situations. Under-hydration and over-hydration during peri-operative period can affect tissue perfusion and cause mortality (Marik et al.,2011). Clinical studies have proven that only 50% of the hemodynamically unstable ICU patients are fluid responsive (Marik et al., 2009). Administering optimum amount of fluids in the operating theatres and ICUs has shown to improve patient outcomes, including reduced morbidity and shorter hospital stays (Gan et al., 2002). These studies are based on the physiological principle of Frank-Starling mechanism.

2.1.1 Frank-Starling Mechanism

Cardiac output (CO) is the amount of blood pumped into the systemic circulation per minute. For the body to function efficiently, the heart needs to pump blood in sufficient amounts to ensure adequate oxygen delivery to vital organs. Cardiac output is equal to the product of the heart rate (HR) and stroke volume (SV). Changes in either HR or SV can impact CO.

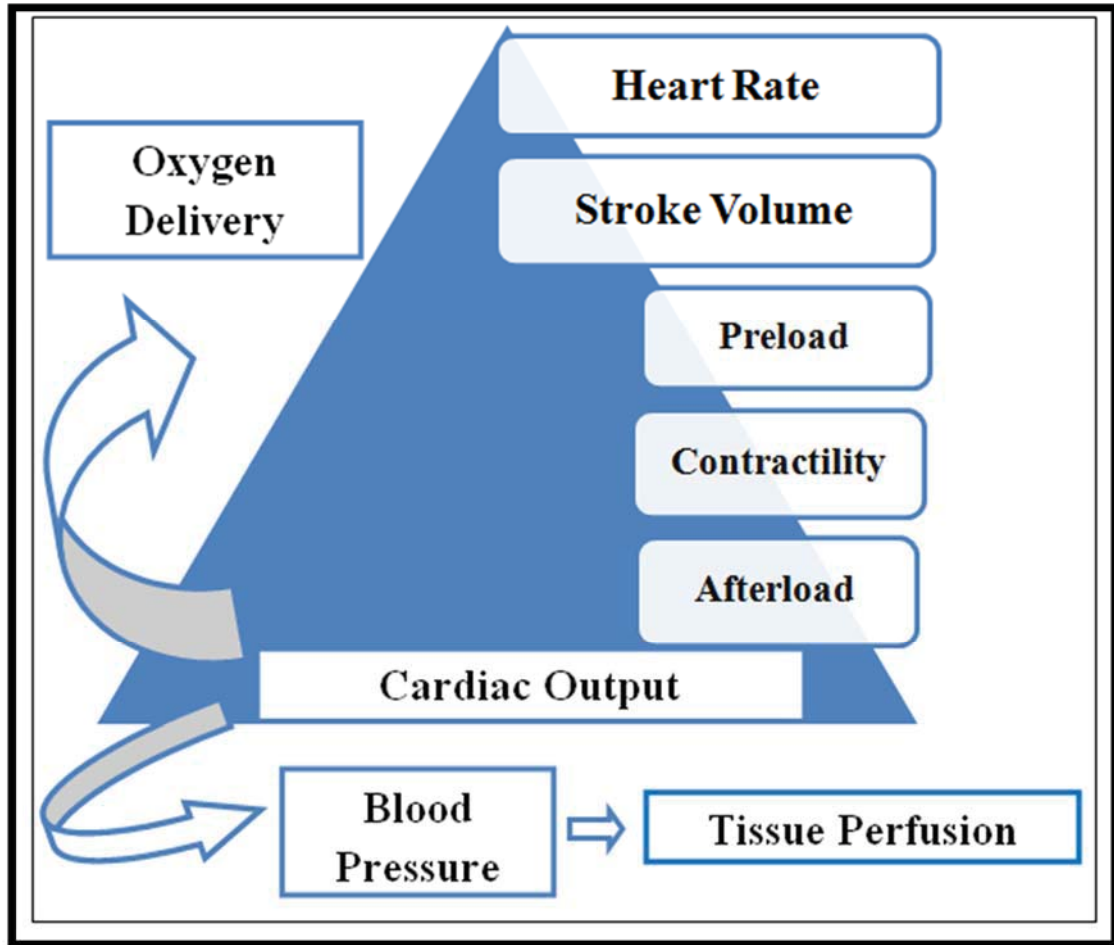


Figure 2.1. Determinants of cardiac output and its relationship with blood pressure and oxygen delivery

Figure 2.1 summarizes the determinants of CO, its relationship with blood pressure and effect on tissue perfusion and oxygen delivery. Cardiac output is determined by HR and SV (Figure 2.1) and SV is further affected by preload, afterload and contractile function. Hence, HR, preload, contractility and afterload are the determinants of CO.

An optimum cardiac output ensures good tissue perfusion and oxygen delivery to the vital organs (Figure 2.1). The interdependence of these variables is a vital concept while treating a hemodynamically unstable patient.

Ventricular preload is defined as the maximum length of the myocardial fiber at the end of diastole and hence it depicts the ventricular end-diastolic volume (Mohamed & Mullenheim, 2012). An altered ventricular preload leads to changes in ventricular contraction and SV. Preload increases when the ventricular filling and end-diastolic pressure increase as a result of increased venous return to the heart. The stretching of the myocytes causes an increase in the sarcomere length that leads to force generation, thus facilitating ejection of additional venous return and thereby increasing SV. This ability of heart to increase its systolic function, SV and CO in response to changes in ventricular preload is termed as Frank-Starling mechanism or Starling's law of the heart (Levitov & Marik, 2012). Similarly, a decrease in venous return would result in reduced ventricular filling and end-diastolic pressure and a decreased SV on Frank-Starling curve (Klabunde, 2012). This mechanism is best described by the length-tension and force-velocity relationships for cardiac muscle fibers.

In response to increased preload, the active tension developed by muscle fiber increases leading to an increase in the fiber shortening velocity at a given afterload and inotropy state.

One possible explanation to the interrelation of preload to contractile force is that an increase in the sarcomere length increases the sensitization of troponin C to calcium that further increases the activity of cross bridges and the amount of tension developed by the muscle fiber. This effect is called length dependent activation (Klabunde, 2012).

Tests that predict response to volume expansion challenge the Frank-Starling curve. These tests aid in fluid optimization in critical patients in peri-operative setting and ICUs to assess intravascular status and likelihood that a patient will respond to fluid challenge by exhibiting increase in SV (Hofer & Cannesson, 2011). Determining the cardiac preload is essential for a patient that is in shock. This is explained by preload dependence, which is the ability of heart to increase the SV in response to an increase in the volume of inflowing blood.

Graphically, the Frank-Starling curve for the heart is curvilinear as seen in Figure 2.2. The X axis is represented by preload or end-diastolic volume while the Y axis is represented by CO or SV. It comprises of two parts- a steep portion and a flat or plateau portion. Since the actin myosin linkages in a functional heart cannot be detached, there is no descending portion in this curve (Marik et al., 2011).

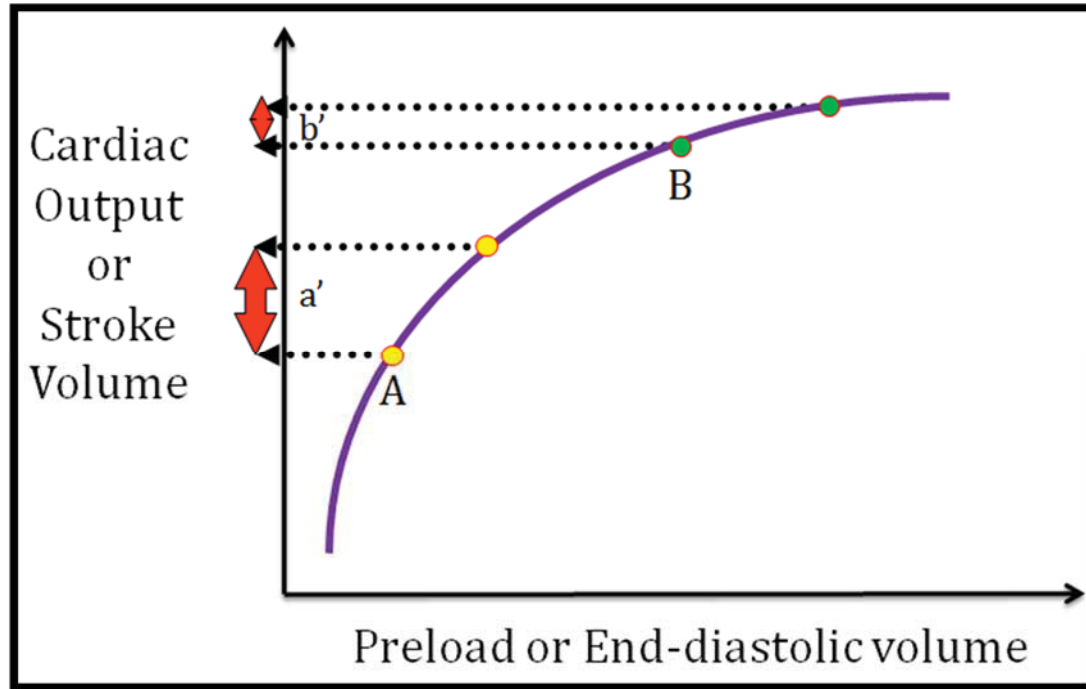


Figure 2.2 Frank–Starling curve

[X axis represents preload or end-diastolic volume and Y axis represents cardiac output (CO) or stroke volume (SV). Patient A is hypovolemic and lies on steep portion of the curve. Preload modification with fluid therapy increases CO or SV seen as a'. Patient B lies on the flat portion of the curve. An increase in left ventricular preload does not change the CO or SV seen as b'.]

The first part is called the steep part where patient A is hypovolemic and is located in Figure 2.2. Hypovolemic patients that are fluid responders have low cardiac preload and they lie on this portion of the curve. This preload dependent part signifies that an increase in ventricular preload with volume expansion significantly increases the CO and SV marked by a' in Figure 2.2. This further improves the oxygen delivery and peripheral tissue perfusion.

The goal is to achieve maximum contractility and ventricular end-diastolic volume. This is achievable until optimal preload is attained at which the SV remains constant. Optimal preload coincides with maximum overlap of actin myosin myofibrils (Marik et al., 2011). In a normal functioning heart, both ventricles lie on ascending portion of this part. This provides a preload reserve for the heart in conditions of acute stress (Braunwald et al., 1988).

The second part of the curve is the flat or plateau part on which patient B lies in Figure 2.2. Patients with impaired ventricular function with elevated preload lie on this portion of the curve. This preload independent part signifies that fluid loading to modify the preload will have negligible effect on the SV and CO seen as b' in Figure 2.2. This would mean no further improvement in the oxygen delivery and peripheral tissue perfusion. Fluid challenges administered to fluid non-responders with one of their two ventricles or both lying on this flat part cause adverse effects increasing the risk of mortality.

Depending upon the ventricular contractility function, a family of Frank-Starling curves are possible for a given preload that may be located on the steep part for a patient or on the flat part for another. These family of curves are defined by afterload and inotropy of the heart. An increase in afterload or decreased inotropy would shift the curve down and to the right. On the other hand, a decrease in afterload and increased inotropy would shift the curve up and to the left (Klabunde, 2012). Hence, a single curve cannot predict the absolute measure of a preload.

The best way to predict fluid responsiveness utilizes this important concept and tests the intrinsic ability of the heart to respond to fluid loading by making transient modifications in ventricular preload. This can be achieved using effects of mechanical ventilation on venous return (Slama & Maizel, 2011).

2.1.2 Heart-Lung Interactions

Functional hemodynamic monitoring refers to evaluation of cardiovascular stability using ventilation induced cyclic changes in the loading conditions of right and left ventricles, measured by physiological variables like pulse pressure variation (PPV) and stroke volume variation (SVV) (Hofer & Cannesson, 2011). To understand this idea better, it is important to study the cardiopulmonary interactions that form the basis of accurate hemodynamic monitoring. Spontaneous breathing as well as mechanical ventilation can affect cardiac performance by contributing to circulatory changes like venous return and diastolic cardiac filling and ejection (Pinsky, 2007; Hofer & Cannesson, 2011). These changes may be aggravated in disease conditions.

During spontaneous inspiration, expansion of lungs and diaphragm causes negative swings in intra-pulmonary pressure (IPP) and intra-pleural pressure (IPLP) resulting in the air being drawn in. This further decreases the right atrial pressure causing increased venous return and preload of the right ventricle. This causes a movement of intra-ventricular septum into the left ventricle which further decreases the left ventricular end-diastolic volume, left ventricular diastolic compliance and left ventricular preload (Pinsky, 2007). The outcome of this is reduced left ventricular stroke volume (LVSV).

The summary of these events is illustrated in Figure 2.3 in the form of a flow diagram. Vigorous inspiratory efforts will augment the IPP swings. During expiration, IPP and IPLP increase and reduces these effects (Pinsky, 2007; Hofer & Cannesson, 2011).

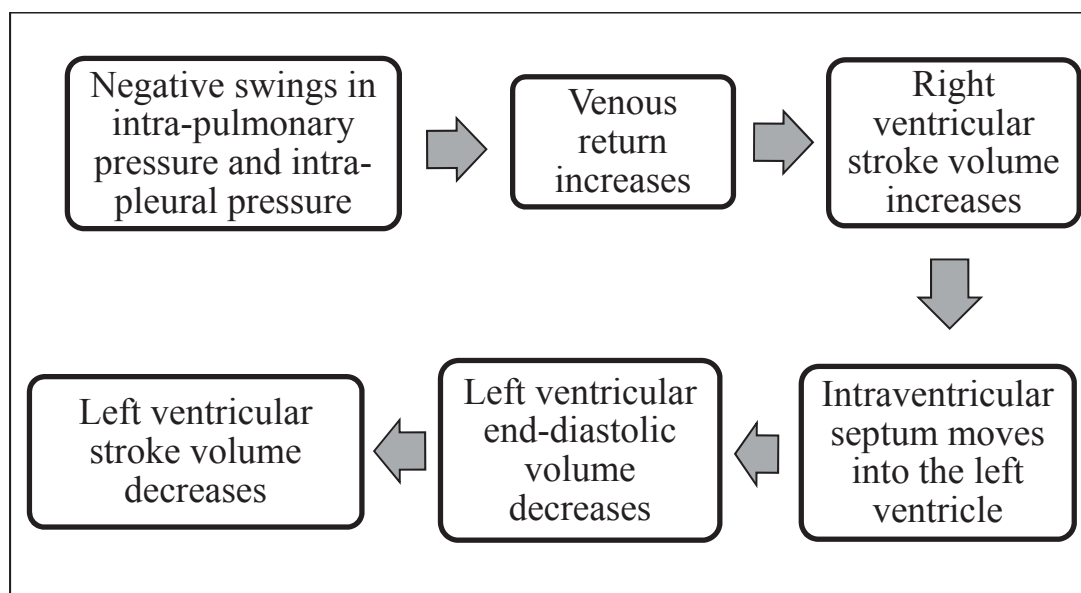


Figure 2.3. Summary of heart-lung interactions occurring at inspiration during spontaneous breathing

On the other hand, mechanical ventilation uses an opposite principle creating a positive pressure inside the ventilator, thus pushing the respiratory gas into the lungs. This is well understood by looking at Figure 2.4. As seen in Figure 2.4, during insufflation, there is a decrease in venous return pressure gradient that is related to an increase in IPP. On the other hand, on expiration, a decrease in the IPP causes an increase in venous return.

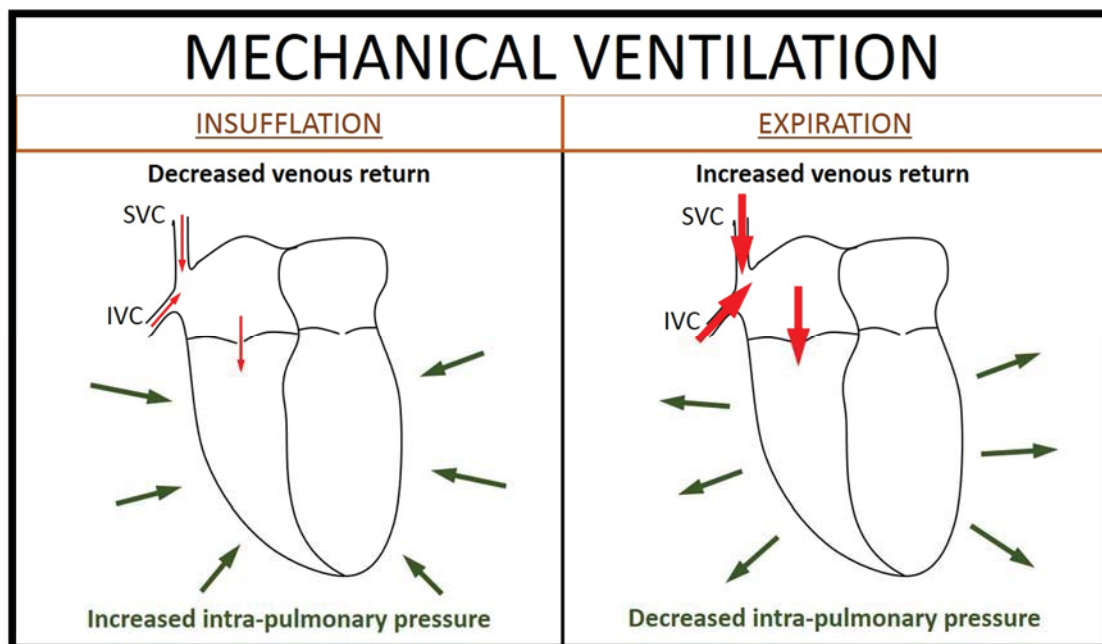


Figure 2.4. Variations of intra-pulmonary pressure induced by the mechanical ventilation during insufflation and expiration and its effect on venous return

[During insufflation (left figure), there is a decrease in venous return pressure gradient (small red arrows) that is related to an increase in IPP (green arrows). During expiration (right figure), a decrease in the IPP (green arrows) causes an increase in venous return (big red arrows)]

During mechanical ventilation, a chain of hemodynamic events occur as a result of variations in pleural pressure and transpulmonary pressure (TPP) as shown in Figure 2.5. An increase in pleural pressure decreases right ventricular preload and simultaneous increase in TPP increases the right ventricular afterload (Permutt et al., 1989). These two changes cause a reduction in right ventricular stroke volume (RVSV) which is at its minimum at end of inspiration (Theres, 1999).

This inspiratory decrease in RSVV and right ventricular preload with increase in right ventricular afterload causes a reduction in left ventricular preload and LVSV after a delay of 2-3 beats which is termed as the blood-pulmonary transit time (time required for the blood to reach the left ventricle) (Scharf et al., 1980). Left ventricular stroke volume is at its minimum during expiration provided the respiratory rate is within normal limits (Michard & Teboul, 2000). At this time, the pulse pressure, systolic pressure and aortic blood velocity is observed to be minimum.

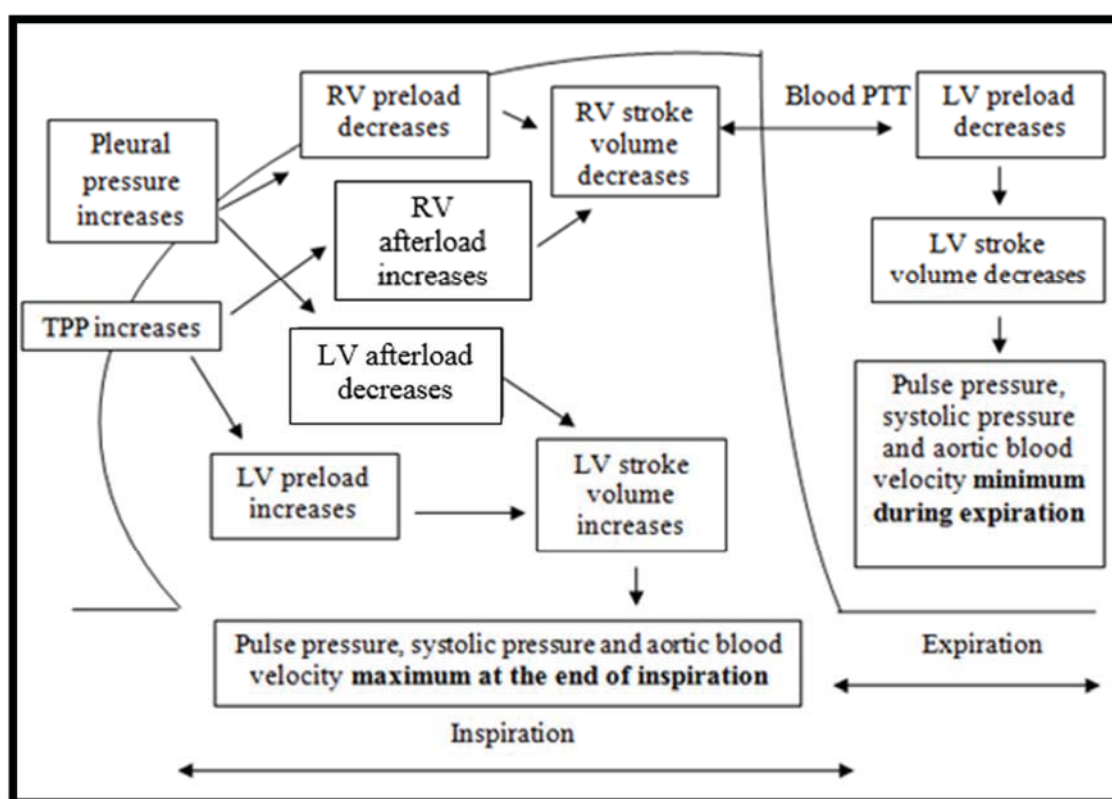


Figure 2.5 Summary of heart-lung interactions occurring during mechanical ventilation [LV-Left ventricular; RV-Right ventricular; TPP-Transpulmonary pressure; Blood PTT- Blood pulmonary transit time; events occur during inspiration (curved portion) and expiration (flat portion). Modified from Marik et al., 2011]

Sometimes, two other pathways can occur following mechanical insufflation. Firstly, in hypervolemic patients, a transient increase in left ventricular preload occurs due to the sudden rush of blood out of the alveolar vessels due to increase in TPP (Figure 2.5). In patients with left ventricular systolic dysfunction, an increase in pleural pressure during inspiration reduces the left ventricular afterload (Figure 2.5). These two occurrences contribute in minority to respiratory changes in LVSV by slightly increasing left ventricular ejection during inspiration (Michard & Teboul, 2000). To summarize, LVSV is maximum at the end of the inspiration and minimum during the expiration. The cyclic changes in LVSV are mainly related to the expiratory decrease in left ventricular preload due to the inspiratory decrease in RSV (Michard & Teboul, 2000; Marik et al., 2011).

These cyclic changes in SV are expected to be enhanced in both, left and right ventricles when they function on the steep part rather than flat part of the Frank-Starling curve. The magnitude of these changes is used as a marker of biventricular preload dependence (Mohamed & Mullenheim, 2012). This ventricular interdependence is due to series effects, augmentation of systolic function, diastolic septal interaction, pericardial constraint or a combination of these (Frenneaux & Williams, 2007). Understanding heart-lung interactions during mechanical ventilation is vital while considering volume expansion to treat the fall in preload. This concept aids in increasing the CO when the ventricles are functioning on the ascending segment of Frank-Starling curve.

Right ventricular dilation will limit the increase in CO upon administering fluid challenges if the ventricles operate on flat part of Frank-Starling curve and right ventricular ischemia develops (Smeding, 2010). The dynamic indicators of preload responsiveness like SVV, PPV, aortic blood velocity and PVI utilize these important heart-lung interactions and respiratory variations in SV during mechanical ventilation to predict fluid responsiveness in critical patients (Guerin et al., 2013).

2.2 Measurement of PVI

The introduction of plethysmography in assessment of hemodynamic function is considered a boon in the human critical care practices and health-care settings across the globe. It is a continuous, noninvasive monitoring index that is available in most contemporary pulse oximeters. The plethysmograph displays a waveform which is a representation of pulsatile changes in peripheral blood flow from which evaluations of peripheral circulation and certain systemic circulatory abnormalities can be achieved (Dennis, 2000). Plethysmographic signal that is extracted from the infrared light absorption gives rise to the displayed plethysmographic waveform. Changes in blood volume at the site of measurement expresses the pulsatile peripheral blood flow calculated in real time. Since the plethysmograph depicts the blood volume changes and direct arterial blood pressure tracing denotes pressure changes, cyclic variations in plethysmographic waveform will reflect similar changes in blood pressure tracing that will correspond to the patient's fluid volume status (Masimo, 2005b).

2.2.1 Instrument

Masimo is an Irvine, California-based medical technology company that is famous for inventing measure-through motion and low perfusion pulse oximetry and pulse co-oximetry technologies. In 2007, Masimo's SET introduced a novel concept in the field of pulse oximetry by introducing PVI, a new algorithm that could noninvasively and continuously assess intravascular fluid status of patients. This is the only company that launched three non-invasive devices namely Radical 57, Radical 87 and Radical 7 that measure the PVI (Masimo, 2005b).

2.2.2 Signal Extraction Technology

Conventional pulse oximeters employ the 'red-over-infrared' technology that are based on the assumption that the only pulsatile blood is arterial blood that is being measured at the site. However, venous blood also pulsates as it is sensitive to local effects of disturbance during patient motion. Also, venous blood significantly contributes to the total optical density during motion as it strongly absorbs light. Venous blood itself represents lesser saturation than arterial blood. Due to these reasons, conventional pulse oximeters tend to read low values during patient motion. This inability to distinguish between arterial and venous blood is sometimes termed as 'noise'. Understanding the concept of how motion affects the tissue and venous blood, Masimo's SET aims towards identifying signal from venous blood and isolating it using parallel engines and adaptive digital filters that eliminate it. Thus, a superior performance is delivered by measuring a true value in episodes of motion, low perfusion, intense ambient light and electrocautery.

Moreover, innovative sensor technology utilizes more than 7 wavelengths of light (Rainbow SET) to extract blood constituent data that depends on light absorption. The components of SET include Discrete Saturation Transform (DST) algorithm and Low Noise Optical Probe (LNOP) that provide the above advantages over conventional pulse oximetry. Estimation of PVI applies SET contributing to significant advancement in the field of pulse oximetry (Goldman et al., 2000; Masimo, 2005d).

2.2.3 Anatomic Site of Measurement

Plethysmographic signal in the pulse oximeter sensor measures changes in the light absorption of the vascular bed at the anatomic site of measurement. The changes in the infrared waveform represent the changes in the blood volume during the respiratory cycle. The most common sites of measurement for plethysmographic waveform in order to measure PVI in humans are finger, ear, forehead and foot in case of infants and neonates. The resulting waveform is influenced by the vasomotor tone and light absorption (Shelley et al., 2006).

Although most of the studies for PVI evaluation have chosen finger as the site (Cannesson et al., 2007; Cannesson et al., 2008; Zimmermann et al., 2010), there were two studies (Desgranges et al., 2011; Pavlakovitch et al., 2011) that selected finger, ear and forehead and compared the PVI values in mechanically ventilated patients undergoing surgeries. The goal of these studies was to check the accuracy of PVI to predict fluid responsiveness in alternative sites (ear and forehead) assuming they exhibited less sensitivity to changes in vasomotor tone.

Desgranges et al. (2011) concluded that the other two sites (PVI_{ear} : sensitivity 74% and specificity 74%; PVI_{forehead} : sensitivity 89% and specificity 78%) could be viable alternatives for the finger site (PVI_{finger} : sensitivity 74% and specificity 67%) in monitoring PVI however, no significant variation in PVI was observed in the three groups. Pavlakovitch et al. (2011) reported similar results stating sites on ear and forehead provided better accuracy as compared to a finger.

2.2.4 Calculation

Clinicians initially studied the plethysmographic waveform to simply check the signal processing of the pulse oximeter and assess changes in perfusion. Later on, they realized this waveform was capable of providing useful physiological information about their patients. One example of such physiological data was observing the respiratory induced changes during mechanical ventilation in the plethysmographic waveform amplitude (ΔPOP) and correlating it to PPV during the same respiratory cycle. However, the calculation of ΔPOP requires sophisticated computer software that is way too complicated. Plethysmographic Variability Index visually corresponds to ΔPOP as displayed on the pulse oximeter, however it is calculated by different means (Masimo, 2005c).

Masimo's SET pulse oximetry is the first to make PVI available commercially in practices across the globe that aids in automatic and continuous measurement of changes in respiration in plethysmographic waveform that can be picked up noninvasively by the pulse oximetry sensor at the anatomic site of measurement.

Calculation of PVI is based on PI which is displayed on most pulse oximeters including the ones using Masimo's SET (Masimo, 2005c). Perfusion Index is a relative value that depends upon the patient's clinical status and simply assesses tissue perfusion and blood flow at the site of measurement. A graphical representation of the measurement of PI is shown in Figure 2.6.

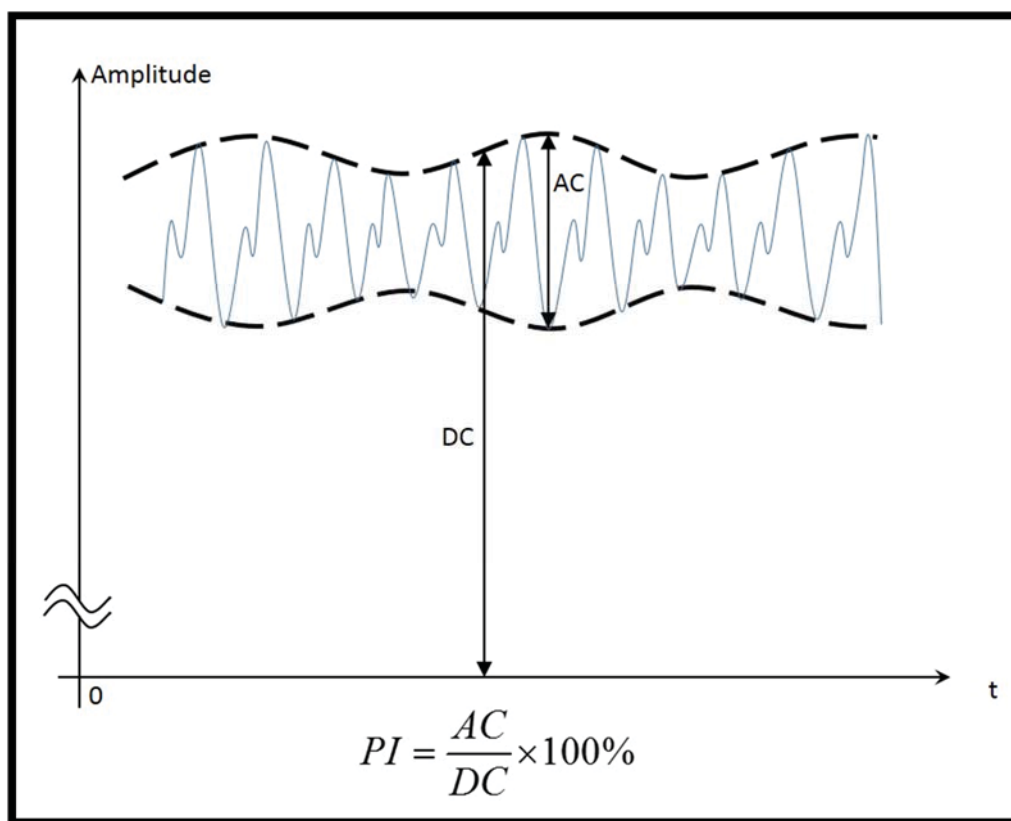


Figure 2.6 Measurement of Perfusion Index

[PI-Perfusion Index; X axis represents time (t) and Y axis represents amplitude of the waveform. Perfusion Index is a ratio of the pulsatile arterial blood fraction (AC or variable component) to the nonpulsatile blood fraction (DC or constant component). Modified from Masimo, 2005c]

Perfusion Index demonstrates the pulse strength at the sensor site as shown in Figure 2.6, it is expressed as a ratio of the pulsatile arterial blood fraction (AC or variable component) that absorbs variable amount of infrared light from the pulse oximeter signal to the non-pulsatile blood fraction (DC or constant component) which absorbs constant amount of infrared light (Masimo, 2005c). The infrared light is utilized since it is less altered by arterial saturation than red light.

The measurement of PVI involves mathematical calculations using PI. These calculations are automatically performed by the internal software installed in the Masimo pulse oximeters. The maximum PI value and a minimum PI value at several points on the plethysmographic waveform are considered, these calculations are then averaged over 2 minutes (min) and what is displayed on the pulse oximeter screen is a cumulative value of PVI over respiratory cycles (Masimo, 2005b and 2005c). Larger variation in the maximum and minimum PI values yields higher PVI values, whereas, smaller variation in maximum and minimum PI values yields lower PVI values. The respiratory variations depend upon the individual's intravascular volume status and are enhanced and better visualized when the individual is under mechanical ventilation (Masimo, 2005b and 2005c). Figure 2.7 shows how PVI is calculated from PI.

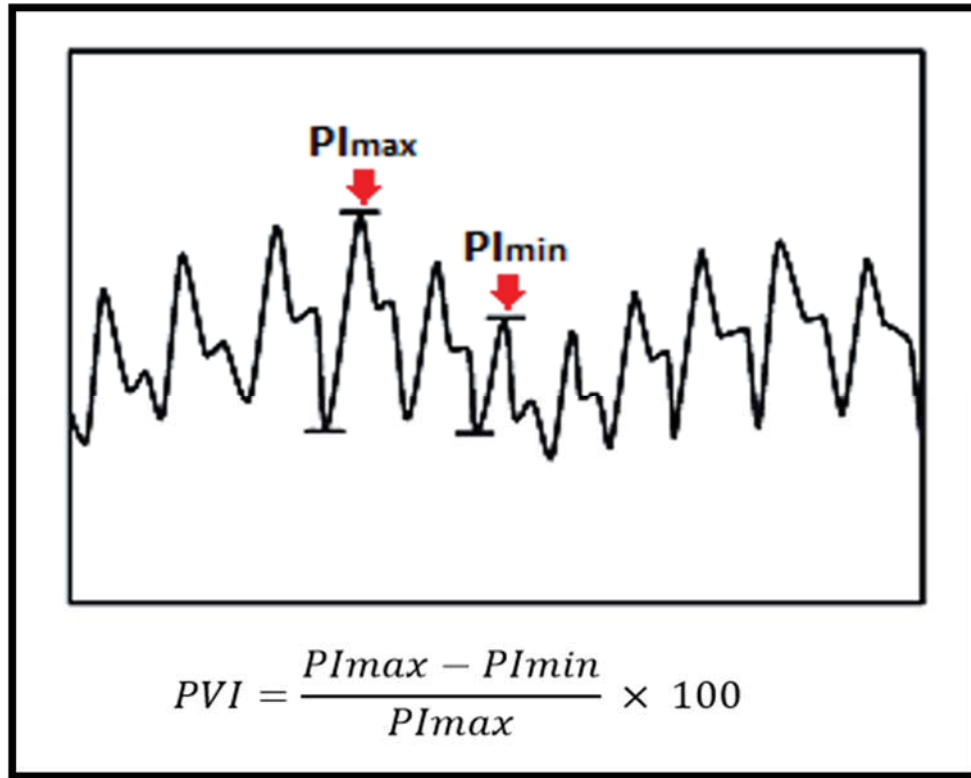


Figure 2.7 Measurement of Plethysmographic Variability Index

[PI-Perfusion Index; PVI-Plethysmographic Variability Index. The highest and lowest amplitude of the plethysmographic waveform over a respiratory cycle yields a maximum and minimum PI values. These values are used in the above mathematical formula to compute PVI. Modified from Masimo, 2005c]

As shown in the Figure 2.7, the highest amplitude of the plethysmographic waveform over a respiratory cycle yields a maximum PI value and lowest amplitude yields a minimum PI value. These maximum and minimum values are then used in the above mathematical formula to compute PVI. Plethysmographic Variability Index measures the dynamic changes in PI that occurs during a respiratory cycle and this relevant influence of PI on PVI has been published by a study (Broch et al., 2011).

Data on PVI and PI with the help of Masimo pulse oximetry was collected on 81 patients undergoing elective coronary artery surgery provided with mechanical ventilation. Patients who were seen to respond by increasing their stroke volume index ($SVI \geq 15\%$) after passive leg raise (PLR), performed with elevation of legs in the horizontal plane at 45° , were termed as responders and the ones who failed to respond to PLR were called non-responders. The data was collected before PLR (baseline), during PLR and after PLR. On the basis of their results, PLR did not induce any changes in PI. In patients with higher PI ($>4\%$), PVI displayed a marked improvement in its ability to predict changes in SVI indicating accuracy of PVI to predict fluid responsiveness increases with $PI > 4\%$. The authors attributed the low PI values to the poor pulse oximetry waveform and its interdependence with various factors such as hypothermia, hypotension, vasoactive drugs, vasoconstriction and peripheral hypo-perfusion owing to constant and prolonged contact of the pulse oximeter sensor with the anatomic site of measurement.

2.2.5 Common Values

Cannesson et al. (2008) published the first study investigating the ability of PVI to predict fluid responsiveness in the operating theatre. General anesthesia (GA) was induced in 25 mechanically ventilated patients undergoing coronary artery bypass grafting. The data recorded included cardiac index (CI), PPV, ΔPOP and PVI before and after volume expansion. A significant reduction was observed in PPV, ΔPOP and PVI after volume expansion with no significant change in PI. There was a significant relationship between ΔPOP and PVI before and after volume expansion.

Plethysmographic Variability Index value of greater than 14% before volume expansion was set as a cut off to discriminate between fluid responders (defined as increase in $CI \geq 15\%$) and non-responders with 81% sensitivity and 100% specificity.

Since this study was the first to publish data on PVI in a clinical setting, Masimo complies with these findings and states that higher the PVI value ($>14\%$) prior to volume expansion, more likely will the patient respond to fluid therapy. On the other hand, lower PVI values ($<14\%$) prior to volume expansion predicts that a patient will not respond to fluid therapy. Numerous other studies have reported different cut off values for PVI in mechanically ventilated adults and children. The cut off values for PVI in these studies vary because the human patients in these studies have undergone specific surgeries (cardiac vs abdominal vs hepatic vs cesarean sections) and are suffering from different severity of illness (septic vs ICU vs surgical patients). Also, the performance of PVI in these studies has been compared to different gold standard methods of predicting fluid responsiveness such as PPV, SVV, aortic blood velocity and systolic pressure variation.

Table 2.1 lists work of various authors who have studied predictability and accuracy of PVI in anesthetized surgical patients, ICU patients and septic patients including adults, children and neonates which were provided mechanical ventilation. The area under the curve of receiver operator curves, sensitivity and specificity along with cut off values of PVI discriminating fluid responders from non-responders is shown in Table 2.1.

Table 2.1 Studies evaluating accuracy of PVI in assessing fluid responsiveness in mechanically ventilated adults and children

Study	Patients (Number)	AUC (95 % CI)	Cut off (%)	Sensitivity (%)	Specificity (%)
Adults					
(Feissel et al., 2013)	Septic (31)	0.97 (0.83-0.99)	19	94	87
(Monnet et al., 2013)	ICU (42)	0.68 (NR)	≥16	47	90
(Haas et al., 2012)	Cardiac surgery (18)	0.95 (NR)	≥16	100	89
(Fu et al., 2012)	Retroperitoneal tumors (55)	NR	≥13.5	NR	NR
(Lahner et al., 2012)	Abdominal surgery (20)	0.67 (NR)	>8	100	44
(Broch et al., 2011)	CABG (81)	0.60 (0.47-0.72)	≥14	41	72
(Loupec et al., 2011)	ICU (45)	0.88 (0.74-0.96)	17	95	91
(Biais et al., 2011)	ICU (67)	0.80±0.06	≥11	70	71
(Desgranges et al., 2011)	Cardiac surgery (28)	0.84 (0.69-0.99)	≥12	74	67
(Hood & Wilson, 2011)	Colorectal surgery (25)	0.96 (0.88-1.00)	≥10	86	100
(Zimmermann et al., 2010)	General surgery (20)	0.97 (0.91-1.00)	≥9.5	93	100
(Cai et al., 2010)	General surgery (25)	0.93 (0.83-1.04)	≥15.5	88.2	87.5
(Desebbe et al., 2010)	CABG (21)	0.81 (0.53-1.02)	12	83	80
(Feissel et al., 2009)	Septic (43)	NR	20	84	90
(Cannesson et al., 2008)	CABG (25)	0.93 (0.83-1.03)	≥14	81	100
Neonates and Children					
(Bagci et al., 2013)	Newborns (29)	NR	≥18	86	NR
(Byon et al., 2013)	Neurosurgery (33)	0.77 (0.60-0.94)	≥11	73	87
(Renner et al., 2011)	Congenital heart surgery (27)	0.78 (0.61-0.88)	13	84	61
(De Souza et al., 2011)	Children 6-14 yr Neurosurgery (11)	0.63 (0.38-0.84)	10	NR	NR

[NR- Not reported; CABG-Coronary artery bypass grafting; ICU-Intensive care unit; Table modified from Masimo, 2005c]

2.2.6 Accuracy in Predicting Fluid Responsiveness

The accuracy of PVI as a potential index for monitoring fluid responsiveness is presented in Figure 2.8.

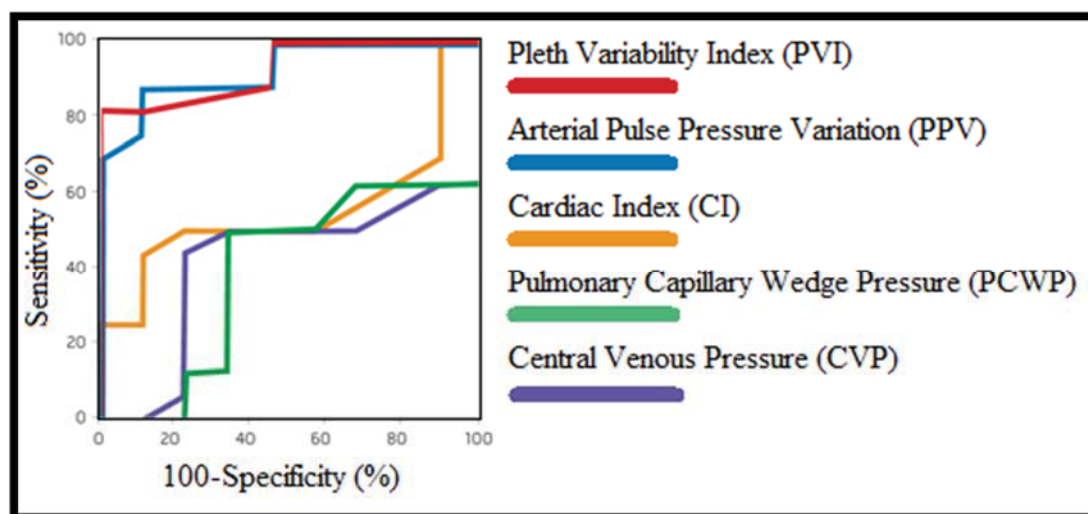


Figure 2.8 Receiver operator curves showing dynamic and static indices for predicting fluid responsiveness

[Dynamic indices are PVI-Plethysmographic Variability Index; PPV-pulse pressure variation; Static indices are CI-cardiac index, PCWP-pulmonary capillary wedge pressure and CVP-central venous pressure; Modified from Masimo, 2005c]

One of the earliest works (Cannesson et al., 2008) proposing this idea compared the areas under the receiver operating characteristic curves that plot false positives against true positives for all cut off values of various dynamic and static indices for the prediction of fluid responsiveness.

Dynamic indices included in the study and are represented in Figure 2.8 are PPV and PVI while the static indices are CI, pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP). The sensitivity and specificity of these various indices are dependent on the cut off value above or below which the test is able to accurately predict fluid responsiveness. The sensitivity depicted detection of fluid responders while specificity depicted detection of fluid non-responders. It was observed that receiver operating characteristic curves of dynamic indicators of fluid responsiveness like PVI and PPV displayed high sensitivity and specificity (represented by red line for PVI and blue line for PPV) as compared to the static indicators like CI (yellow line), PCWP (green line) and CVP (blue line). Moreover, noninvasive PVI was reported to have same accuracy as invasive PPV in monitoring fluid responsiveness and was also superior to the other invasive static indices (CI, PCWP and CVP) as shown in Figure 2.8.

2.3 Utility of PVI in Humans

Fluid therapy is the first line of treatment for patients suffering from acute circulatory failure associated with sepsis or hypovolemia. It aids in improving the cardiac output and tissue perfusion. However, volume expansion should be planned with appropriate monitoring to avoid any adverse effects related to fluid overload in such patients (Marik et al., 2011). Bedside monitoring has always been a challenge in diagnosing these adverse effects (Hofer & Cannesson, 2011). The utility of Masimo's noninvasive and continuous pulse oximetry device has been proved helpful in studying the respiratory variations in plethysmographic waveform using a novel algorithm termed PVI.

A good example of clinical utility of PVI was a studied by a group of authors (Cannesson et al., 2008) who reported a significant reduction in PVI values seen in fluid responders over a period of 10 min of fluid administration. Plethysmographic Variability Index value as high as 21% at baseline (before fluid therapy) was detected in a fluid responder. This value decreased slowly over the 10 min period to 9%. In the fluid non-responders, baseline PVI value of 9% reduced progressively to 6% by the end of volume expansion indicating no significant change. This experiment showed the ability of this index to detect the change in an individual's intravascular volume status following fluid administration.

2.3.1 ICU Patients

A study (Loupec et al., 2011) investigated the performance of PVI in monitoring fluid responsiveness in 40 mechanically ventilated patients with circulatory insufficiency admitted in the ICU. Increase in $CO \geq 15\%$ after a fluid challenge with hydroxyethyl starch over 10 min was an indicator of fluid responsiveness. They documented 21 patients as responders and 19 patients as non-responders. Plethysmographic Variability Index and PPV were significantly higher in responders as compared to non-responders. With a sensitivity of 95% and specificity of 91%, PVI value of 17% was set as a cut off to differentiate responders from non-responders. It was further concluded that a higher baseline value of PVI correlated with a higher percentage of improvement in cardiac output after fluid loading.

Another study (Biais et al., 2011) explored the possibility of vasopressive drugs like norepinephrine (NE) administered to ICU patients affecting the PVI assessment. At the same time they also studied the correlation between PPV and PVI. In 67 mechanically ventilated patients in the ICU that were administered NE, $PVI > 11\%$ established a relation with patients with a $PPV > 13\%$ with a sensitivity of 70% and a specificity of 71%. It was concluded that administering NE affected the correlation between PVI and PPV along with altering the ability of PVI to predict $PPV > 13\%$ in ICU patients.

A group of authors (Bhismadev et al., 2012) investigated the role of PVI in neurosurgical ICU in order to suggest a cut off value of fluid responder (patients who increased their aortic velocity-time integral (VTI_{ao}) that was calculated by transthoracic echocardiography by greater than or equal to 15%. The cut off value of PVI was observed to be 15% (sensitivity 78% and specificity 72%). On the other hand, Bridges (2012) was the first to study the reliability of PVI in assessing fluid responsiveness during the resuscitation of severely injured combat trauma patients. Plethysmographic Variability Index was seen to correlate with systolic pressure variation (SPV) and PPV. Plethysmographic Variability Index value of 15.5% was seen to discriminate fluid response status for SPV (sensitivity 83% and specificity 92%) and PPV (sensitivity 77% and specificity 97%).

Monnet et al. (2013) inspected the reliability of PVI for predicting fluid responsiveness in patients receiving NE infusions. They reported a baseline $PVI \geq 16\%$ that could predict fluid responsiveness with a sensitivity of 47% and specificity of 90% in 42 critically ill patients assisted with mechanical ventilation. The reliability of PVI was found to be lesser than PPV and SVV for predicting fluid responsiveness in critically ill patients receiving NE. Also, the plethysmographic signal was untraceable on the pulse oximeter for a significant proportion of patients suggesting PVI lacks utility in patients receiving NE.

2.3.2 Septic Patients

Circulatory derangements are always seen in patients presented with septic shock that lead to hypovolemia and tissue hypoperfusion. These two factors finally lead to multi-organ dysfunction. Hence it is important to detect sepsis and its sequels at the right stage and treat it with necessary interventions to avoid its progression to multi-organ dysfunction. Hemodynamic monitoring plays an important role in identifying septic patients and monitoring their response to therapy.

A few clinicians planned a series of studies (Feissel et al., 2009 and 2013) to inspect if plethysmographic waveforms could be used with accuracy in monitoring fluid responsiveness in septic mechanically ventilated patients. In 2009, they tested the ability of PVI extracted from Masimo's pulse oximeter as a new parameter for assessing fluid responsiveness in patients suffering from septic shock. Fluids were infused in patients that exhibited $PPV \geq 15\%$ and PLR was performed in patients that exhibited $PPV < 15\%$.

Plethysmographic Variability Index was then compared with PPV and Δ POP to find a cut off value that could predict PPV>15%. Patients who exhibited an increase in VTI_{ao} >15% in response to fluids or PLR were called responders. It was observed that there was a correlation between PPV and PVI, Δ POP and PVI and PPV and Δ POP. A cut off PVI value of 20% identified patients with PPV>15% with sensitivity 84% and specificity 90%. Patients with PVI>20% were termed as responders and with PVI<20% were PLR non-responders.

A recent pilot study in 2013 by the same authors looked at the feasibility of PVI in predicting fluid responsiveness in early stage of septic shock. Colloid fluids were administered in 31 septic patients which were sedated and mechanically ventilated. Those patients in whom a 15% increase in VTI_{ao} was seen were termed as responders. On this basis, 16 patients were identified as responders and 15 as non-responders. Mean PVI value before colloid administration were higher in responders ($30\pm 9\%$) as compared to non-responders ($8\pm 5\%$). Baseline PVI values correlated to percent changes in VTI_{ao} after colloid treatment. A PVI value of 19% differentiated responders from non-responders with sensitivity 94% and specificity 87% indicating this index could be conveniently used in patients in early phase of septic shock.

2.3.3 Effect of Anesthetic Drugs

General anesthetic agents and pre-anesthetics are known to induce considerable changes in sympathetic and parasympathetic tone, dynamics of blood flow and regulatory mechanisms controlling the heart and vasculature.

These events eventually affect the peripheral perfusion that further reflects changes in vasomotor tone. Most common outcome in anesthesia induced patients is hypotension. Similarly, regional nerve blockades can cause a change in the blood volume in the respective region.

A study (Allred et al., 2008) determined if PI and PVI correlated with successful regional nerve blockade in 6 adult patients receiving regional anesthesia for surgery of the lower extremities. Perfusion Index and PVI along with other parameters were recorded over 5 min prior to the block and then every minute thereafter for 10 min. It was observed that successful regional anesthesia resulting in increased perfusion could be easily detected by changes in PI and PVI. Following this work, Takeyama & Yoshikawa (2009) examined the changes in PVI during a spinal block. They attached PI & PVI sensor to upper limbs and PI sensor to lower limbs. Blood pressure (BP) was measured simultaneously. It was observed that BP decreased but PI of lower and upper limbs increased during high spinal block as a result of vasodilation and increased blood flow of upper limbs. It was thought that an increasing PI value minimized the respiratory changes of PI ($PI_{max}-PI_{min}$), thereby consequently decreasing PVI of upper limbs.

An interesting study (Tsuchiya et al., 2010) investigated the utility of PVI in evaluating volume status in propofol induced hypotensive patients. It was concluded that $PVI > 15\%$ could predict MAP decrease (>25 mmHg) with sensitivity 79% and specificity 71% indicating PVI could identify patients at high risk of anesthesia induced hypotension.

Desebbe et al (2010) tested the ability of PVI in evaluating the hemodynamic changes in mechanically ventilated patients under GA. They suggested that PVI was affected by tidal volume and positive end-expiratory pressure (PEEP). Plethysmographic Variability Index threshold value of 12% was reported to predict hemodynamic instability induced by PEEP for tidal volume (V_T) 8 ml/kg with a sensitivity 83% and specificity 80% indicating the reliability of PVI in detecting hemodynamic effects induced by PEEP when $V_T > 8$ ml/kg in patients under GA.

Fukui et al., (2011) compared PPV and PVI as dynamic parameters of hemodynamic monitoring in 24 patients administered with epidural anesthesia. The two parameters had fair amount of bias between them before and after epidural anesthesia and were not compatible with each other. On the other hand, another study (Imai et al., 2011) investigated changes in PI and PVI of the finger (unblocked area) and the toe (blocked area) immediately after spinal anesthesia and in lithotomy position maintained throughout surgery. Perfusion Index at the toe changed in response to vasodilation after spinal anesthesia more quickly than unblocked areas due to differential vasodilation following spinal anesthesia. Plethysmographic Variability Index value at the finger and toe was unaffected after spinal anesthesia but PVI at the toe immediately decreased after patients were placed in the lithotomy position. Sebastiani et al. (2012) compared changes in the PI and PVI in both blocked and unblocked arms during interscalene nerve blocks. They inferred that PI increased after successful interscalene nerve blockade and could be used for successful block placement.

Plethysmographic Variability Index values before and after volume expansion aided in predicting fluid responsiveness in patients with both blocked and unblocked arms.

Another study (Mizuno et al., 2012) investigated the effect of propofol and other GA agents with opioid analgesics on PI and PVI in patients undergoing elective surgeries. A significant increase in PI ($2.1 \pm 1.7\%$ to $3.8 \pm 2.2\%$) and a significant decrease in PVI ($22.9 \pm 8.1\%$ to $17.1 \pm 7.2\%$) was observed that reflected peripheral vasodilation and decreased sympathetic tone during GA. A recent study (Mousa, 2013) recorded the effect of hypercapnia on PI and PVI during propofol and remefentanil anesthesia. The authors hypothesized that the vasomotor changes induced by hypercapnia could affect PI values, which in turn could reduce the accuracy of PVI. The results exhibited a significant increase in PI and a significant decrease in PVI with occurrence of hypercapnia.

2.3.4 Patients Undergoing Different Surgeries

PVI as a dynamic marker to predict response to fluid challenges has been studied in cardiac, abdominal, hepatic and various elective surgeries. The plethysmographic waveform variations correlate with the patient's intravascular volume status that aid in preventing hemodynamic instability during major surgeries.

2.3.4.1 Cardiac Surgeries

Wyffels et al. (2007) and Cannesson et al. (2007) were the first to demonstrate the use of ventilation induced Δ POP in predicting changes in CO after volume expansion in patients undergoing cardiac surgery.

Cannesson et al. (2008) proposed PVI values that could categorize the patients into fluid responders and non-responders. The study determined that $PVI > 14\%$ before volume expansion distinguished non-responders from responders with 81% sensitivity and 100% specificity. A significant relationship between PVI before volume expansion and change in CI after volume expansion was reported.

Guinet et al. (2011) tested the reliability of PVI in comparison with PPV in patients undergoing vascular surgery. Interestingly, there was no strong correlation noted between PVI and PPV and PVI did not prove to be as reliable as PPV in monitoring fluid optimization. A group of clinicians (Fischer et al., 2012) evaluated PVI as a predictive index in fluid expansion in patients undergoing conventional cardiac surgery and found it to not be reliable since it displayed a wide gray zone (12-24%). In contrast to this study, Haas et al. (2012) documented PVI to be as accurate as SVV in assessing intravascular volume status in patients after cardiopulmonary bypass. A threshold value for PVI was measured as greater than or equal to 16% with 100% sensitivity and 88.9% specificity.

2.3.4.2 Abdominal Surgeries

A study (Forget et al., 2010) inspected the role of PVI in guiding intra-operative fluid therapy, in order to reduce lactate levels by improving circulatory perfusion of patients undergoing major abdominal surgeries. Eighty-two patients were categorized under PVI group (41 patients) and control group (40 patients). It was observed that PVI directed fluid management reduced amount of total fluids and crystalloids given peri-operatively and lactate levels during and after surgery as compared to control group.

Zimmermann et al. (2010) compared accuracy of SVV and PVI in 20 patients undergoing major abdominal surgeries, before and after volume expansion. Though SVV displayed the best correlation to volume induced changes in SVI, both these dynamic indicators proved to equally predict fluid responsiveness.

Hood & Wilson (2011) recorded esophageal doppler SV and PVI measured from finger and ear sites in 25 patients undergoing colorectal resection. Intra-operatively, PVI measured from finger was seen to predict increase in SV in contrast to PVI taken from ear. Abdullah et al. (2012) compared corrected flow time of transesophageal doppler and PVI to guide fluid optimization in 60 patients. They recorded no significant differences in the amount of fluids, hemodynamic parameters and overall mortality and morbidity in between both groups. A recent study (Lahner et al., 2012) recorded a cut off value greater than 8% for PVI with sensitivity of 100% and specificity of 44% in patients undergoing major abdominal surgeries.

2.3.4.3 Hepatic Surgeries

Orthotopic Liver Transplantation (OLT) is a complicated surgery in which occlusion of inferior vena cava (IVC) and cross-clamping of the portal vein cause alterations in cardiac output leading to hemodynamic disorders. Wray et al. (2008) tested efficiency of PVI in detecting these alterations in 22 patients. Plethysmographic Variability Index successfully detected acute changes in CO in patients undergoing OLT during cross-clamping and reperfusion phases.

Similarly, Lobo et al., (2009) observed that PVI responded to preload changes during clamping and unclamping of inferior vena cava in 16 patients undergoing liver transplant operation. Plethysmographic Variability Index was seen to rapidly increase in all individuals in response to inferior vena cava clamping (11.4 ± 4.3 to 25.2 ± 4.4) and decreased in all individuals after unclamping (25.2 ± 4.4 to 8.9 ± 3.8) indicating its ability to respond to preload changes. Perfusion Index on the other hand had opposite effect as to PVI. Another study (Vos et al., 2013) compared three dynamic indices of monitoring hemodynamic optimization i.e. SVV, PPV and PVI to identify fluid changes in 30 patients undergoing hepatic resection. All three variables were seen to predict preload changes to a similar extent however, PVI failed to track fluid changes after volume expansion in these patients.

2.3.4.4 Cesarean Section

Chassard et al. (2010) investigated the strength of PVI in detecting hemodynamic derangements and hypovolemia encountered during cesarean section and the need for administering vasopressors in pregnant women under spinal anesthesia. The study was carried out in 20 spontaneously breathing pregnant women and several parameters including PVI were recorded before and after fluid administration. It was observed that volume expansion in pregnant women at term had no effect on PVI and the baseline PVI could not predict vasopressor needs following spinal anesthesia. Following this work, Yoshioka et al. (2011) and Yokose et al. (2013) carried out similar experiment and concluded that pre-operative and pre-anesthetic PVI values could predict hypotension induced by spinal anesthesia for cesarean delivery.

2.3.4.5 Miscellaneous Surgeries

The effects of laparoscopy on various dynamic variables like PVI, Δ POP, PPV and SVV were studied by a group of authors (Hoiseith et al., 2010) in order to study their response to fluid challenges. The variables were studied in 20 adults before and during pneumoperitoneum (10-12 mmHg) and their relation with changes in SV was evaluated after fluid challenge during surgery. Plethysmographic Variability Index and Δ POP were seen to increase during pneumoperitoneum. All the four dynamic variables were poor predictors of fluid responsiveness during ongoing laparoscopic surgery. Pulse pressure variation and SVV identified changes in SV successfully whereas Δ POP and PVI did not.

The effect of skin incision on PVI was investigated by Takeyama et al. (2011) on 24 mechanically ventilated patients belonging to ASA I or II who opted for elective surgeries. Perfusion Index, PVI and SVV were measured just before the skin incision and after 1 and 5 min after incision. The incision did not affect SVV but PI significantly decreased whereas PVI increased significantly from 9.5% to 13.5%. Fluctuations in vasomotor tone were seen to affect PI that significantly influenced PVI readings. Thuraisingham et al., (2012) reported that goal directed fluid therapy guided by respiratory variations in the plethysmographic waveform in moderate risk surgery patients decreased the occurrence of postoperative complications which resulted in faster recovery time, shorter hospital stays and improved patient outcomes.

Fu et al. (2012) compared the strength of SVV and PVI in 55 Hans Chinese patients undergoing resection of primary retroperitoneal tumors. Changes in SVV were seen to significantly correlate with PVI after volume expansion. A significant decrease was noted in values of SVV and PVI in fluid responders (who demonstrated increase in $SVI \geq 10\%$ after volume expansion) indicating both variables equally predicted fluid responsiveness. The best threshold PVI value to predict fluid responsiveness was noted as greater than or equal to 13.5%.

Yin & Ho (2012) carried out a systematic review and meta-analysis evaluating accuracy of PVI derived from Masimo's pulse oximeter extracting data from available literature. They reviewed ten studies and overall diagnostic odd ratio (16.0; 95%CI 5-48) and area under the summary receiver operating characteristic curve (0.87; 95%CI 0.78-0.95) for PVI was proposed to be good. Interestingly, the reason for some discrepancy was attributed to lower accuracy of PVI in spontaneously breathing or pediatric patients and to those studies that opted for preload challenges other than colloid fluids.

Delayed graft function (DGF) is known to be the most commonly encountered complication after kidney transplant. This makes intra-operative hemodynamic stabilization important in order to preserve kidney function after surgery. Jazaerli et al. (2013) explored if intra-operative PVI or CVP values could help avoid these complications. No correlation between PVI and CVP was noted and $PVI > 8.3\%$ successfully predicted occurrence of DGF.

2.3.5 Neonates and Infants

Optimum fluid resuscitation is a vital intervention in children that needs to be carefully monitored in operating rooms, pediatric and neonatal ICUs. If overlooked, it can lead to dangerous consequences such as pulmonary edema. Dynamic variables are based on heart-lung interactions induced by mechanical ventilation and are often used as potential predictors of preload changes that occur after volume expansion. Goldstein et al. (2007) produced a case study of an infant diagnosed with left congenital diaphragmatic hernia. Plethysmographic Variability Index was seen to significantly increase after all drainage taps that was attributed to the release of intrathoracic pressure.

One of the earliest work (Chandler et al., 2010) demonstrating the use of dynamic variables in monitoring preload changes in pediatric population studied the relationship between PVI, PPV and manually calculated plethysmograph variation (PlethV) in mechanically ventilated children belonging to two age groups (<2 years and 2-10 years). In younger age group, a strong correlation was seen between PVI with both PPV and PlethV while the correlation reduced between them in older age group. Other studies by Chandler et al. (2011 and 2012) compared static indices like CVP and PAWP and dynamic indices like PPV, Δ POP and PVI as predictors of fluid responsiveness in children. Surprisingly, the authors found poor correlation between static and dynamic indices to predict any changes in CO after administration of fluid bolus. They also observed a strong relationship between PVI-PPV and PVI- Δ POP.

Naguib et al. (2011) carried out a study in pediatric patients undergoing congenital cardiac surgery. They reported the need to administer lesser crystalloid replacement fluids in patients with baseline PVI<14% in contrast to patients with baseline PVI>14% in order to preserve the same hemodynamics during hemodilution. De Souza et al. (2011) found respiratory variations in aortic flow peak velocity (ΔV_{peak}) measured by doppler echocardiography as the most appropriate variable to predict fluid responsiveness in comparison to arterial pulse pressure, PPV, ΔPOP and PVI in mechanically ventilated children undergoing GA.

Another study by Renner et al. (2011) produced similar results reporting ΔV_{peak} as the best predictor of volume responsiveness in comparison to VTI_{ao} and PVI. Plethysmographic Variability Index value ($\geq 13\%$) was set as a cut off to discriminate between fluid responders and non-responders with 84% sensitivity and 61% specificity. Feldman et al. (2012) reported that PVI could not be used as an alternative for PPV in predicting preload changes in pediatric population undergoing spine fusion. They reported no variation in PVI during a change from supine to prone position in pediatric population.

The effect of patent ductus arteriosus on PI and PVI was assessed by Vidal et al. (2013) in preterm neonates. Ductal persistence and flow pattern did not influence PI but did affect PVI in preterm neonates of less than 29 weeks of gestation. Another study (Latini et al., 2012) established reference range for PVI values in spontaneously breathing newborns. The median PVI value on the first day of life was 20%.

The 10th and 90th percentile cut off values were 12% (95%CI 11–12) and 28% (95%CI 27–29), respectively, with the 97.5th percentile of 35% (95%CI 34–38).

Bagci et al. (2013) documented the median PVI value during arterial hypotension in newborns as 23% (20-25%) which after volume expansion was observed to be 16% (13-18%). Julien et al. (2013) found PVI to be accurate while predicting fluid load response during non-cardiac surgery in children. Furthermore, another study (Byon et al., 2013) compared clinical utility of static variables like CVP and dynamic variable like PVI, PPV, SVV, ΔV_{peak} and inferior vena cava diameter. Among all these variables, ΔV_{peak} and PVI were found to successfully predict fluid responsiveness in mechanically ventilated children undergoing neurosurgery. A recent review by Gan et al. (2013) analyzed several studies that investigated static and dynamic predictors of fluid responsiveness to assess their overall reliability and accuracy. Aortic flow peak velocity was the only consistent predictor in children. Static variables failed to predict fluid responsiveness in children, which was evident in adults too. Dynamic variables based on arterial blood pressure were not found to be reliable in children, whereas the documentation on plethysmography continues to be ambiguous.

2.3.6 Spontaneously Breathing Patients

Numerous studies that have closely studied the concept of heart-lung interactions during mechanical ventilation and utilized it in predicting fluid responsiveness with the help of dynamic indicators. This scenario of heart-lung interactions changes as far as spontaneously breathing is concerned.

This is majorly due to the negative cyclic changes in IPP that leads to increases in right ventricular end-diastolic volume that further decreases left ventricular diastolic compliance by the process of ventricular interdependence, which decreases LVSV. These respiratory changes can prove insufficient in modifying cardiac loading of ventricles until the respiratory variations in LVSV can be measured. Hence, it becomes difficult to predict and measure these respiratory variations in LVSV in spontaneously breathing patients as compared to mechanical ventilation (Cannesson et al., 2011; Soubrier et al., 2007). The unreliability of spontaneous ventilation aiding to define preload changes could be attributed to the variability in tidal volume or increase in intra-abdominal pressure enhancing preload changes (Backer & Pinsky, 2007). Only a few studies are available investigating PVI in spontaneously breathing patients.

Passive leg raise is a simple reversible diagnostic maneuver in which the patient's legs are elevated to desired angle such as 45° without patient's involvement (Monnet & Teboul, 2010). This allows blood to flow from the legs towards the heart, thus transiently increasing blood pressure, ventricular preloads and hemodynamic parameters like CO and SV. These effects are used to guide fluid resuscitation in arrhythmic or spontaneously breathing patients (Monnet & Teboul, 2010). Passive leg raise causes a rapid and transient increase of 300 ml in fluid volume by shifting blood volume to the central compartment. In spontaneously breathing patients, who are at a risk of developing hypovolemia, PLR can be a useful tool for assessing fluid responsiveness. It not only increases preload in normotensive subjects but also decreases peripheral vascular resistance (Monnet et al., 2006).

Figure 2.9 shows the positioning of a patient in semi-recumbent position (left) and after PLR (right) at 45° . As shown in the figure, PLR enables the transfer of blood from legs and abdominal compartments to the heart, transiently acting as an endogenous fluid challenge.

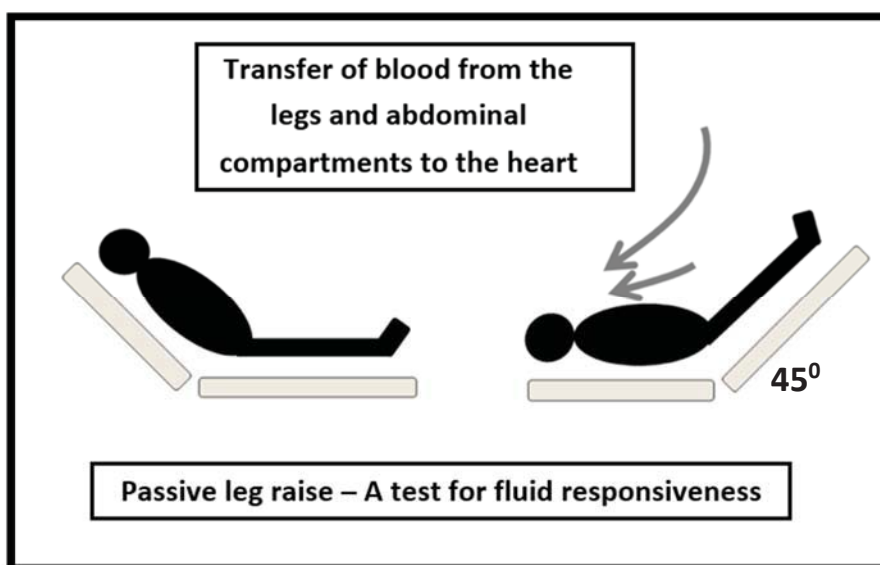


Figure 2.9 Passive Leg Raise

[Modified from Marik et al. (2011)]

One of the earliest works to determine if plethysmographic waveforms could be useful during PLR was carried out by Delorme et al. (2007). They recorded Δ POP along with other parameters in 25 spontaneously breathing volunteers at baseline (semi-recumbent position), during PLR at 60° at 1 min, 3 min and 5 min and after putting the patient back in the semi-recumbent position (5 min rest).

They observed that PLR significantly decreased median Δ POP from 16% (baseline; 95%CI=11%-23%) to 11% (during PLR; 95%CI=8%-14%) and then increased to 13% (After 5 min rest; 95%CI=10%-21%).

Following this work, Keller et al. (2008) recorded PVI and CO during and after PLR in 25 spontaneous breathing volunteers. Baseline 1 measurements were taken with volunteers in the semi-recumbent position. Then, the lower limbs were lifted straight at 45° with the trunk lowered in the supine position (during PLR), and volunteers were left in this position for 5 min. Measurements during PLR were obtained 3 min after leg elevation. A third set of measurements was recorded after 5 min of rest after returning to semi-recumbent position (baseline 2). Responders to fluid loading induced by PLR were defined as volunteers that increased their CO by 12.5% after PLR. Significant changes in CO and PVI were noted during and after PLR. A significant decrease in PVI was observed from baseline 1 to PLR at 3 min ($21.5 \pm 8.0\%$ to $18.3 \pm 9.4\%$). It then increased significantly when the volunteers were returned to semi-recumbent position (baseline 2; $18.3 \pm 9.4\%$ to $25.4 \pm 10.6\%$). A cut off value of PVI higher than 19% predicted response to PLR (sensitivity 82% and specificity 57%) but turned out to be a weak predictor of fluid responsiveness.

Further on, Schoonjans et al. (2010) compared the accuracy of PVI and PPV after PLR maneuver in determining intravascular volume status in hypovolemic patients. The parameters were recorded before and after a hemodialysis session.

PVI significantly increased after hemodialysis session (from 18% to 22%) while PPV did not alter significantly. However, both parameters were not seen to enhance the accuracy in detecting the hypovolemia induced by hemodialysis. Another study (Hoiseith et al., 2010) explored the relation between PVI and changes in SV in a hypovolemic model and observed no significant relation between them, suggesting the inaccuracy of PVI in detecting hypovolemia during spontaneous ventilation.

2.4 Plethysmographic Variability Index in Veterinary Patients

Fluid therapy is one of the most common and vital facet of patient care in ICUs and anesthetized patients in veterinary practice. Fluid administration corrects the acid-base balance, replaces essential electrolytes and improves intravascular volume status in order to prevent or treat hypovolemia and dehydration. If fluid therapy is not carefully monitored according to the needs of the patient, it can lead to deleterious effects like interstitial edema and pulmonary edema. This can worsen the patient's health and lead to high morbidity and mortality due to sheer negligence. Interstitial edema progressively affects cellular oxygen exchange and oxygen delivery and causes impaired enzyme function, cellular swelling and lysis (Mazzaferro, 2008).

Goal directed fluid therapy in veterinary practice involves using various monitoring tools to assess fluid responsiveness in patients. Traditional static indicators like CVP representing cardiac filling pressure, has been used extensively used in veterinary practice.

However it is claimed to be unreliable by many due to being a late marker of detecting changes in blood volume and its dependency on factors such as HR and ventricular function that can be altered in a diseased animal or under anesthesia (Kumar et al., 2004; Marik et al., 2008; Renner et al., 2009; and Muir, 2013). Dynamic indices like PVI have gained immense popularity in human medicine as predictors of preload changes following volume expansion.

The only available literature describing the use of PVI in animals was reported by Ricco et al. (2012) and Muir (2013). Ricco and colleagues investigated if PVI could indicate changes in circulating volume in dogs. Hemorrhagic shock was induced by bleeding in 14 beagles anesthetized with infusions of propofol and rocuronium, to achieve a mean blood pressure (MBP) of 40 mmHg. Cardiac output (thermodilution method), CVP, MAP, and PVI were recorded and calculated parameters included SVI and CI.

This data was collected at baseline (B), after hemorrhage (H), after transfusion (T) and after colloid administration (hetastarch at 20 ml/kg). After hemorrhage, PVI increased significantly from 8.9 ± 2 (B) to 21.6 ± 5.4 (H), while CI, SVI, CVP and MAP decreased. All indices returned to normal after transfusion (PVI value reduced to 8.3 ± 4.4), except CVP which was seen to increase. After colloid administration, MAP and SVI increased, and PVI decreased (5.5 ± 2.1). The authors concluded that PVI could successfully detect hypovolemia and its return to normovolemia. Since the dogs were administered rocuronium (neuromuscular blocking agent), it can be assumed that they were mechanically ventilated.

Since, this experiment was published as an abstract, it was difficult to retrieve detailed information on how the study was performed and data analysis documented during the study.

On the other hand, Muir (2013) discussed the traditional and new methods like PVI estimation in monitoring fluid therapy in animals. It gave an overview of types of hypovolemia and the dangers associated with them. Furthermore, it suggested five main considerations behind planning fluid therapy such as pre-operative fluid loss, fasting loss and insensible loss, surgical and traumatic loss along with hypotension that is most commonly encountered under anesthesia. It also recommended making protocols for perioperative fluid therapy by considering all these five factors and actually calculating the amount of fluid to be administered individually to each patient depending upon their needs.

Under evaluation of PVI in clinical cases, it presented data collected from 113 dogs and 12 cats suffering from intra-operative hypotension. Fluid boluses were administered in the form of hetastarch, tetrastarch and plasmalyte. The fluid doses were in the range of 3-15 ml/kg given over 10-15 min. PVI before (baseline) and after fluid loading was recorded. The author observed marked improvement in arterial pulse and a decrease in the baseline value of PVI. Twenty-three dogs and 3 cats were not seen to respond to these fluid challenges and had to be treated with a catecholamine like Dopamine or NE.

Although this article was one of the first to introduce an interesting modality like PVI to the field of veterinary medicine, it failed to provide a detail review on the relationship of PVI with other cardiorespiratory parameters routinely recorded in dogs and cats under anesthesia. It did not establish a common range for PVI in the 125 clinical cases and instead it considered an arbitrary cut off value of greater than 20% to depict hypotension and to treat it with fluid replacement therapy. There is no available literature or evidence to support the assumption regarding this cut off value illustrating hypotension. Moreover, no data on the blood pressure was made available in this study to confirm if hypotension coincided with higher PVI values in animals. The type of ventilation (spontaneous vs mechanical) provided and site of measurement used in these anesthetized animals was also not mentioned in this study.

Since these two references are the only evidence on PVI in animals that we have, no data on its use is available, specifically in critical patients, septic patients, spontaneously breathing vs mechanically ventilated patients, newborn and young animals. This encourages a need to carry out extensive evaluation of this clinical modality in animals that includes establishing a common range for PVI and demonstrating its relation with various clinical variables routinely recorded in anesthetized and ICU patients exposed to spontaneous ventilation.

2.5 Factors Affecting PVI

The most vital factor influencing PVI values is PI according to a study reviewed earlier (Broch et al., 2011). Since PI is a simple representation of the peripheral perfusion or the blood flow at the sensor site, factors affecting blood volume and flow will affect PI (Masimo, 2005a). The same factors can directly or indirectly affect PVI. A list of factors reviewed in the previous literature and some additional variables have been listed in Table 2.2 that can potentially affect PVI values. Factors 1-11 have been already discussed over this chapter. Table 2.2 summarizes factors studied by various authors in different studies that can potentially influence PVI values.

Table 2.2 Factors affecting PVI values

No.	Study	Factors affecting PVI
1	Broch et al. (2011)	Perfusion Index
2	Biais et al. (2011) and Monnet et al. (2013)	Norepinephrine
3	Desebbe et al. (2010) and Hofer & Cannesson (2011)	Positive end-expiratory pressure
4	Desebbe et al. (2010) and Roeth et al. (2012)	Tidal volume
5	Mousa (2013)	Hypercapnia
6	Yin & Ho 2012)	Spontaneous breathing
7	Goldstein et al. (2007)	Intrathoracic pressure
8	Latini et al. (2012)	Pulse rate
9	Backer & Pinsky (2007)	Intraabdominal pressure
10	Delerme et al. (2007) and Keller et al. (2008)	Body position (passive leg raise)
11	Schoonjans et al. (2010)	Hypovolemia
12	Desgranges et al. (2011) and Matsunaga et al. (2011)	Site of measurement
13	Sandroni et al. (2012) and Yin & Ho (2012)	Amount and type of fluids
14	Roeth et al. (2012)	Heart rate
15	Hofer & Cannesson (2011)	Arrhythmias
16	Hofer & Cannesson (2011)	Open chest conditions

[PVI-Plethysmographic Variability Index; Data summarized from different studies]

Furthermore, it has been observed that PI and PVI recorded at the finger site were more sensitive to vasomotor tone displaying significant variation before and after skin incision, than the values recorded at the forehead (Desgranges et al., 2011; Matsunaga et al., 2011; Pavlakovitch et al., 2011). In a review of dynamic indicators of fluid responsiveness, Bouchacourt et al. (2013) concluded that an increase in vasomotor tone reduced the accuracy of dynamic variables like PVI from accurately predicting fluid responsiveness.

A meta-analysis (Sandroni et al., 2012) revealed that, both Δ POP and PVI were reliable indicators of fluid responsiveness to at least 500 ml or 7–8 ml/kg of infusion, in mechanically ventilated adult patients presented with normal sinus rhythm. Both indices failed to predict responses when smaller boluses were administered. Another systematic review (Yin & Ho, 2012) reported lower accuracy of PVI in studies that opted for preload challenges other than colloid fluids. Roeth et al. (2012) documented a significant increase in PVI values as an effect of increasing HR and tidal volume. Similarly, Desebbe et al. (2010) published that PVI could be considered reliable in detecting hemodynamic effects induced by PEEP, when $V_T > 8$ ml/kg in patients. Bouchacourt (2012) observed an increase in dynamic variables like PVI, Δ POP, PPV and SVV with hypovolemia during low V_T (6 ml/kg) and high V_T (12 ml/kg) in a hemorrhagic animal model (rabbit). Another review article (Hofer & Cannesson, 2011) stated the effect of arrhythmias, open chest conditions and elevated PEEP on dynamic variables.

2.6 Clinical Implications of PVI

Plethysmographic Variability Index has gained immense popularity within short span of time because it is a non-invasive, automated, continuous bedside monitoring tool which is easy to use, portable and relatively inexpensive. Masimo's SET measures a true value of PVI even in episodes of motion, low perfusion, intense ambient light and electrocautery, thus gaining an upper hand over conventional pulse oximeters. It is announced by various clinicians as a new algorithm for monitoring intravascular fluid status of ICU and anesthetized patients (Masimo, 2005b and 2005c).

Plethysmographic Variability Index demonstrates good accuracy in discriminating between fluid responders (patients that respond positively to fluid loading by increasing their CO/SV by 10-15%) (Mohamed & Mullenheim, 2012) and non-responders (patients that show no change in CO/SV after fluid loading). With this potential, it helps to guide fluid optimization in critical and surgical patients by giving an idea about their fluid volume status and deciding whether the patients actually need fluids to correct the volume imbalances or no. This helps in optimizing the patient's cardiac performance and improve organ perfusion (Masimo, 2005b and 2005c). By doing so, it aids in avoiding post-operative complications and reduces hospital stays (Gan et al., 2002). Its involvement in therapeutic optimization in hospitals improves patient outcomes (Renner et al., 2009).

The ability of PVI to detect changes in the relationship between intrathoracic airway pressure and intravascular fluid volume cannot be overlooked (Masimo, 2005b). This is especially important in patients suffering from asthma. During asthma, the intrathoracic pressure rises due to airway resistance during peak inspiration. This causes a transient decrease in preload and induces hemodynamic changes resulting in reduced SV and CO, eventually decreasing pulse pressure variation. Plethysmographic Variability Index is useful in monitoring these cyclic changes during respiratory variations in plethysmogram especially in respiratory and cardiac diseases (Masimo, 2005c).

Hypotension is commonly encountered in anesthetized patients. The patients at risk of developing hypotension are identified by PVI at an early stage, thereby taking precautionary measures and promoting patient care peri-operatively (Tsuchiya et al., 2010; Yoshioka et al., 2011). During hypovolemia, the intravascular volume reduces and is greatly affected by minor changes in airway pressure during normal respiration eventually causing cyclic changes in SV and CO. These effects are more enhanced during mechanical ventilation which can be picked up by PVI. Goal directed therapy using PVI as a monitoring device is known to reduce intra-operative and post-operative lactate levels (Forget et al., 2010). Its use in guiding therapeutic decisions in anesthetized patients undergoing surgeries like cardiac, hepatic, abdominal and cesarean sections has proven to improve patients health status peri-operatively and reduce post-operative morbidity and mortality (Masimo, 2005c).

Another significant use of PVI is optimizing of ventilator settings (Desebbe et al., 2010; Masimo, 2005c). Plethysmographic Variability Index is known to predict the effect of PEEP on hemodynamic parameters like CI that can help clinicians optimize oxygen consumption and oxygen delivery to tissues in ICU patients (Desebbe et al., 2010). Being a noninvasive tool, it has been a boon in pediatric and neonatal practice to screen cardiopulmonary disorders (Latini et al., 2012; Naguib et al., 2011).

2.7 Limitations of PVI

Although PVI has proven to be a promising clinical modality, it is subjected to limitations that reduce its accuracy during arrhythmias, open chest conditions, right heart failure causing intra-abdominal pressure, spontaneous breathing, $V_T < 8$ ml/kg and monitoring of pediatric and neonatal patients (Masimo, 2005c; Backer & Pinsky, 2007; Hofer & Cannesson, 2011; Yin & Ho, 2012). Available literature on its use in pediatric population shows contrasting results in various studies discussed earlier leading to discrepancy in its utility (Yin & Ho, 2012).

It is evident from the available literature that PVI proves to be an accurate indicator of fluid responsiveness in mechanically ventilated patients under anesthesia presenting normal sinus rhythm. The inconsistent heart-lung interactions, vasomotor tone and use of vasopressors, limits its utility. Sometimes, dynamic variables like PPV and SVV are preferred over PVI in patients that either require or already have an arterial line (Masimo, 2005c).

As far as limitations pertaining to technology are concerned, tachycardia, abnormal waveforms, abnormal large dichrotic notches, plethysmogram affected by extensive patient movement can sometimes affect calculation of PI, in turn affecting PVI accuracy (Masimo, 2005c).

2.8 Other Hemodynamic Indices for Guiding Fluid Therapy

Determination of accurate hemodynamic variables help avoid deleterious effects of fluid loading in critical and surgical patients. Various authors have experimented with static and dynamic preload determining variables to assess the intravascular fluid status of patients. Table 2.3 lists all static hemodynamic indices of predicting fluid responsiveness and Table 2.4 lists all dynamic indices of predicting fluid responsiveness that have been used in the past and in present, in clinical settings and experimental studies.

Table 2.3 Static hemodynamic indices for predicting fluid responsiveness

Classification	Static indices	Monitoring technique
Filling pressures	Central venous pressure	Central venous catheter
	Pulmonary artery wedge pressure	Pulmonary artery catheter
Volumetric variables	Right/left ventricular end-diastolic volume/area	Transesophageal echocardiography
	Continuous end-diastolic volume	Volumetric pulmonary artery catheter
	Intrathoracic blood volume	PiCCO device
	Global end-diastolic volume	PiCCO device

[PiCCO: Pulse Contour Cardiac Output Monitoring System (Renner et al., 2009)]

Table 2.4 Dynamic indices for predicting fluid responsiveness

Dynamic indices	Definition	Monitoring technique
Pulse pressure variation (PPV)	Pulse pressure variation calculated from mean values of 4 minimum and maximum SVs averaged during previous 30 sec	Invasive arterial pressure PiCCO, LIDCO
Systolic pressure variation (SPV)	Systolic arterial pressure variation during one mechanical respiratory cycle	Invasive arterial pressure Appropriate monitor
Stroke volume variation (SVV)	Stroke volume variation calculated from mean values of 4 minimum and maximum SVs averaged during previous 30 sec	PiCCO, LIDCO
Peak aortic flow velocity variation (ΔV_{peak})	Peak aortic flow velocity variation during one mechanical respiratory cycle	Doppler Echocardiography
Delta down (Δ down)	Difference between systolic arterial pressure in apnea and at end-expiration (minimal value during one mechanical respiratory cycle)	Invasive arterial pressure Appropriate monitor
Delta up (Δ up)	Difference between systolic arterial pressure at end-inspiration and in apnea (maximal value during one mechanical respiratory cycle)	Invasive arterial pressure Appropriate monitor
Inferior vena cava diameter (IVCD)	Cyclic changes in superior and inferior vena-caval diameter are measured to calculate the collapsibility index. Non-SV related	Echocardiography

[PiCCO-Pulse Contour Cardiac Output Monitoring System; LIDCO-Cardiac Output Monitoring System; SV-Stroke volume Modified from Renner et al. (2009)]

Similarly, static volumetric indices like left ventricular end diastolic area have not shown good reliability in predicting volume responsiveness (Michard & Teboul, 2002). This could be attributed to the fact that end diastolic volume before volume infusion will be unable to assess the ventricular chamber compliance. The relationship between end diastolic volume and SV is governed by ventricular function and contractility. During ventricular dysfunction and reduced ventricular compliance, both end diastolic volume and SV will be affected. In this case, a patient would be a non-responder to fluid challenges (Mohamed & Mullenheim, 2012).

On the other hand, the dynamic indices are widely used and have shown to consistently predict fluid responsiveness in clinical practices (Michard & Teboul, 2002). They are based on the concept of heart-lung interactions induced by mechanical ventilation. These dynamic indicators better study the respiratory induced variations in LVSV during mechanical ventilation. Sometimes, variations in surrogates of SV like systolic pressure or pulse pressure are measured. Pulse contour analysis is used for real time monitoring of SV (Renner et al., 2009; Cannesson & Forget, 2010). It is evident that most of the dynamic indices as shown in Table 2.4 have a common denominator SV (except inferior vena cava diameter) that is highly dependent on the volume of pre-infused fluids (Renner et al., 2009).

Dynamic indices have been shown to be superior to static indices for predicting volume responsiveness in critically ill patients and have been routinely used in experimental studies and clinical practices across the globe. Although more clinical trials using these variables are required to assess whether they affect patient outcomes.

Also more information is required to learn the behavior of these variables in presence of cardiopulmonary pathologies (Enomoto & Harder, 2010). Most of the studies that test these variables were investigated on patients receiving mechanical ventilation who were in sinus rhythm that are either sedated or anesthetized. They receive high tidal volumes without spontaneous ventilation. This is not encountered in routine practice and that is where the limitations of these variables crop up. In these cases, the focus then shifts to tests like PLR (Mohamed & Mullenheim, 2012).

CHAPTER 3. MATERIALS AND METHODS

3.1 Animals

Seventy-three dogs that were admitted to the Purdue Veterinary Teaching Hospital, Indiana, were included in the present study. These dogs were admitted to the hospital from April 2013 to October 2013. They belonged to the ASA (American Society of Anesthesiologists) status I to III. They were scheduled to undergo either soft tissue or orthopedic surgeries or diagnostic procedures such as magnetic resonance imaging (MRI) or computed tomography (CT) scans. Pre-operative measurements of packed cell volume (PCV) and total protein (TP) were taken for each patient as a part of pre-operative health check up by the clinicians.

3.2 Animal Preparation

The dogs were brought to the small animal anesthetic induction area and were prepared for their scheduled surgery or diagnostic procedures. The anesthetic protocols were determined by the anesthesiologist on duty. Table 3.1 presents the breed, age, sex and weight of the 73 dogs used in the study. The population of 73 dogs involved young and geriatric male and female patients. The mean age of the dogs was 4.72 ± 3.20 years and the mean weight was 23.76 ± 14.02 kg.

Table 3.1 Breed, age, sex and weight of 73 dogs in the study

Breed	Age	Sex	Weight
Cocker Spaniel (3)	<1 year (2)	Male (41)	<5kg (6)
Beagle (1)	1- <3 years (21)	Female (32)	5- <10 kg (6)
Bernese Mountain (2)	3- <5 years (17)		10- <15 kg (7)
Borzoi (1)	5- <7 years (11)		15- <20 kg (11)
Boston Terrier (1)	7- <9 years (10)		20- <25 kg (8)
Boxer (2)	≥9 years (12)		25- <30 kg (14)
English Bull Dog (2)			30- <35 kg (7)
Papillon (1)			35- <40 kg (7)
Dachshund (4)			40- <45 kg (3)
Doberman (1)			≥45 kg (4)
English Setter (1)			
German Shephard (3)			
German Shorthaired Pointer (2)			
Greyhound (1)			
Havanese Terrier (1)			
Labrador Retriever (11)			
Mastiff (2)			
Mixed breed (21)			
Pitbull (3)			
Pomeranian (2)			
Pug (2)			
Shih Tzu (1)			
Siberian Husky (3)			
Welsh Corgi (1)			
Welsh Springer Spaniel (1)			

[Kg-Kilograms and number of dogs in parenthesis]

Anesthetic protocols with specific premedication drugs are shown in Table 3.2.

Table 3.2 Anesthetic protocols used for 73 dogs in the study

Premedication drug	Abbreviation	Induction drug	Number of Cases
Acepromazine + Dexmedetomidine + Hydromorphone	ADH	Propofol	11
Acepromazine + Hydromorphone	AH	Propofol	46
Acepromazine + Butorphanol	AB	Propofol	8
Dexmedetomidine + Hydromorphone	DH	Propofol	8

The premedication used is shown in the Table 3.2. All the dogs were induced with propofol to effect for endotracheal intubation. Once intubated, they were maintained on isoflurane to effect according to their procedures. All the patients were allowed to spontaneously breathe. When apnea or hypoventilation occurred, assisted ventilation (one breath every 30 seconds) was performed. Fluid rate was either at 5 mL/kg/hr or 10 mL/kg/hr using crystalloids (Plasmalyte®) during the anesthetic procedures. Recumbency positions were recorded as either dorsal, lateral or sternal recumbency.

Eye lubricant ointment was applied immediately after anesthetic induction. The patient was kept warm with a heating pad and towels. Masimo's pulse oximetry device (Masimo Corp., Irvine, CA, USA) Radical 57 was used to obtain SpO₂, PVI and PI values. The pulse oximeter probe was consistently placed on left quadrant of the tongue. It took around 2-4 min on average for the device to stabilize the pulse waveform and calculate the PI and PVI values. Non-invasive blood pressures (systolic, diastolic and mean) were measured routinely with blood pressure monitors by placing a blood pressure cuff on the hind limb or the front limb.

The electrocardiogram (ECG) with a limb lead was used to monitor cardiac arrhythmias continuously. The heart rate was obtained from pulse oximetry. The respiratory rate was obtained from capnography. The body temperature was recorded using a rectal thermometer. Figure 3.1 shows PVI, PI and SpO₂ values were obtained using Masimo Radical 57 pulse oximeter with the sensor probe placed on the tongue of the anesthetized dog.



Figure 3.1 Masimo Radical 57 sensor placed on the tongue of an anesthetized dog

3.3 Variables and Times of Measurement

The variables recorded were PVI, PI, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate (RR), SpO₂ and body temperature (Temp) in spontaneously breathing dogs at 5 min, 10 min, 15 min and 20 min after anesthetic induction. Pre-operative PCV and TP values were also obtained along with premedication protocol, body recumbency position and rate of fluid administration.

A schematic representation of the entire methodology of the present study is shown in Figure 3.2.

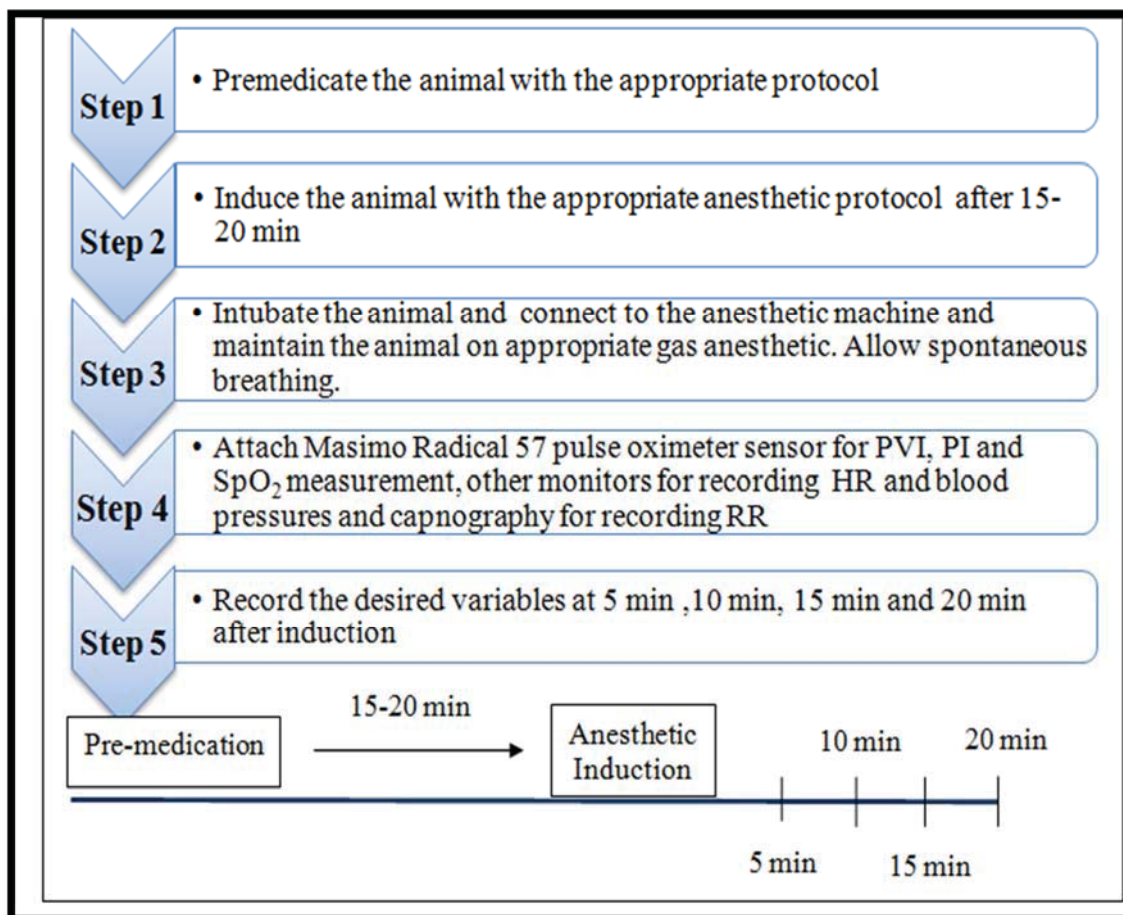


Figure 3.2 Study design and time points for data collection

[PVI-Plethysmographic Variability Index; PI-Perfusion Index; SpO₂-Oxygen saturation of hemoglobin; HR-Heart rate; RR-Respiratory rate]

3.4 Statistical Analysis of the Data

To understand the data distribution of the PVI values in the current population, the values were not grouped under time points, they were treated individually in order to understand how they were distributed over specific PVI ranges (5-10%, 10-15% and so on). The extreme values, median, upper and lower quartiles for all the variables were calculated. The Shapiro-Wilk test was used to test the normality of the data.

The data correlation between the cardio-respiratory variables and PVI was assessed using non-parametric Spearman's rho coefficient (r_s) that worked as a measure of statistical dependence between the two variables in question. Non-parametric Kruskal-Wallis one-way analysis of variance by ranks was used for comparing two or more independent samples and groups of unequal sizes. $P < 0.05$ was considered as statistically significant. All statistical analysis was performed using STATA v.11.1 (Stata Corp, College Station, Texas).

CHAPTER 4. RESULTS

4.1 Data Description

Cardiorespiratory variables, Temp, pre-operative PCV and TP values, PVI and PI were collected in 73 dogs at 5 min, 10 min, 15 min and 20 min after anesthetic induction. Out of these 73 cases, 11 were diagnostic procedures, 27 were orthopedic surgeries and 35 were soft tissue surgeries. The ASA status of these animals was all within ASA I to III (ASA I: 10; ASA II: 45; ASA III: 18). All the dogs had a pre-operative PCV and TP measurement performed prior to anesthesia.

Out of the 73 cases admitted to the study, 46 dogs were premedicated with acepromazine-hydromorphone (AH), 8 dogs with acepromazine-butorphanol (AB), 11 dogs with acepromazine-dexmedetomidine-hydromorphone (ADH) and 8 dogs with dexmedetomidine-hydromorphone (DH). All the dogs were induced with propofol and maintained on isoflurane. Crystalloid fluids (Plasmalyte®) was started as either at 5 mL/kg/hr (28 dogs) or 10 mL/kg/hr (45 dogs) depending upon the patient's physical status and fluid requirement. Data on PVI were obtained when dogs were in the following body positions: (a) dorsal recumbency (26 dogs); (b) lateral recumbency (21 dogs); and (c) sternal recumbency (26 dogs). The summary of the data is presented in Table 4.1.

Table 4.1 Number of dogs in the study (n=73) and distribution according to the type of procedure, ASA status, premedication protocol, rate of crystalloid fluids administered and body recumbent position

Type of procedure	ASA Status	Premedication Protocol	Rate of crystalloids (mL/kg/hr)	Recumbency Position
Diagnostic (11)	I (10)	AH (46)	5 (28)	Dorsal (26)
Orthopedic (27)	II (45)	AB (8)	10 (45)	Lateral (21)
Soft Tissue (35)	III (18)	DH (8)		Sternal (26)
		ADH (11)		

[ASA-American Society of Anesthesiologists; AH-Acepromazine-Hydromorphone; AB-Acepromazine-Butorphanol; DH-Dexmedetomidine-Hydromorphone; ADH-Acepromazine-Dexmedetomidine-Hydromorphone; Frequency of dogs in parenthesis]

Extreme values and quartile ranges were calculated for PVI, PI and clinical variables like HR, SBP, MBP, DBP, RR, SpO₂, Temp, pre-operative PCV and TP measurements are shown in table 4.2. The data was recorded at 5, 10, 15 and 20 min after anesthetic induction.

Table 4.2 Data distribution for Plethysmographic Variability

Index, Perfusion Index, cardiorespiratory variables, temperature and pre-operative packed cell volume and total protein values in 73 dogs

Variable	Minimum value	25th Percentile	Median value	75th Percentile	Maximum value
PVI (%)	5	12	18	24	61
PI (%)	0.14	1	1.7	2.8	9.7
HR (beats/min)	40	72	92	110	160
SBP (mmHg)	60	97	109	123	193
MBP (mmHg)	38	74	83	92	163
DBP (mmHg)	24	55	64	76	143
RR (breaths/min)	2	4	7	10	20
SpO ₂ (%)	88	97	98	99	100
Temp (°F)	97.8	99.9	100.6	101.7	104.2
PCV (%)	19	41	46	52	57
TP (gm/dl)	4	5.9	6.5	7.4	8.6

[Cardiorespiratory variables are HR-Heart rate; SBP-Systolic blood pressure; MBP-Mean blood pressure; DBP-Diastolic blood pressure; RR-Respiratory rate and SpO₂-Oxygen saturation of hemoglobin. Others are Temp-Temperature; PCV-Packed Cell Volume and TP-Total protein. Data was obtained and averaged collectively from 5, 10, 15 and 20 minutes after anesthetic induction]

The detail data on individual variables are stated as follows;

4.2 Plethysmographic Variability Index

The minimum value was 5% at 5 min after induction in an ADH dog. The maximum value was 61% at 5 min after induction in a DH dog.

The second maximum value was 43% at 5 min after induction in a AH dog. The maximum value of 61% was considered as an outlier since major distribution of PVI values was reported to be between 5-43%. Hence, the common range of PVI in this study was 5-43%. Table 4.2 shows the median value for PVI was 18%. The common range of PVI in 73 dogs using a box and whisker plot is shown in Figure 4.1.

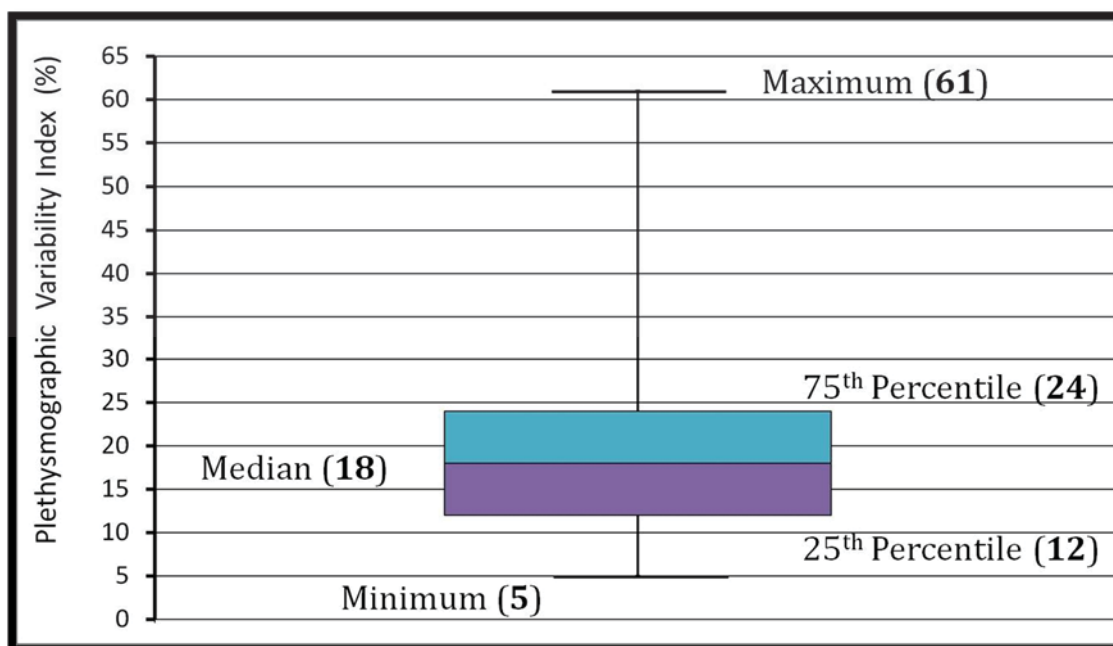


Figure 4.1 Data distribution of Plethysmographic Variability Index values in 73 dogs collected within 20 minutes after anesthetic induction

In Figure 4.1, data are presented as box plots (median and interquartile range [IQR]). Whiskers show range or extend to 1.5 times the IQR, whichever is smaller. Extreme values and quartile ranges are shown in parenthesis.

The upper end of the whisker box plot is the maximum PVI value and the lower end is the minimum value of PVI in the population. The other quartile ranges are also marked in the figure and the values are in parenthesis.

Frequency of data distribution of PVI values in 73 dogs is shown in Figure 4.2. Data was obtained and averaged collectively from 5, 10, 15 and 20 min after anesthetic induction.

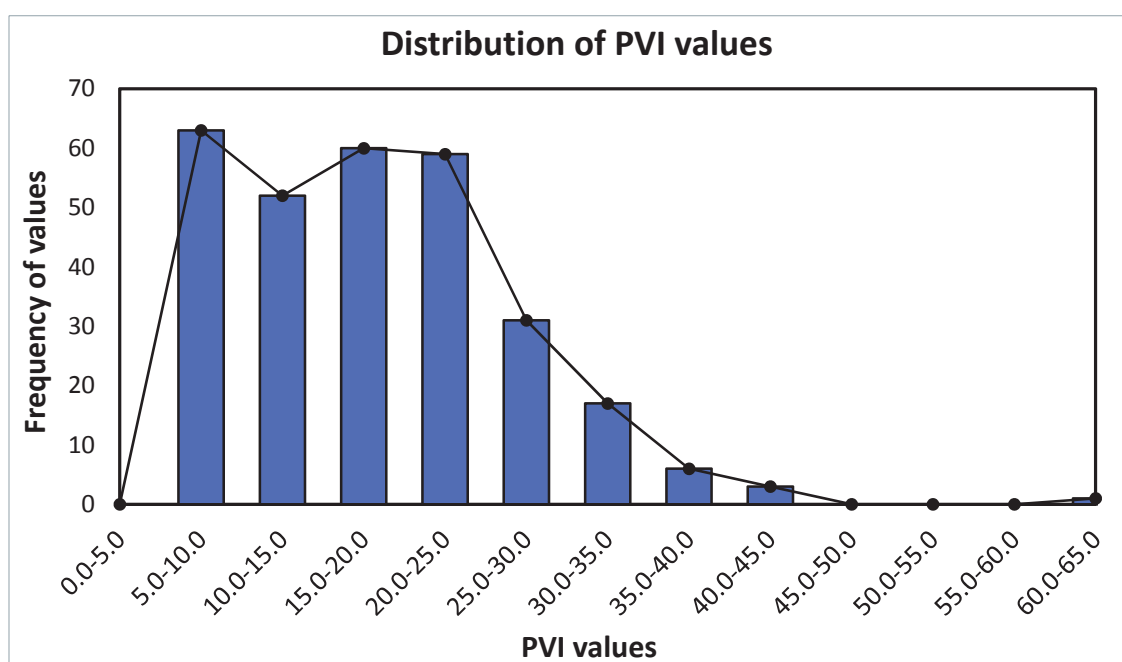


Figure 4.2. Frequency of Plethysmographic Variability Index data distribution in 73 dogs within 20 minutes after anesthetic induction.

As shown in Figure 4.2, the maximum number of values fall in the range of 5-10%, followed by 15-20% and 20-25%. The dip in the curve occurs due to the fall in the frequency of PVI values in the range of 10-15%. Leaving the outlier (61%) aside, all the values are seen to be distributed between 5-43%.

4.3 Perfusion Index

The minimum value was 0.14% at 15 min after induction in an AH dog. The maximum value was 9.7% in an AH dog that had consistent high PI>9% at all the time points. The median PI value was 1.7%. The relationship between PVI and PI in 73 dogs within 20 min of anesthetic induction is shown in Figure 4.3.

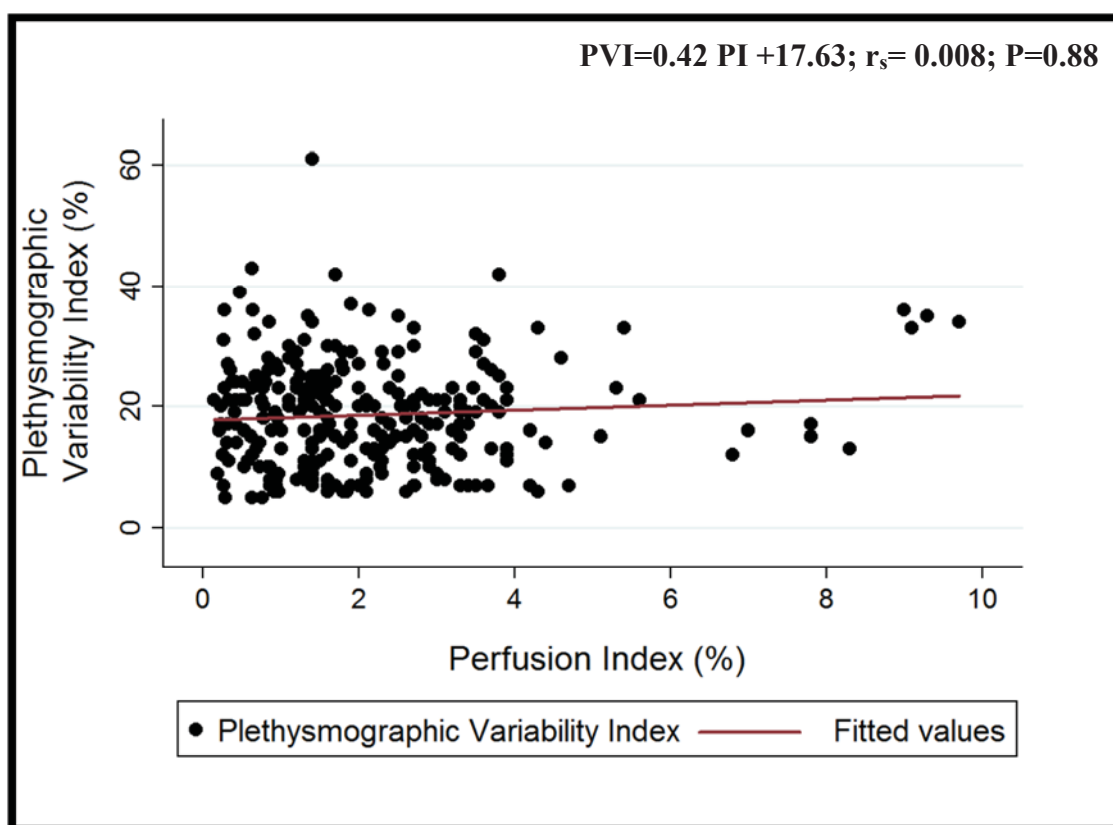


Figure 4.3. Relationship of Plethysmographic Variability Index and Perfusion Index in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.3, the scatter plot with a regression line displays relationship of PVI (Y axis) as to PI (X axis). The regression equation, correlation coefficient and P value for the two variables is shown on the top right corner of the figure. The scatter plot shows that both variables are independent and had no significant correlation with each other.

4.4 Cardiorespiratory Variables

4.4.1 Heart Rate

Bradycardia, defined as HR less than 60 beats/min (Alvaides et al., 2008), occurred at all the time points (5 min, 10 min, 15 min and 20 min after anesthetic induction) in 4 dogs (AH:3; ADH:1). Bradycardia also occurred in 8 other dogs during the study period and subsided without treatments. The lowest HR was 40 beats/min at 10 min after induction in an ADH dog. The highest HR was 160 beats/min at 20 min after induction in an AH dog. As seen in Table 4.2, it is evident that most of the dogs in the population had a normal HR following induction. There was no correlation observed between PVI and HR in 73 dogs within 20 min of anesthetic induction. The relationship between PI and HR in 73 dogs within 20 min of anesthetic induction is shown in Figure 4.4.

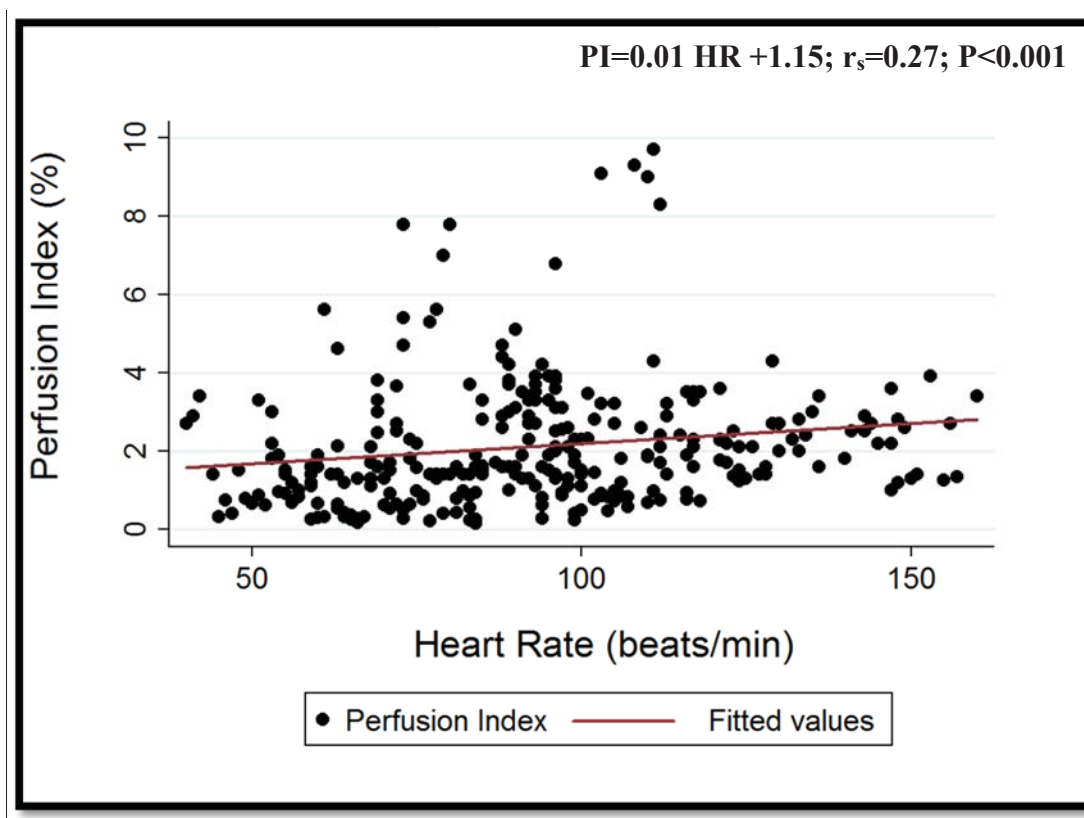


Figure 4.4 Relationship of Perfusion Index and heart rate in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.4, the scatter plot with a regression line displays the relationship of PI (Y axis) with HR (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s=0.27; P<0.001$).

4.4.2 Blood Pressure

4.4.2.1 Systolic Blood Pressure

The lowest SBP was 60 mmHg at 5 min after induction in an AH dog. The highest SBP was 193 mmHg at 5 min after induction in a DH dog.

Hypotension defined as SBP<80 mmHg (Redondo et al., 2007) was observed only in 1 dog throughout the 20 min of recording. Hypotension was also observed in 3 dogs during the study period that normalized without treatment. As seen in Table 4.2, it is evident that most of the dogs in the population had a normal blood pressure within 20 minutes after anesthetic induction. Figure 4.5 represents the relationship between PVI and SBP in 73 dogs within 20 min of anesthetic induction.

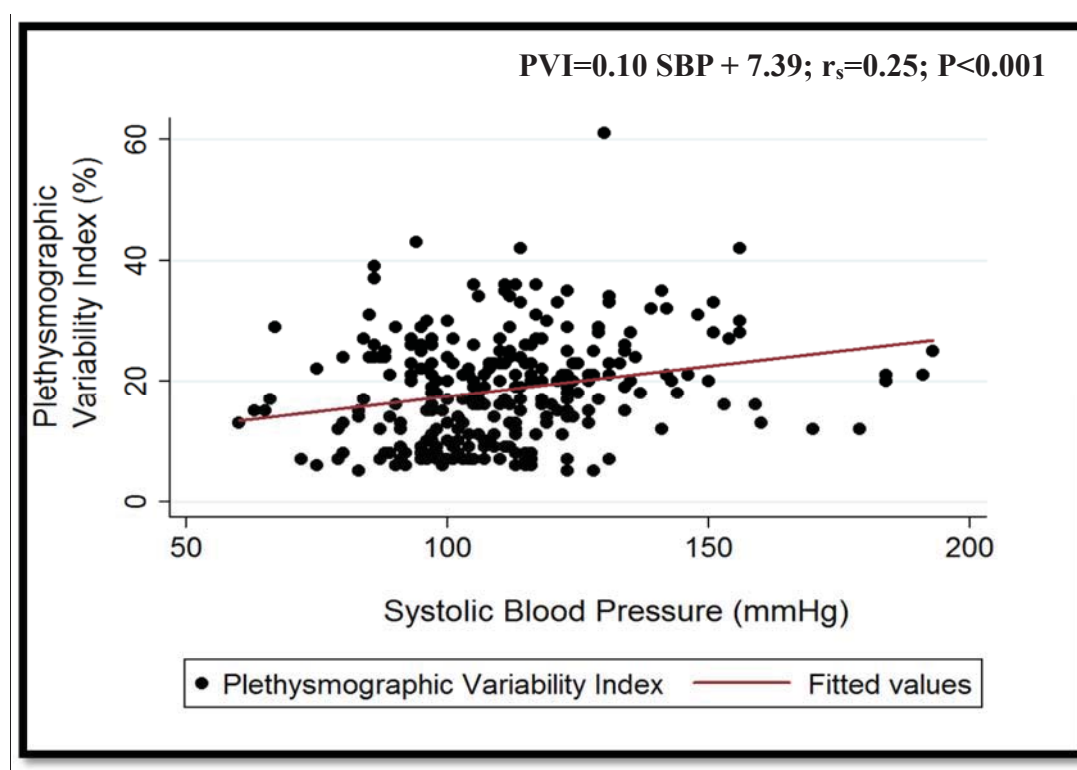


Figure 4.5 Relationship of Plethysmographic Variability Index and systolic blood pressure in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.5, the scatter plot with a regression line displays the relationship of PVI (Y axis) with SBP (X axis).

The scatter plot shows that both these variables are positively correlated with each other ($r_s=0.25$; $P<0.001$). Similarly, there was a positive relationship between PI and SBP ($r_s=0.15$; $P=0.01$).

4.4.2.2 Mean Blood Pressure

The lowest MBP was 38 mmHg at 5 min after induction in an AH dog. The highest MBP was 163 mmHg at 5-10 min after induction in a DH dog. Hypotension defined as $MBP < 60$ mmHg (Redondo et al., 2007) was observed only in 3 dogs (AH:2; AB:1) throughout the 20 min of recording. Hypotension was also observed in 6 dogs (AH:5; DH:1) during the study period that normalized without treatment. As seen in Table 4.2, it is evident that most of the dogs in the population had a normal blood pressure following induction. Figure 4.6 represents the relationship between PVI and MBP in 73 dogs within 20 min of anesthetic induction.

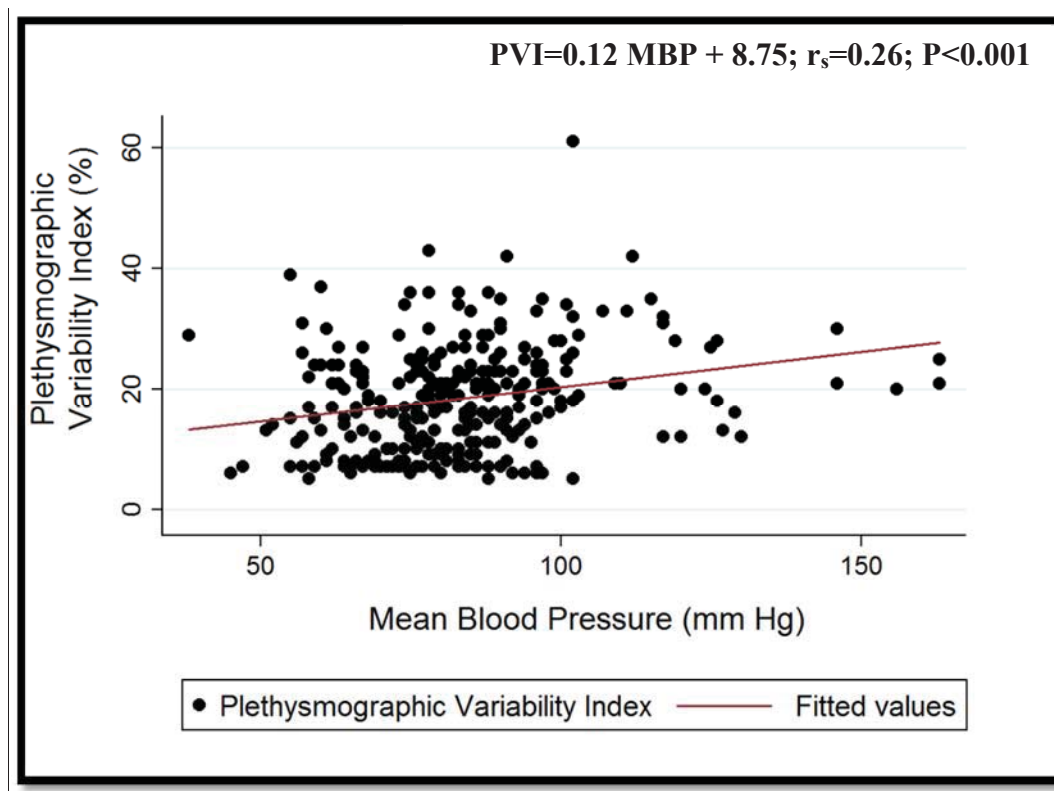


Figure 4.6 Relationship of Plethysmographic Variability Index and mean blood pressure in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.6, the scatter plot with a regression line displays the relationship of PVI (Y axis) with MBP (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s = 0.26; P < 0.001$).

Figure 4.7 represents the relationship between PI and MBP in 73 dogs within 20 min of anesthetic induction.

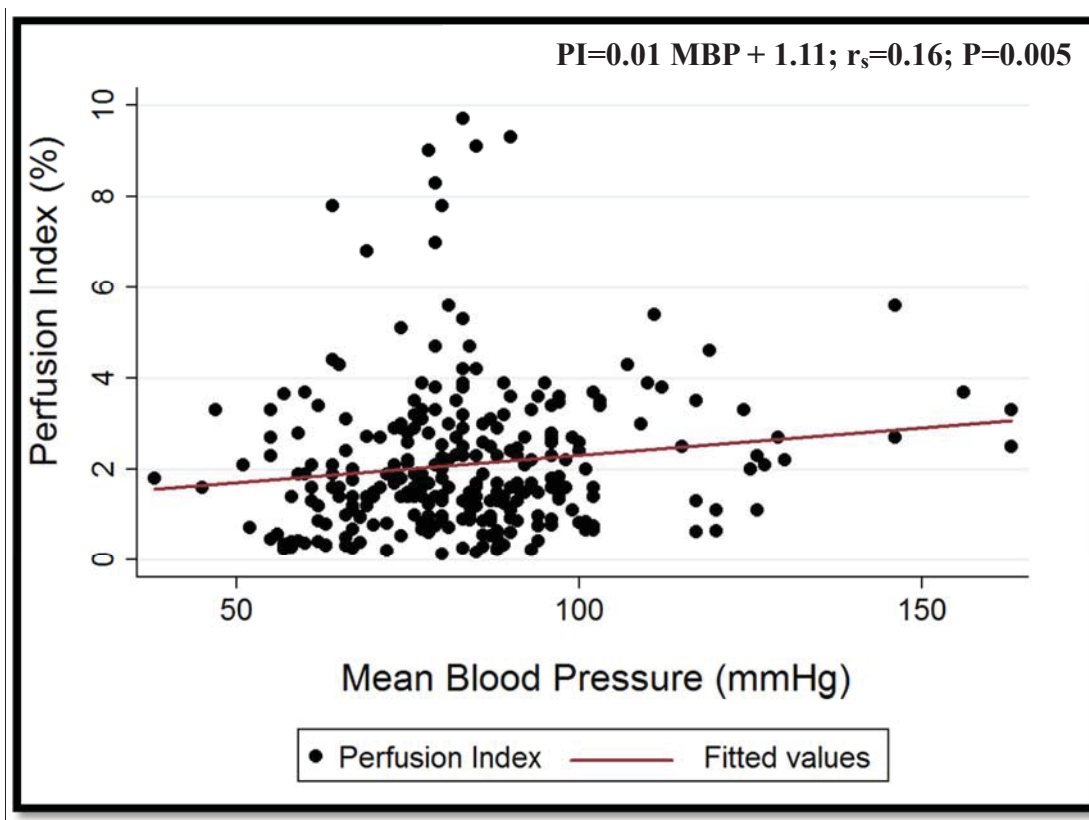


Figure 4.7 Relationship of Perfusion Index and mean blood pressure in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.7, the scatter plot with a regression line displays the relationship of PI (Y axis) with MBP (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s=0.16$; P=0.005).

4.4.2.3 Diastolic Blood Pressure

The lowest DBP was 24 mmHg at 5 min in an AH dog. The highest DBP was 143 mmHg at 10 min after induction in a DH dog. Figure 4.8 represents the relationship between PVI and DBP in 73 dogs within 20 min of anesthetic induction.

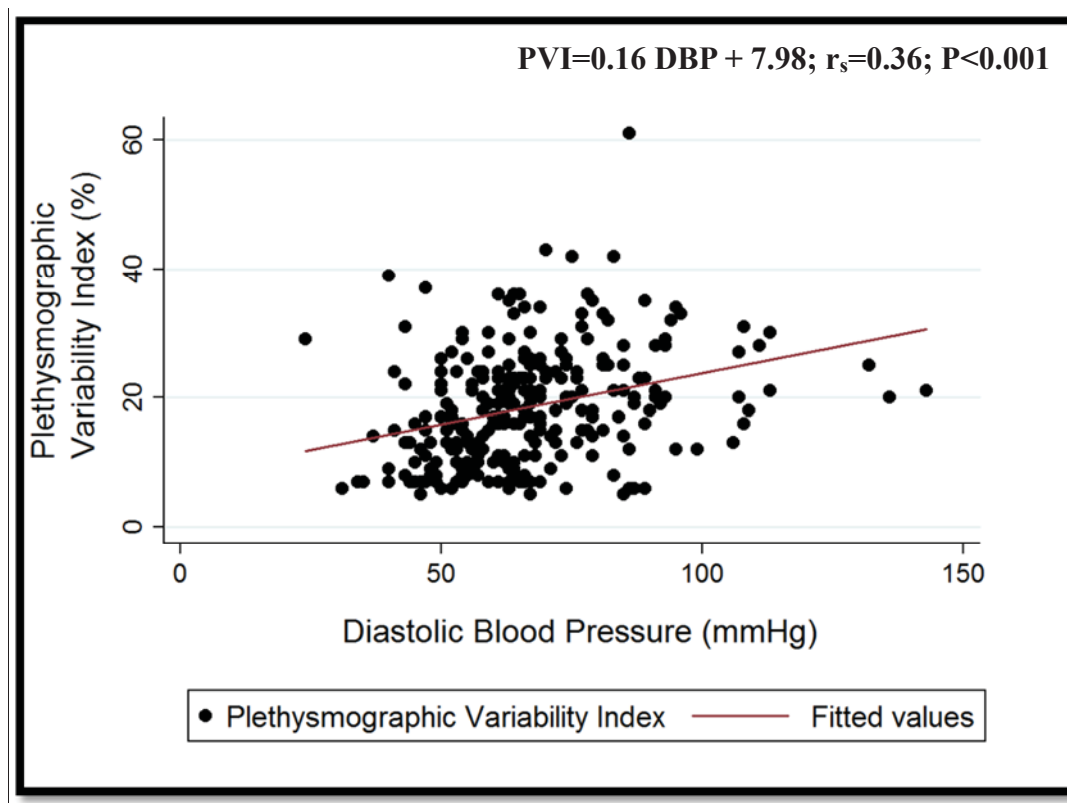


Figure 4.8 Relationship of Plethysmographic Variability Index and diastolic blood pressure in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.8, the scatter plot with a regression line displays the relationship of PVI (Y axis) with DBP (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s = 0.36; P < 0.001$). This positive correlation of PVI was strongest with DBP as compared to SBP and MBP. However, PI and DBP were observed to be independent and had no significant correlation with each other.

4.4.3 Respiratory Rate

The dogs were allowed to spontaneously breathe and in case of apnea or hypoventilation, assisted ventilation was carried out once every 30 seconds until spontaneous breathing resumed. The lowest RR was 2 breaths/min at 5 min after induction in an AH dog. The highest RR was 20 breaths/min at 5 min after induction in an AH dog. There was no significant correlation observed between PVI and RR in 73 dogs within 20 min of anesthetic induction. Figure 4.9 describes the relationship between PI and RR in 73 dogs within 20 min of anesthetic induction

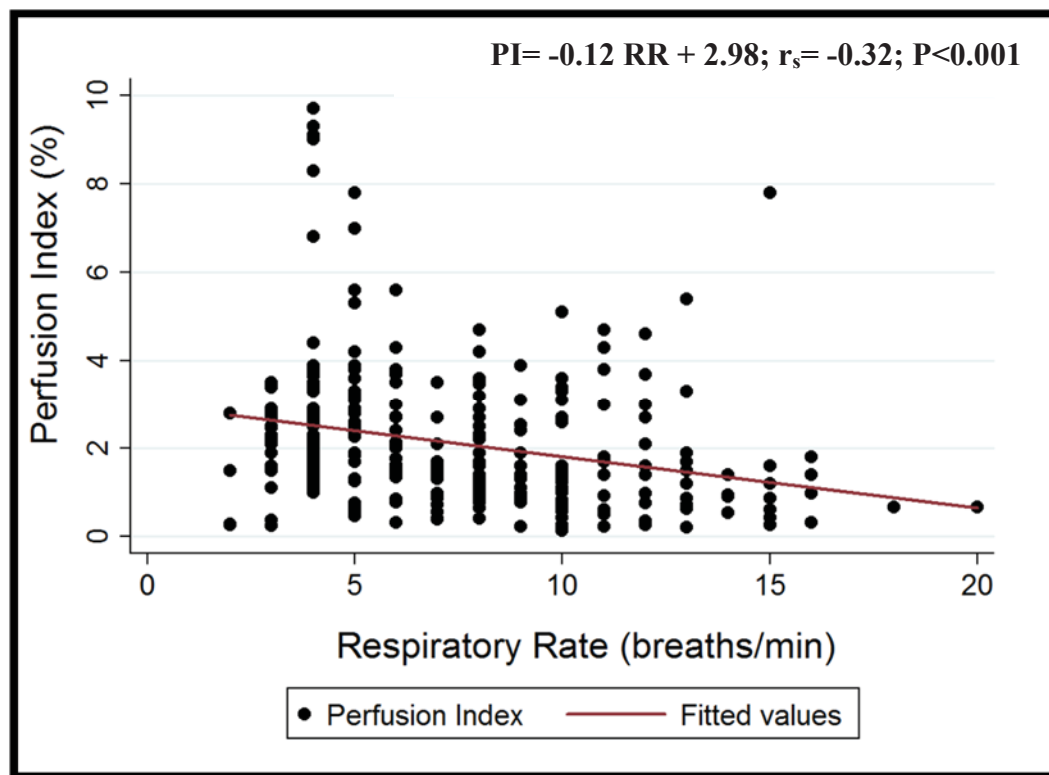


Figure 4.9 Relationship of Perfusion Index and respiratory rate in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.9, the scatter plot with a regression line displays the relationship of PI (Y axis) with RR (X axis). The scatter plot shows that both these variables are negatively correlated with each other ($r_s = -0.32; P < 0.001$).

4.4.4 Oxygen Saturation of Hemoglobin

The SpO₂ values were recorded when all the dogs were maintained on 100 % oxygen during isoflurane anesthesia. The lowest SpO₂ was 88% at 10 min after induction in a DH dog. As seen in Table 4.2, it is evident that most of the dogs had good oxygen saturation and did not suffer from hypoxemia.

There was no significant correlation established between PVI and SpO₂. Figure 4.10 describes the relationship between PI and SpO₂ in 73 dogs within 20 min of anesthetic induction.

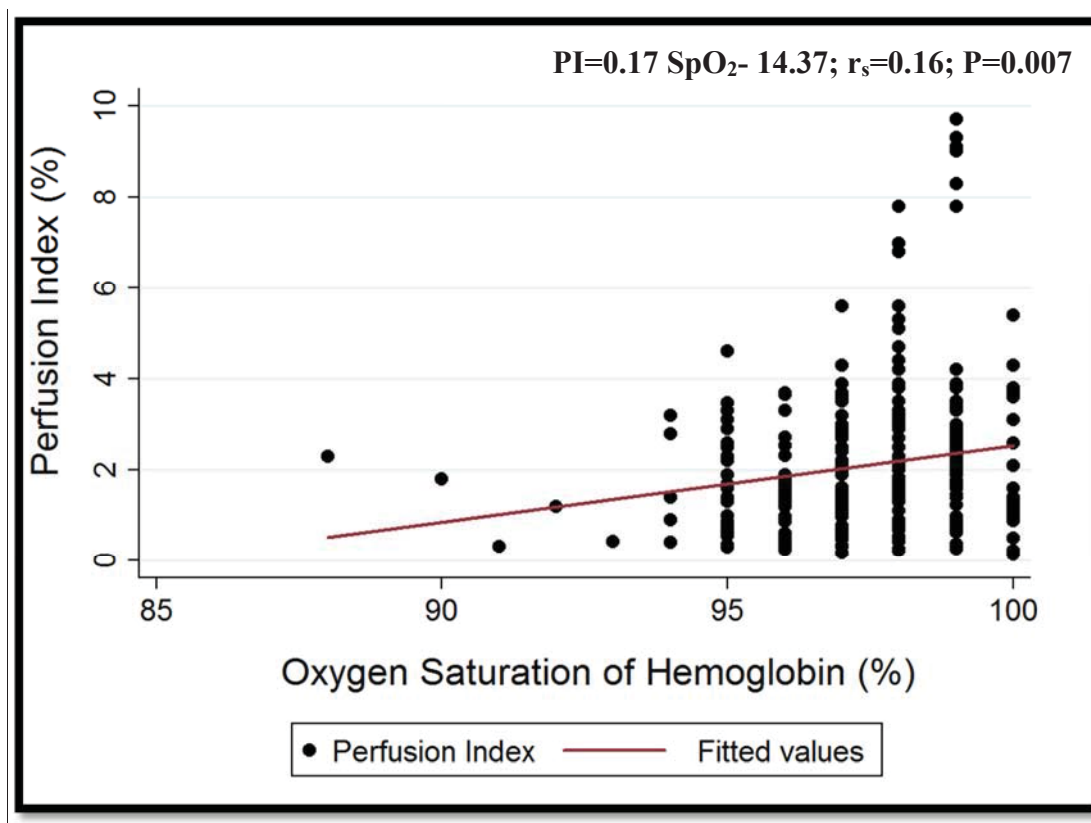


Figure 4.10 Relationship of Perfusion Index and oxygen saturation of hemoglobin (SpO₂) in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.10, the scatter plot with a regression line displays the relationship of PI (Y axis) with SpO₂ (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s = 0.16$; P=0.007).

4.5 Temperature

The lowest Temp was 97.8⁰F in an AH dog for all points of time. The highest Temp was 104.2⁰F in AB dog for all points of time. As seen in Table 4.2, the temperature was well maintained for most of the anesthetized dogs. Figure 4.11 describes the relationship between PVI and Temp in 73 dogs within 20 min of anesthetic induction.

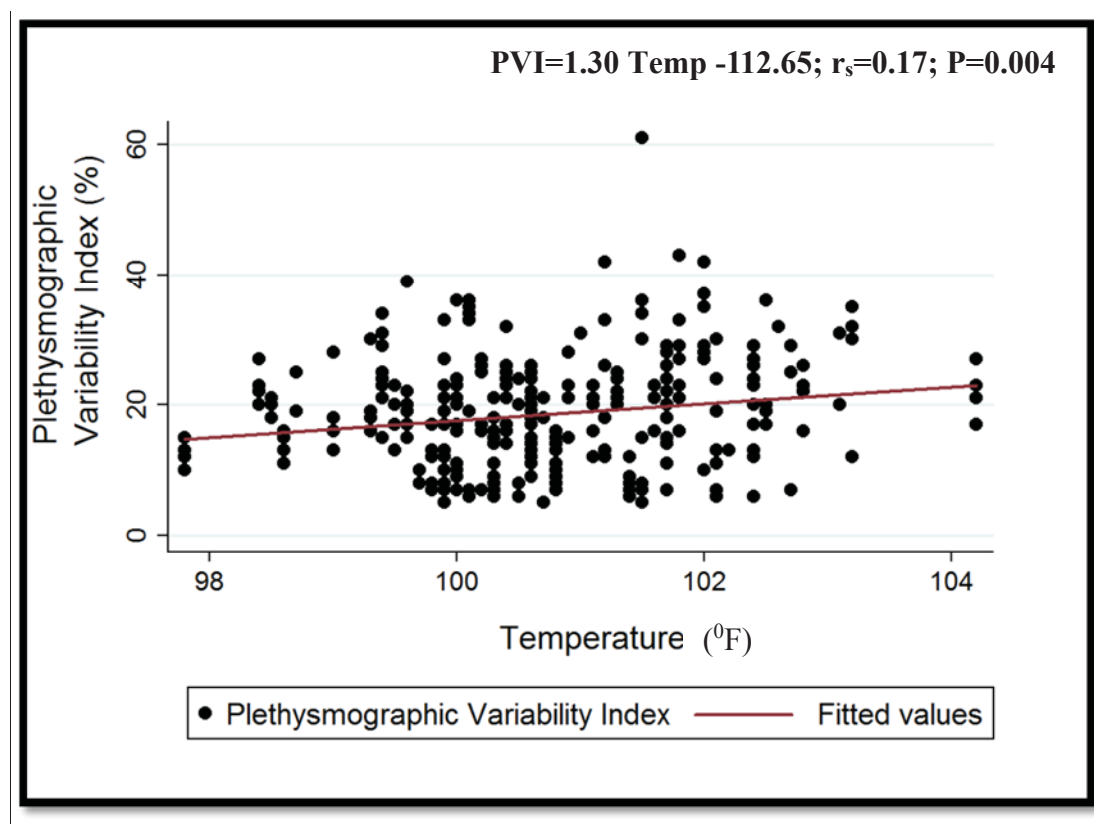


Figure 4.11 Relationship of Plethysmographic Variability Index and temperature in 73 dogs within 20 minutes after anesthetic induction

As shown in Figure 4.11, the scatter plot with a regression line displays the relationship of PVI (Y axis) with Temp (X axis). The scatter plot shows that both these variables are positively correlated with each other ($r_s=0.17$; $P=0.004$). No significant correlation was found between PI and Temp.

4.6 Packed Cell Volume

All the 73 dogs in the current study had a pre-operative measurement of PCV performed as a routine diagnostic test prior to undergoing anesthesia. The lowest PCV was 19% which was in an AH dog suffering from hemoabdomen. The highest PCV was 57%. The normal PCV range was considered 37-57% (Kahn & Scott, 2010). As seen in Table 4.2, most of the dogs undergoing anesthesia had a normal pre-operative PCV measurement. Figure 4.12 describes the relationship between pre-operative PCV value and PVI in 73 dogs at 5 min of anesthetic induction.

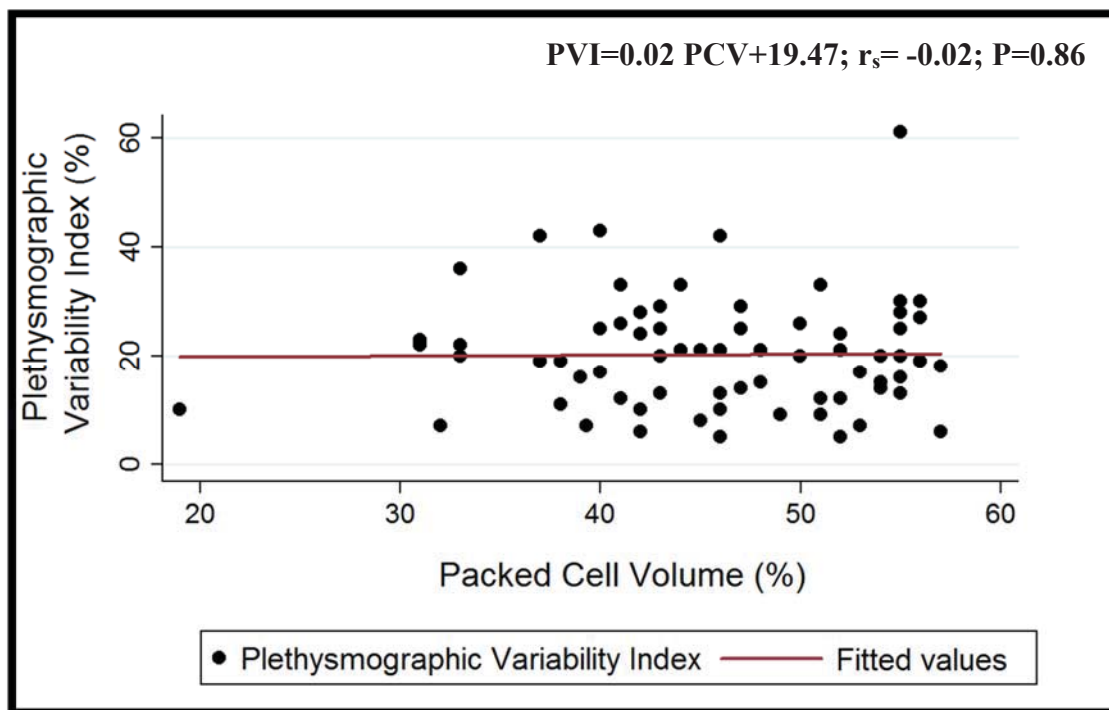


Figure 4.12 Relationship of Plethysmographic Variability Index at 5 minutes after anesthetic induction and pre-operative packed cell volume

As shown in Figure 4.12, the scatter plot with a regression line displays the relationship of PVI values at 5 min after anesthetic induction (Y axis) with PCV (X axis). The scatter plot shows that both these variables are independent and there was no significant correlation found between them. Similarly, there was no significant correlation between PI and pre-operative PCV values.

4.7 Total Protein

The 73 dogs in the current study had a pre-operative measurement of TP performed as a routine diagnostic test prior to anesthesia. The lowest TP was 4 gm/dl in an ADH dog suffering from abdominal mass. The highest TP recorded was 8.6 gm/dl. The normal TP range was considered 5.4-7.4 gm/dl (Kahn & Scott, 2010). As seen in Table 4.2, most of the dogs undergoing anesthesia had a normal pre-operative TP measurement. Figure 4.13 describes the relationship between pre-operative TP value and PVI in 73 dogs at 5 min of anesthetic induction.

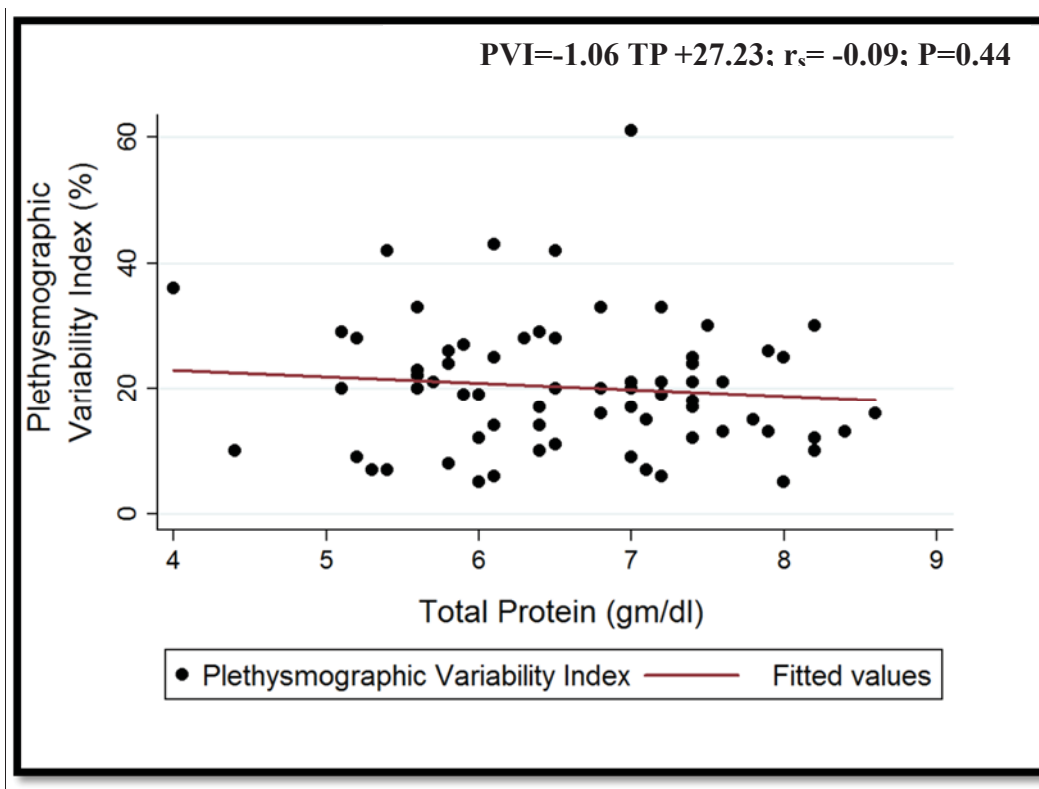


Figure 4.13 Relationship of Plethysmographic Variability Index at 5 minutes after anesthetic induction and pre-operative total protein

As shown in Figure 4.12, the scatter plot with a regression line displays the relationship of PVI values at 5 min after anesthetic induction (Y axis) with TP (X axis). The scatter plot shows that both variables do not have a significant correlation with each other. Similarly, no significant correlation was found between PI and pre-operative TP values.

4.8 Premedication Protocol

Of 73 cases, 46 dogs were premedicated with AH, 8 dogs with AB, 11 dogs with ADH and 8 dogs with DH. Figure 4.14 describes the relationship between premedication protocol and the PVI values with a box and whisker plot.

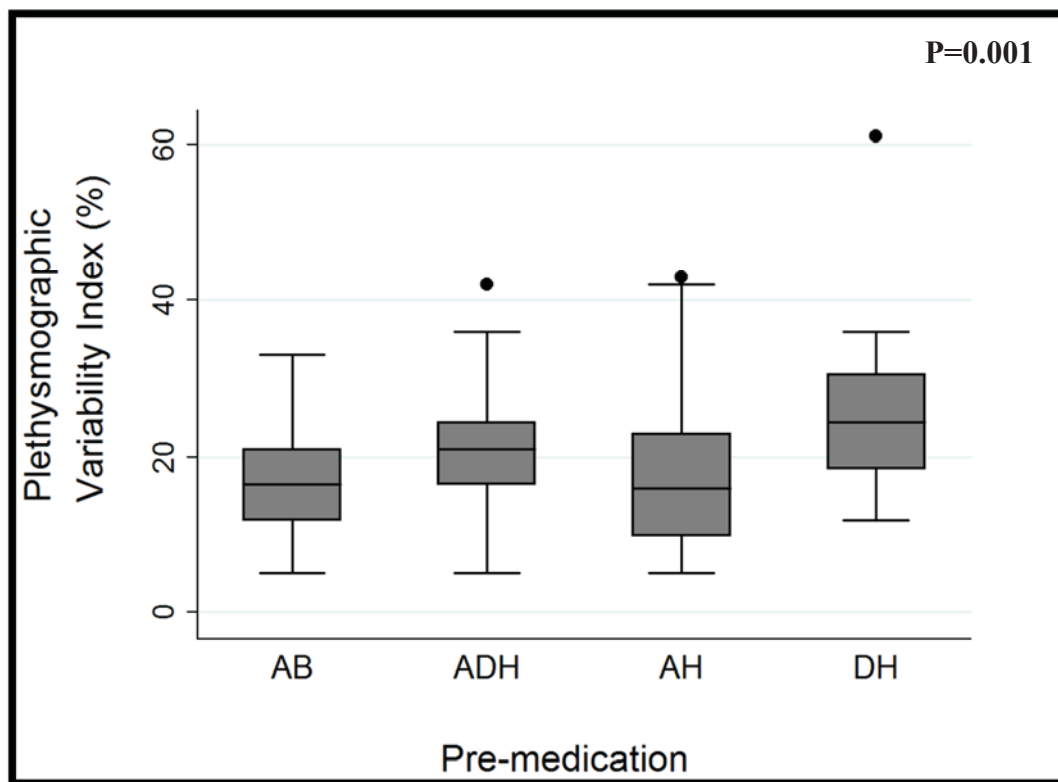


Figure 4.14 Relationship of Plethysmographic Variability Index with premedication protocol in 73 dogs within 20 minutes after anesthetic induction

[AB-Acepromazine-Butorphanol; AH-Acepromazine-Hydromorphone; ADH-Acepromazine-Dexmedetomidine-Hydromorphone; DH-Dexmedetomidine-Hydromorphone]

As seen in Figure 4.14, the relationship of PVI (Y axis) is described with premedication protocol (X axis). PVI significantly varied from different premedication protocols (Kruskal-Wallis test; $P=0.001$). Plethysmographic Variability Index values were seen to be fairly consistent with acepromazine containing protocols (AB and AH). However, when dexmedetomidine was used, the PVI values were seen to increase significantly as seen with DH and ADH treatment groups. The highest PVI value of 61% was seen as an outlier recorded in a DH dog.

Figure 4.15 describes the relationship between the PVI values (Y axis) and premedication protocol over time points (X axis) with a box and whisker plot.

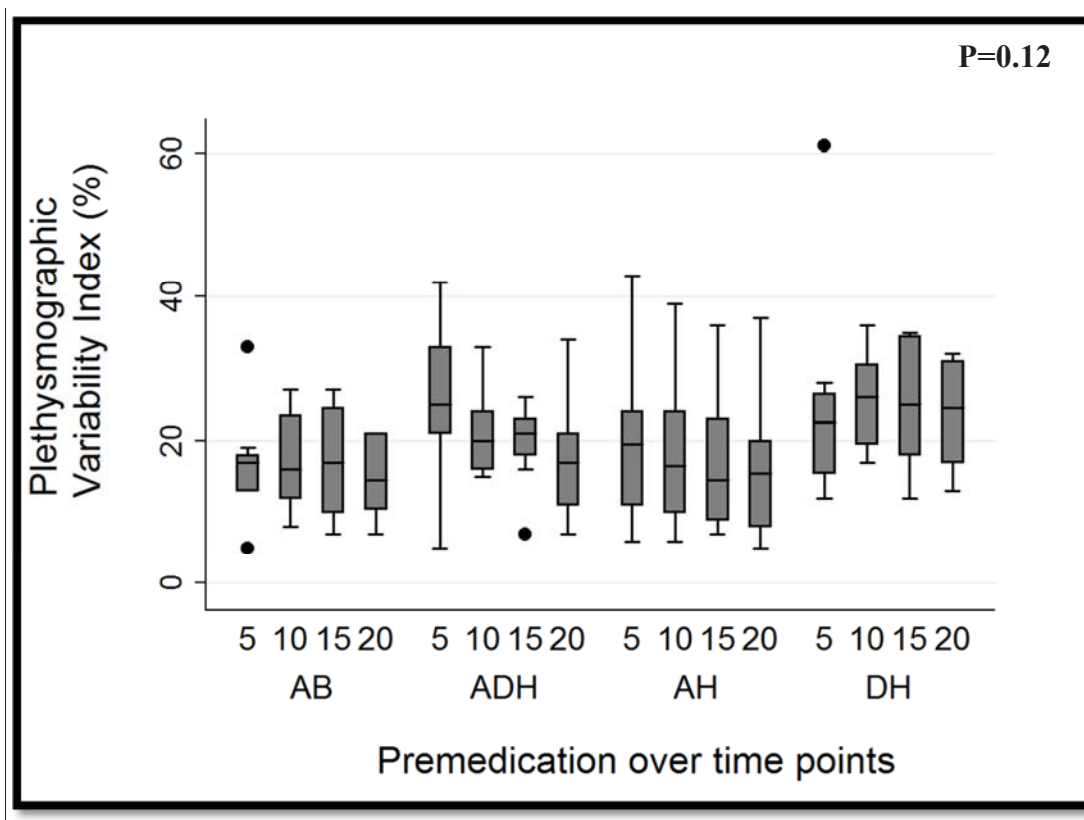


Figure 4.15 Relationship of Plethysmographic Variability Index with premedication protocol in 73 dogs recorded over 5, 10, 15 and 20 minutes after anesthetic induction

[AB-Acepromazine-Butorphanol; AH-Acepromazine-Hydromorphone; ADH-Acepromazine-Dexmedetomidine-Hydromorphone; DH-Dexmedetomidine-Hydromorphone]

As seen in Figure 4.15, data are presented as box plots. In 73 dogs, PVI values did not seem to differ over time points with the premedication protocol administered.

Figure 4.16 describes the relationship of PI (Y axis) with the premedication protocol (X axis) with a box and whisker plot.

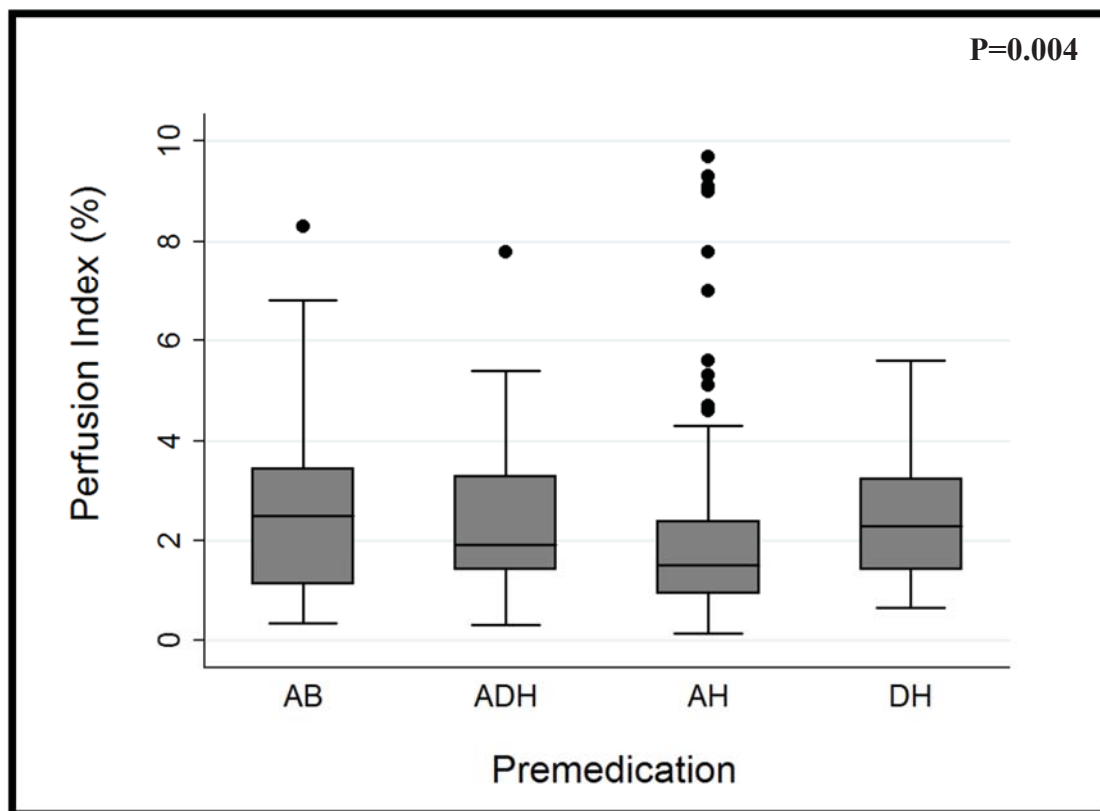


Figure 4.16 Relationship of Perfusion Index with premedication protocol in 73 dogs within 20 minutes after anesthetic induction.

As shown in Figure 4.16, data are presented as box plots. Perfusion Index values were significantly influenced by the premedication group. (Kruskal-Wallis test; $P=0.004$). The dogs in the AH group displayed higher PI values as compared to the dogs in the three other groups (AB, DH and ADH). The dots are the outliers which were high values that were seen the most in AH premedication.

4.9 Body Recumbent Position

Data on PVI were collected while the anesthetized dogs were in the dorsal recumbency (26 dogs), lateral recumbency (21 dogs) and sternal recumbency (26 dogs). Figure 4.17 displays a relationship between PVI (Y axis) and recumbency position (X axis) using box and whisker plots.

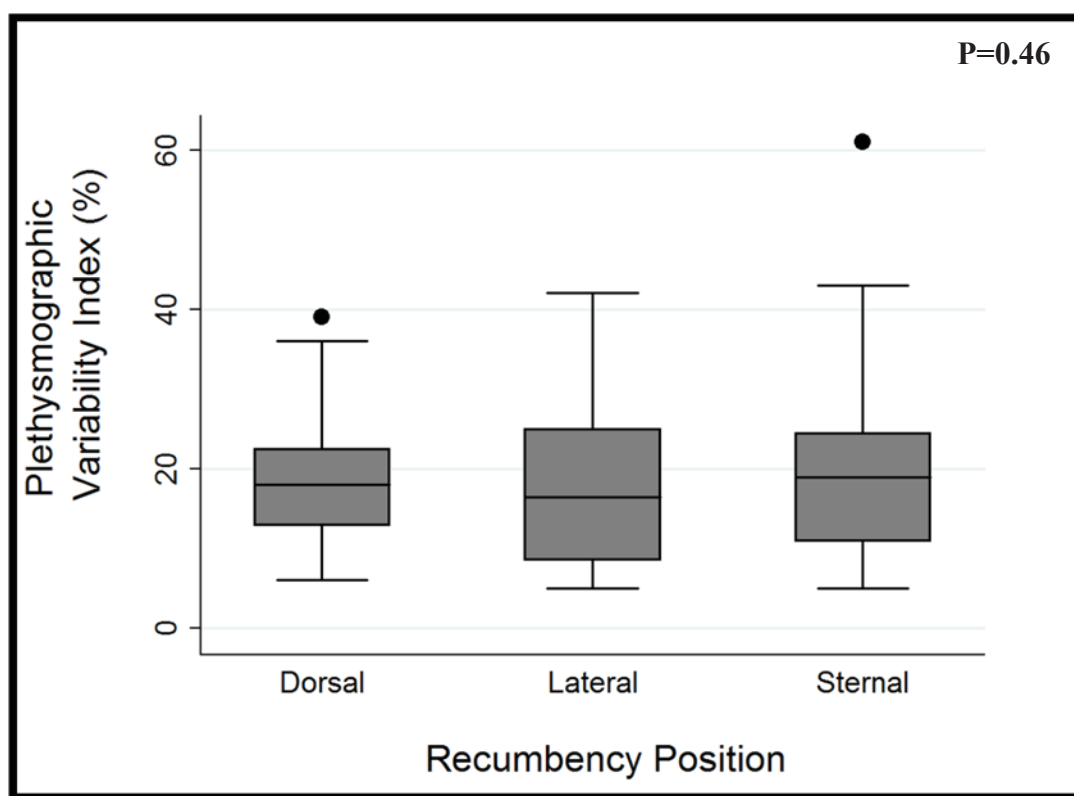


Figure 4.17 Relationship of Plethysmographic Variability Index with recumbency positions in 73 dogs within 20 minutes after anesthetic induction

As seen in Figure 4.17, data are presented as box plots. Plethysmographic Variability Index values were not seen to change significantly with different body recumbent positions.

The similar result was seen with PI values which also did not change significantly with change in body positions.

4.10 Rate of Crystalloid Fluids Administration

In the current study, 28 dogs were administered 5 mL/kg/hr and 45 dogs were administered 10 mL/kg/hr, depending upon their physical and hydration status and the fluid requirement. This resulted in a necessity to study the effects of two different fluid rates on PVI. Figure 4.18 describes the relationship of PVI (Y axis) with two different fluid rates, 5 mL/kg/hr and 10 mL/kg/hr (X axis) using a box and whisker plot.

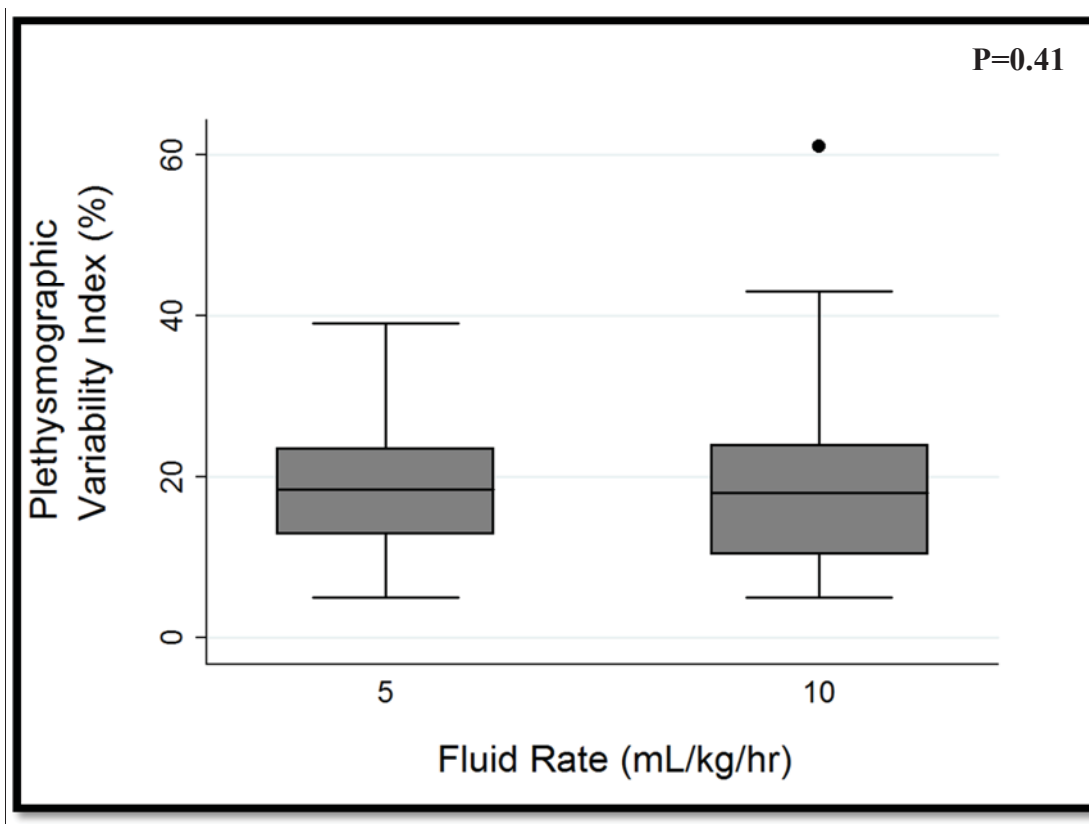


Figure 4.18 Relationship of Plethysmographic Variability Index with rate of crystalloid fluids administration in 73 dogs within 20 minutes after anesthetic induction

As seen in Figure 4.18, data are presented as box plots (median and IQR). Plethysmographic Variability Index values did not change significantly with two different fluid rates (5 mL/kg/hr or 10 mL/kg/hr) over 5 to 20 min after anesthetic induction. A similar result was seen with PI values which also did not change significantly with change in fluid rates.

Figure 4.19 describes the relationship of DBP (Y axis) with two different fluid rates, 5 mL/kg/hr and 10 mL/kg/hr (X axis) by using a whisker box plot.

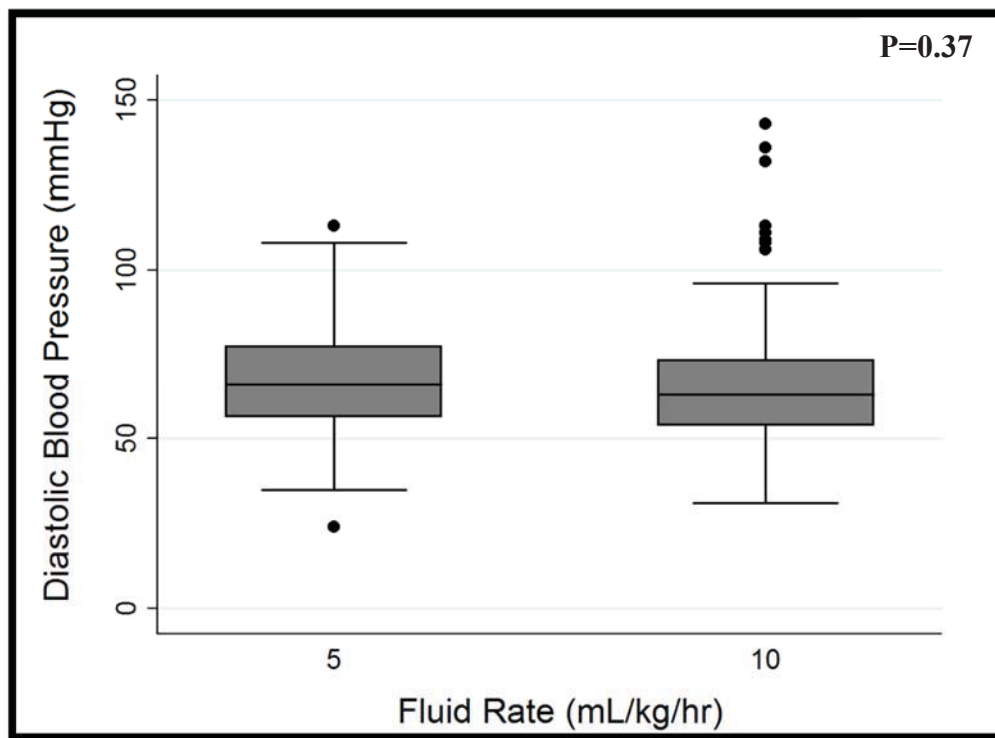


Figure 4.19 Relationship of diastolic blood pressure with rate of crystalloid fluid administration in 73 dogs within 20 minutes after anesthetic induction

As seen in Figure 4.19, data are presented as box plots (median and IQR). Diastolic blood pressure values did not change significantly between the two different fluid rates (5 mL/kg/hr or 10 mL/kg/hr) over 5 to 20 min after anesthetic induction.

CHAPTER 5. DISCUSSION

5.1 Justification for the Study Design

The current clinical study was carried out to answer preliminary questions about PVI in anesthetized veterinary patients (dogs). The study included spontaneously breathing dogs since it was thought to be a practical approach, considering that most of the anesthetized patients in small animal practice are under spontaneous ventilation and that mechanical ventilation is employed rarely. Cardiorespiratory variables, pre-operative PCV and TP measurements, PVI and PI were collected in 73 dogs at 5 min, 10 min, 15 min and 20 min after anesthetic induction. The data collected in 5 cats contributed as minority in the study and hence were excluded from analysis. The study was confined to dogs because the Masimo sensor probe is a human device and is more applicable to dogs than other animals.

In this study, the data collection was performed at 5 min, 10 min, 15 min and 20 min after anesthetic induction. The time intervals for data collection were decided in order to observe the effect of premedication on the PVI values of the patient in the early isoflurane maintenance phase. The first 20 min after induction is an appropriate phase where hypotension is likely to occur due to the effects of premedication, propofol induction and isoflurane maintenance.

These time intervals are suitable for assessing the temporal relationship between PVI values and hypotension. Also, it was important to note the change in body positions that occurred during the surgical preparation phase (roughly 20 min prior to the surgery) and their effect on the PVI values. Moreover, it was easier to collect the data in the anesthetized animals than it would be in the awake animal. Awake animals tend to struggle and it is difficult for the sensor probe to be secured in place and pick up appropriate signal for plethysmographic waveform to calculate the PI and PVI. Obtaining a reading in an animal prior to anesthetic induction was not possible since the Masimo's pulse oximetry device takes at least 2-4 min to display the first PVI reading, once the sensor is placed on the site of measurement. Thus, to maintain a consistency for collecting and further analyzing the data statistically, these time intervals were selected.

Of the 73 cases used in this study 11 were diagnostic procedures, 27 were orthopedic surgeries and 35 were soft tissue surgeries. The ASA status of these animals were between ASA I to III (ASA I: 10; ASA II: 45; ASA III; 18). Collecting data on patients under ASA IV and ASA V was avoided since the patients have severe illness and thus are systemically compromised so comparing their PVI values to patients that are relatively healthy (ASA I to III) could confound interpretation and analysis.

5.2 Common Range for PVI

Until now, a common range of PVI had not been established in the available literature for animals. In the current study, the minimum PVI value was 5% and maximum PVI value was 61%. The most PVI values in the study were distributed between 5-43%. The PVI value of 61% was considered as an outlier. This indicates that in spontaneously breathing, isoflurane anesthetized dogs with the PVI value obtained from the tongue, the PVI value was between 5% and 43%. This common range helps us to understand high vs low PVI values in future studies in the clinical practice and likely to guide the therapeutic decisions. The median value for PVI was 18%. This indicates that 50% of the times, the PVI value is either lower than 18% or higher than 18%.

In humans (Cannesson et al., 2008), a PVI value of 14% could help discriminate between fluid responders and non-responders. Clinicians worldwide adopted this value in clinical settings. Other human studies on PVI proposed different cut off values in mechanically ventilated adults and children (Masimo, 2005c). The cut off values seemed to change with different degrees of severity of clinical conditions (ICU vs surgical vs septic patients) and also since these studies employed different methods against which the performance of PVI was tested. However, it is interesting that these cut off values do not seem to differ significantly in adults vs children or even amongst different studies and are close to 14%. Although in the present study, the predictive ability of PVI in determining fluid responsiveness was not tested, the median value (18%) seems to lie close to the cut off values observed in human studies.

Out of the two available PVI studies in small animals, some of the baseline PVI values before fluid expansion in dogs and cats suffering from intra-operative hypotension (Muir, 2013) seemed to lie close to the median in the present study (18%). Interestingly, the assumed value of PVI greater than 20%, which was considered to indicate hypovolemia, was close to the median PVI value (18%) obtained in the current study. The baseline PVI values in the hemorrhagic model study (Ricco et al., 2012) were lower than 10%. The reason behind the inter-study difference in the baseline PVI values needs further evaluation and explanation. Based on this study results, it was concluded that the common PVI range in the spontaneously breathing anesthetized dogs was between 5-43%. Future studies are needed in order to decide how to use these values for making therapeutic decisions.

5.3 Relationship with PI

Plethysmographic Variability Index values are automatically and mathematically calculated using an internal software installed in the Masimo's pulse oximeters. Hence, it was vital to know whether PVI and PI influence each other. Most of the recorded PI values were greater than or equal to 1%. There was no correlation between the PVI and PI values indicating these two variables are uncorrelated in the present study. This was in accordance with other studies (Cannesson et al., 2008; Desebbe et al., 2010; Desgranges et al., 2011; Loupec et al., 2011) that also reported no change in PI, although PVI was observed to vary. The possible reason for the lack of relationship between PVI and PI values was that PVI is mathematically calculated using a formula that incorporates PI and these mathematical calculations involve maximum and minimum values of PI on the plethysmographic waveform that are present at hundreds of points on this waveform.

It is not just single calculation that helps display the PVI value automatically on the screen. Hence, what is seen on the pulse oximetry device is the cumulative PVI value which is averaged from hundreds of calculations involving PI over several respiratory cycles. This could be one of the reasons why PVI was not seen to be directly influenced by PI. Furthermore, the variations in PI and PVI values on comparing spontaneous and mechanical ventilation cannot be overlooked.

A human study (Broch et al., 2011) examined whether the predictive value of PVI to discriminate between fluid responders and non-responders depends on different values of PI in mechanically ventilated patients. The study grouped the patients with $PI > 2\%$; $> 3\%$; $> 4\%$ and $> 5\%$. They found that only $PI > 4\%$ reliably predicted PVI as a fluid responsiveness. Since PI signifies the strength of the pulse signal at the site of measurement (Masimo, 2005a), it can be inferred that the anatomic site of measurement that was used in the present study (tongue) was a reliable site to study PVI. However, the relatively low PI values as compared to the other human studies could be due to either hypotension or vasoconstriction (dexmedetomidine). This is important to note while planning future studies in veterinary practice so that PVI can be interpreted more accurately. This would also mean searching for other anatomic sites of measurement (ventral base of tail, ear, paw pad and vulva) to ensure that higher PI values are obtained to increase the reliability of PVI values.

5.4 Cardiorespiratory Variables

5.4.1 Relationship with HR

Since HR can physiologically alter the preload responsiveness (Klabunde, 2012), factors affecting HR can also affect PVI. Out of 73 dogs, bradycardia (HR<60 beats/min; Redondo et al., 2007) was observed in total 12 dogs within 20 min of anesthetic induction. The bradycardia was transient and the HR returned to normal range without any treatment by 20 to 30 min. The statistic result in current study showed that there was no correlation observed between PVI and HR.

This result is in agreement with a study in humans (Tsuchiya et al., 2010), in which no correlation was found between PVI values recorded before anesthetic induction and changes in HR during anesthetic induction. Available literature for the relationship between PVI and HR is limited. There is just one human study (Roeth et al., 2012) specifically defining the relationship between HR and PVI. In that study, the patients were subjected to vascular surgery and their PVI and HR were monitored during mechanically ventilation. It was found that when HR increased from 80 beats/min to 110 beats/min, the PVI significantly increased by 4%. This type of correlation was not observed in the current study dogs, likely due to the difference in species, class of ASA status, type of procedure (diagnostic/surgical) and mode of ventilation. In contrast to PVI, PI and HR had positive correlation ($r_s=0.27$; $P<0.001$) in the current study.

Perfusion Index represents the pulse signal at the site of measurement which is seen in the form of the plethysmographic waveform running synchronously with each pulse beat. In normal sinus heart rhythm, the pulse rate equals the HR. This could be one of the reasons why PI and HR shared a positive relationship in the current study. This result is different from human study. Roeth et al. (2012) did not observe any correlation between PI and HR. However, another study (Hager et al., 2004) reported that PI decreased significantly with the increase in HR when the patient responded to the painful stimuli. The authors reported that PI was a reliable indicator of pain. In the present study, there was no pain stimulus.

Perfusion Index can be also be affected by vasoconstriction and vasodilation as stimulated by temperature, volume, and anesthetics. These could be the reasons why the above results contradicted the results from the present study (PI and HR are positively correlated). However, more studies are required to confirm the significance of these parameters. Whether the relationship of PVI and PI with variables like HR can differ with type of ventilation cannot be confirmed without doing further studies.

5.4.2 Relationship with Blood Pressures

Hypotension, defined as MBP<60 mmHg or SBP<80 mmHg (Redondo et al., 2007), was seen in approximately 9 out of 73 dogs in the study that was resolved without treatment. The vasoconstrictive effects of dexmedetomidine in premedication groups (ADH and DH) caused increase in blood pressure. The present study reported positive correlation between the blood pressure and PVI which was the strongest with DBP. Increase in DBP indicates vasoconstriction and decrease in DBP indicates vasodilation.

With the available literature in humans and animals, it seems that higher PVI values are indicative of better response to fluid therapy. However, these findings seem to differ with severity of illness of the patients and with different clinical settings under which the patients are studied (ICU patients vs normal patients vs anesthetized patients). Various studies investigating the role of PVI in predicting fluid responsiveness did not report hypotension with high PVI values (Cannesson et al., 2008; Zimmermann et al., 2010; Desgranges et al., 2011). On the other hand, several studies (Tsuchiya et al., 2010; Yoshioka et al., 2011; Bagci et al., 2013; Yokose et al., 2013) have shown that pre-anesthesia PVI helps in predicting hypotension during anesthetic induction and spinal anesthesia. These studies also reported to have observed coincidence of higher PVI values with hypotension.

In a dog hemorrhagic model study (Ricco et al., 2012), it has been shown that higher severe hypotension and hypovolemia coincides with increase in PVI values and these PVI values normalize when blood volume was restored. Muir (2013) reported dogs and cats with higher PVI values responding to fluid treatment with crystalloids or colloid boluses, indicated by a decrease in PVI values. However, since the study did not report blood pressure values of these animals, it is difficult to conclude if their findings were similar to the above studies.

Hypotension did not consistently occur in the present study in spite of administering anesthetic drugs that could potentiate hypotension (acepromazine, propofol and isoflurane).

Therefore, it was difficult to draw any conclusion about whether higher PVI values coincide with hypotension. Another inconclusive result of this study was that it could not be determined whether baseline PVI values (5 min after anesthetic induction) could predict hypotension during the later part of the isofurane maintenance phase (10, 15 and 20 min). It was difficult to obtain awake or sedated dog's PVI in the current study because attaching the Masimo sensor probe to the tongue in an awake dog to measure PVI would be difficult. An alternative route of attaching the Masimo sensor probe to the ventral base of the tail to obtain PVI readings in an awake animal should be considered while planning future studies.

Perfusion Index is affected by the vasomotor tone. Lower PI values are seen in states of vasoconstriction while higher PI values are seen in states of vasodilation (Masimo, 2005a). In the present study, the vasomotor tones were mainly affected by the anesthetic drugs (dexmedetomidine vs acepromazine). Higher PI values were seen in dogs premedicated with acepromazine (vasodilative agent) and the lower PI values were seen in the dexmedetomidine (vasoconstrictive agent) treated dogs. However, this result was not consistently observed for all the dogs, in part, these premedicants were also influenced by propofol and isoflurane. The same vasomotor tone could also be assumed why there was a positive correlation between PI and SBP and MBP in the present study. This is similar to a study in humans that reported high baseline PI values could predict incidence of spinal anesthesia induced hypotension in women undergoing cesarean sections (Toyama et al., 2013). Since limited studies are available in this area, more studies are required that focus on this subject.

5.4.3 Relationship with RR

Plethysmographic Variability Index has been extensively studied under mechanical ventilation. Very few studies are available in spontaneously breathing patients. There was no correlation found between PVI and respiratory rate in the present study. However, there was a negative correlation between PI and RR ($r_s = -0.32$; $P < 0.001$). There are no human or animal studies that have specifically examined the relationship of PVI with RR.

In the current study, the anesthetized dogs were allowed to spontaneously breathe and in a few situations of hypoventilation, assisted ventilation was carried out. Most of the human studies employed mechanical ventilation because most of the human patients were in ICU and also those surgical patients were placed on the ventilator. This makes such studies more naturally directed towards controlled ventilation instead of a spontaneous ventilation design. In theory, dynamic indices of predicting fluid responsiveness such as using PVI are more dependent upon the respiratory variations during the cardiopulmonary interactions and pulse strength, that differ with spontaneous vs mechanical ventilation. The positive pressure during inspiration in mechanically ventilated patients induces cyclic blood volume changes in the LVSV. The magnitude of these changes can be better predicted in controlled ventilation as compared to spontaneous ventilation. The hypovolemic mechanically ventilated patients can be more easily identified in these situations since the less volume of blood in these patients causes pronounced respiratory variations that can be better visualized under controlled ventilation (Michard & Teboul, 2000; Pinsky, 2007; Smeding, 2010).

In contrast, during spontaneous ventilation, the tidal volume tends to be varied from breath to breath and this makes the respiratory variations less predictable and less measurable changes in LVSV make the PVI analysis challenging (De Backer & Pinsky, 2007; Soubrier et al., 2007; Hofer & Cannesson, 2011). However, this does not suggest that PVI cannot be used in the spontaneously breathing patients. The PVI measurements are still valid and possible as demonstrated in our study. Most of the veterinary patients in ICU and operating room are spontaneously breathing and mechanical ventilation is not used unless required. This makes our investigation in spontaneously breathing patients of this index more important.

5.4.4 Relationship with SpO₂

Plethysmographic Variability Index, PI and SpO₂ were recorded using the same Masimo Radical 57 pulse oximeter. Hence, knowing if these three variables influence the change in each other is important. The SpO₂ values were recorded when all the dogs were on 100% oxygen after anesthetic induction. Hypoxemia was rarely encountered. The minimum value of 88% was normalized and could be attributed to poor contact of the pulse oximetry sensor probe on the tongue. There was no correlation found between PVI and SpO₂.

In contrast, PI and SpO₂ were seen to be positively correlated with each other. So far, there are no studies reporting specific relationship of these two variables. Since PI and SpO₂ were measured from the same pulse oximetry device, they employ the same principle of infrared light absorption through a pulse signal at the anatomic site of measurement.

Hence, it is logical to assume that these two values would be positively correlated. At times, vasoconstriction (dexmedetomidine) and compression of tissue at site of measurement (tongue) with the sensor probe can also cause low PI and SpO₂ readings. This could be the reason why a low PI could coincide with low SpO₂ reading and high PI associated with higher SpO₂ readings.

5.5 Relationship with Temp

The temperature after anesthetic induction was well maintained with the help of forced hot air blankets for most of the dogs in the study. Three dogs were hypothermic (temperature <99.5⁰F; Redondo et al., 2007) during the study period but the temperature normalized on its own over 15-30 min. There was a positive correlation between PVI and Temp ($r_s=0.17$; $P=0.004$) found in this study. So far, there are no specific studies investigating the relationship between these two variables, hence the reasons for occurrence of these results cannot be justified.

No relationship was reported between PI and Temp in the current study. A human study (Lima et al., 2002) determined the variation of the peripheral PI in healthy adults and related it to the central-to-toe temperature difference in critically ill patients after changes in clinical signs of peripheral perfusion. They reported that changes in the peripheral PI reflect changes in the core-to-toe temperature difference. Impaired organ perfusion occurs during hypovolemia and hypotension. In these situations, when skin blood flow decreases the skin temperature also reduces to preserve vital organ perfusion.

Vasoconstriction accompanies hypothermia that causes blood to shunt away from the skin leading to too poor perfusion and cold extremities. This mechanism explains how hypothermia results in low perfusion states (Masimo, 2005a; Genderen et al., 2013). Hypothetically, if the patients in the current study were hypotensive or hypovolemic, it could lead to consistent hypothermia and change the present relationship of PVI and PI with Temp.

5.6 Relationship with PCV and TP

Estimation of PCV and TP is routinely done pre-operatively to assess the hydrations status of anesthetized veterinary patients. Frequently, fluid therapy protocols are planned according to these values together with the clinical signs of hydration. Hence, it would be useful if these PCV and TP values correlated with the baseline PVI values in the dehydrated patients in order to predict fluid responsiveness during surgery. The correlation of PCV and TP values and PVI has not been studied in humans or animals previously.

In the present study, no significant correlation was found between the PCV and TP values and PVI at 5 min after anesthetic induction. It was difficult to place the pulse oximetry tongue sensor on an awake dog. So, it was not possible to obtain pre-anesthetic PVI values. This was further complicated with the fact that the pulse oximetry device takes at least 2-4 min to obtain a PVI reading. Hence, PVI value was obtained only after the dogs were anesthetized and 5 min after induction was used as the baseline value. In this case, the effect of the anesthetics on the PVI values within these 5 min after induction should be taken into account while interpreting relationship of PCV and TP values with PVI.

5.7 Relationship with Premedication Protocol

The two main premedication drugs used in the present study were acepromazine and dexmedetomidine. These two drugs have different hemodynamic effects and opposite effects on the vasomotor tone. Since the signal extraction and infrared light absorption depends upon the vasomotor tone, it is important to study the influence of these drugs causing vasomotor changes on PVI. There are no human or animal studies that have studied the relationship of these drugs with PVI.

In the present study, PVI and PI were seen to be affected significantly over different premedication protocols within 20 min after induction. The possible explanation is that the anatomic site of measurement used in this study was the tongue, which seems to be very sensitive to the vasomotor changes, especially vasoconstriction caused by dexmedetomidine. This caused the PVI values to be higher in premedication protocols containing dexmedetomidine as compared to the protocols with acepromazine. Similarly PI values were lower under influence of dexmedetomidine (vasoconstriction) and were relatively higher with acepromazine (vasodilation). These observations should be noted while planning future studies on PVI, so that the results are not influenced by the pre-anesthetic drugs and data is not misinterpreted.

Many human studies (Cannesson et al., 2008; Tsuchiya et al., 2010; Zimmermann et al., 2010; Broch et al., 2011; Desgranges et al., 2011; and Loupec et al., 2011) have used propofol as induction agent in the patients to investigate the clinical significance of PVI.

However, only Tsuchiya et al. (2010) studied the relationship of pre-anesthesia PVI values and propofol induced hypotension. Mizuno et al. (2012) reported general anesthesia induction and opioid analgesics significantly increase PI and decrease PVI in adult patients. This suggests the capability of PVI and PI to indirectly detect peripheral hemodynamic changes and microcirculatory effects associated with general anesthesia. Since in present study, the summation effects of different premedication protocols, propofol and isoflurane could have affected the interpretation of PVI and PI to an extent, we need more studies to specifically study the effects of individual anesthetic drugs on these two indices.

5.8 Relationship with Body Recumbent Position

In human medicine, passive leg raise is a simple reversible diagnostic maneuver in which the patient's legs are elevated to 45⁰ without patient's involvement (Monnet & Teboul, 2010), which allows rapid and transient increase of 300 ml in fluid volume by shifting blood volume from the legs to the central compartment. This transiently increases blood pressure, ventricular preloads and hemodynamic parameters that include CO and SV. This technique is then used to discriminate fluid responders and non-responders in spontaneously breathing patients.

Applying this concept to veterinary medicine, in the present study, it was hypothesized that different recumbency positions (dorsal vs sternal vs lateral) would induce similar hemodynamic changes that could possibly be detected by PVI. However, we found no correlation between different recumbency positions and changes of PVI values.

It was possible that these recumbent positions did not induce significant blood volume changes in these dogs or the blood volume changes were too small to influence PVI values.

5.9 Relationship with Rate of Crystalloid Fluids Administration

The present study did not investigate the predictive response of PVI in distinguishing between fluid responders and non-responders. Neither did it test the effects of fluid therapy or colloid challenges on PVI value. However, we did investigate the difference between 5 and 10 mL/kg/hr of fluid administration with the relationship of PVI. All dogs under anesthesia were administered a fluid rate of either 5 mL/kg/hr (28 dogs) or 10 mL/kg/hr (45 dogs). There was no significant difference in PVI values with the two different fluid rates obtained within 20 min after anesthetic induction. This lack of correlation between fluid rates and PVI could be due to inadequate time allowed for fluids to take action within 20 min. Muir (2013) reported changes in PVI values before and after administering crystalloids (5-15 mL/kg over 10-15 min) and colloids (3-15 mL/kg over 10 to 15 min). There are not enough studies in veterinary medicine to draw any conclusion about PVI values and fluid responsiveness based on the current available literature.

5.10 Summary of Results

The current study focused on providing some basic information about PVI in anesthetized dogs. A common range of 5-43% with a median 18% was established in a population of 73 dogs. In the current study, PVI and PI were not influenced by each other and PVI was positively correlated with BP and Temp. The premedication drugs that are routinely used in veterinary practice can affect PVI values.

No change in PVI values following changes in recumbency positions was reported. Furthermore, pre-operative PCV and TP values did not correlate with the baseline PVI value (5 min after anesthetic induction).

CHAPTER 6. SUMMARY AND CONCLUSIONS

Plethysmographic Variability Index is a derivative index of pulse oximetry that allows evaluating an individual's intravascular volume status. This index is used to detect hypovolemia and predict fluid responsiveness in mechanically ventilated human patients. However, only a few studies are available on its application in spontaneously breathing patients.

With the sparse literature on PVI in veterinary patients, the purpose of the current study was to provide basic information regarding this index in anesthetized veterinary patients (dogs) under spontaneous ventilation. In the 73 dogs that were anesthetized for either diagnostic or surgical procedures and belonging to ASA I to III, the objective of the study was to establish a common range for PVI, determine relationship of PVI with PI and variables like HR, SBP, MBP, DBP, RR, SpO₂, Temp, pre-operative PCV and TP values, premedication protocol and recumbency positions and rate of crystalloid fluids administration. The data was collected at 5, 10, 15 and 20 min after anesthetic induction.

A common PVI range of 5-43% with a median 18% was established in a population of 73 dogs. The study reported that PVI and PI are not influenced by each other.

Out of the clinical variables, PVI values were only seen to be positively influenced by the blood pressure measurements (SBP, MBP and DBP) and Temp. However, PI was seen to be positively influenced by HR, blood pressures (SBP and MBP) and SpO₂ and negatively influenced by RR. Also, pre-operative PCV and TP values did not correlate with the baseline PVI value (5 min after anesthetic induction).

The study documented that the premedication protocols used (AH, AB, ADH and DH) affected PVI and PI values. The study observed no change in PVI or PI values following changes in recumbency positions. In addition, there was no influence of two different fluid rates 5 mL/kg/hr or 10 mL/kg/hr on PVI and PI during study period (within 20 min of anesthetic induction). Thus, it was concluded that when evaluating PVI for fluid response in the anesthetized dogs, various clinical factors should be taken into consideration.

After gaining some useful information regarding PVI in veterinary patients through the current study, we need to expand the study for future examination of PVI in investigating whether it can successfully predict fluid responsiveness in animals. This could be achieved by planning extensive hemodynamic studies under mechanical ventilation to measure hemodynamic variables such as CI and SVI before and after fluid administration that can define fluid responsiveness (increase in CI or SVI > 15%). The performance of PVI can be tested against a gold standard method like PPV in discriminating fluid responders and non-responders. Moreover, it is important to find out the difference in change of PVI values with mechanical vs spontaneous ventilation.

This would help us to interpret this index in routine clinical settings where most of the anesthetized and ICU veterinary patients are spontaneously breathing.

Moreover, it is essential to explore the relationship of hypovolemia and hypotension and higher PVI values to see if PVI solely can predict or detect these clinical conditions in anesthetized and ICU patients. The influence of different sites of measurement in animals (tongue vs tail vs ear vs paw pad) on PVI values should be investigated. This will help us in finding a site that is least sensitive to vasomotor changes and can increase the accuracy of PVI by yielding a good pulse signal and high PI values.

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