UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA VETERINÁRIA

COMPARISON OF INVASIVE AND NON-INVASIVE BLOOD PRESSURE MEASUREMENTS IN ANAESTHETISED ADULT HORSES USING AN AUTOMATED MONITOR

RAQUEL COELHO LOYO PEQUITO ANTUNES

ORIENTADOR: Doutor Luís Ressano Garcia Pardon Lamas

TUTORA: Doutora Mariana de Carvalho Torres Magalhães

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2020

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To my grandfather.

Acknowledgments

«Só voa quem se atreve a fazê-lo»

Luís Sepúlveda

Um trabalho de investigação nunca é individual. É, por isso, minha vontade agradecer a todos aqueles que, directa ou indirectamente, contribuíram para a realização deste trabalho.

Aos meus orientadores, Professor Doutor Luís Lamas por me ter recebido no Serviço de Cirurgia e Urgência de Equinos (SCUE) da Faculdade de Medicina Veterinária da Universidade de Lisboa, e por me ter dado a oportunidade de contactar e aprender com os melhores. À Doutora Mariana Magalhães pelo constante acompanhamento, pela partilha de conhecimento e pela exigência que me permitiram crescer tanto. Agradeço-vos ainda a confiança que depositaram em mim.

Ao Doutor Gonçalo Silva agradeço os desafios que me foi colocando e o apoio ao longo deste projecto. Ao Professor Luís Telo da Gama, agradeço a ajuda com a análise estatística.

À Doutora Teresa Rosa, pelos ensinamentos, disponibilidade, ajuda e "empurrões" nos momentos em que mais precisei e que me fazem querer ser mais e melhor.

A todos aqueles que já fizeram ou ainda fazem parte da equipa do SCUE, à Filipa, à Catarina, ao João, à Maria, à Joana e ao Tiago, por toda a paciência e ajuda, por tudo o que me ensinaram, e por acreditarem em mim, tanto dentro como fora da FMV. Quero ainda agradecer aos meus colegas "enfermeiros" por toda a partilha e trabalho desenvolvido nestes anos.

Por acreditar que o conhecimento e a aprendizagem são uma constante e por toda a "bagagem" que me proporcionou, quero deixar o meu agradecimento ao Professor Doutor José Delgado Alves. Obrigada por me ter feito crescer tanto e por toda a confiança que me deu.

Agradeço à Universidade dos Açores, em particular ao Professor João Barcelos, por nunca desistir dos seus meninos. Agradeço aos Açorianos de gema e aos adoptados (Picas, Alice, Margot, Marias, Mafalda e Ana Maria), que me acompanham desde o início do meu percurso na Terceira, por tudo aquilo que me deram, todas as sessões de estudo no "A minha casa" ou no "Alto Sé", a diversão e cultura musical, todos os conselhos, apoio e amizade que vai muito para além das ilhas e, definitivamente, continuará sempre comigo. Agradeço a todos os que se juntaram mais tarde em Lisboa (Patrícia, Joana, "bolo de requeijão", Henrique, Catarina, Sofia e Ritas, Francisca), por se terem tornado essenciais na amizade, pelas risadas e carinho que tornaram o percurso tão mais fácil ao longo destes anos.

Aos meus queridos amigos, Tiago e Bia, pelos lanches e pequenos-almoços da padaria, pelas horas de (video)chamadas, pelas urgências que passamos juntos, pelos desabafos e pausas mesmo quando os dias pareciam não ter fim, por toda a partilha de conhecimento, por saberem sempre o que dizer e pelo apoio incondicional que foi crucial no meu percurso.

Aos de sempre, Joana, Sofias, Martinha, Mariana, André e Azevedo por estarem presentes, pelos momentos essenciais de descontração, motivação e amizade incondicional nos dias críticos. À Francisca pela paciência, por se manter ao meu lado nas alturas de estudo e maior pressão e por ajudar a tornar os dias mais leves e mais relaxados.

À tuna e a tudo o que me trouxe, por me terem ensinado a enfrentar o desconhecido sempre de cabeça erguida, pela preocupação e pelo carinho, e por me incentivarem a continuar e por mostrarem que nunca é tarde para (re)começar.

Por último, mas definitivamente não menos importante, um obrigado muito especial à minha família, e em especial à minha mãe, ao meu pai e ao meu irmão pela tolerância, paciência e compreensão das minhas ausências nas alturas mais atribuladas, e pelo vosso apoio constante nas minhas aventuras ao longo destes anos. São o meu pilar e com vocês tudo se tornou menos difícil. Prometo que este é o (último) curso!

COMPARISON OF INVASIVE AND NON-INVASIVE BLOOD PRESSURE MEASUREMENTS IN ANAESTHETISED ADULT HORSES USING AN AUTOMATED MONITOR

Abstract

Blood pressure is defined as the product of cardiac output (CO) and peripheral vascular resistance (PVR) and is an extremely useful haemodynamic parameter that allows an indirect way of assessing the cardiovascular performance which reflects the organ perfusion. Clinically, arterial blood pressure measurement can be useful for diagnosis, therapeutic monitoring and prognosis of different diseases. It can be obtained either invasively or non-invasively, with pro and cons for each of these. Nowadays, the invasive blood pressure measurement is considered to be the gold-standard in horses undergoing general anaesthesia providing its continuous monitoring. However, to extend its usefulness as a clinical parameter, a trustworthy non-invasive technique which is practical and easily applied to conscious and anaesthetized horses is required.

This study aimed at determining the accuracy and precision of a non-invasive blood pressure measurement method when compared to the gold-standard method (invasive blood pressure). To do so, invasive and non-invasive blood pressure measurements were collected simultaneously using the EDAN iM8 VET multiparameter monitor, in eleven horses presented for elective surgical procedures at an equine referral hospital, between September of 2019 and April of 2020. We started by investigating the correlation between simultaneous invasive and non-invasive methods of blood pressure measurement. Furthermore, we intended to identify whether this correlation differed when conditions like the horse's recumbency and blood pressure range (hypo-, normo-, and hypertension) varied.

We showed that, despite being less accurate than the invasive (gold-standard) method, the non-invasive blood pressure measurement method, using the EDAN iM8 VET multiparameter monitor, is reliable for the use in healthy anaesthetized horses. Moreover, we showed that for the horses in left lateral recumbency a stronger correlation between methods was seen.

Keywords: anaesthesia, horses, invasive blood pressure measurement, non-invasive blood pressure measurement, EDAN iM8 VET monitor

COMPARAÇÃO DA MEDIÇÃO DA PRESSÃO ARTERIAL INVASIVA E NÃO INVASIVA EM CAVALOS ADULTOS ANESTESIADOS USANDO UM MONITOR AUTOMÁTICO

Resumo

A pressão arterial é definida como o produto do débito cardíaco (DC) pela resistência vascular periférica (RVP) e é um parâmetro hemodinâmico extremamente útil, que permite avaliar, indiretamente, o desempenho cardiovascular, refletindo a perfusão dos órgãos. Clinicamente, a medição da pressão arterial pode ser útil para diagnóstico, monitorização terapêutica e prognóstico de diferentes doenças, e pode ser obtida de forma invasiva ou não invasiva, com vantagens e desvantagens para cada um. Atualmente, a medição da pressão arterial invasiva é considerada a técnica padrão em cavalos submetidos a anestesia geral, proporcionando uma monitorização contínua da pressão arterial. No entanto, para alargar a utilidade deste parâmetro hemodinâmico, é necessário ter uma técnica não invasiva confiável, prática e de fácil aplicação, tanto em cavalos conscientes como em anestesiados.

Este estudo teve como objetivo determinar a precisão do método não invasivo de medição da pressão arterial, quando comparado ao método padrão (medição invasiva da pressão arterial). Para tal, as medições da pressão arterial, tanto invasivas como não invasivas, foram recolhidas simultaneamente, usando o monitor multiparamétrico EDAN iM8 VET, em onze cavalos sujeitos a procedimentos cirúrgicos eletivos num hospital de referência, entre setembro de 2019 e abril de 2020. Começamos por investigar a correlação entre medições da pressão arterial efectuadas simultaneamente com os métodos invasivo e não invasivo. Além disso, pretendemos identificar se a correlação diferia quando condições como o decúbito do cavalo durante o procedimento cirúrgico e o intervalo de pressão arterial (hipo, normo e hipertensão) variavam.

Os resultados obtidos sugerem que, apesar de ser menos preciso do que o método invasivo (padrão), o método não invasivo de medição da pressão arterial, usando o monitor multiparamétrico EDAN iM8 VET, é confiável para o uso em cavalos saudáveis anestesiados. Além disso, mostramos que para os cavalos em decúbito lateral esquerdo há uma correlação mais forte entre os métodos estudados.

Palavras-chave: anestesia, cavalos, medição invasiva da pressão arterial, medição não invasiva da pressão arterial, monitor EDAN iM8 VET

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Abbreviations

ALP	Alkaline phosphatase
AV	Atrioventricular
BE	Base excess
BID	*Bis in die* (twice a day)
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CI	Cardiac index
CK	Creatine kinase
Creat	Creatinine
cmH_20	Centimetre of water
CO	Cardiac output
CO_2	Carbon dioxide
CRI	Constant rate infusion
DAP	Diastolic arterial pressure
ECG	Electrocardiogram
$ETCO_2$	End-tidal CO_2
GGT	Gamma glutamyl transferase
HCO_3	Bicarbonate
HR	Heart rate
IBP	Invasive blood pressure
ICU	Intensive care unit
IM	Intramuscular administration
IV	Intravenous administration
Kg	Kilogram
L	Litre
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
Mg	Milligram
Min	Minute
mL	Millilitre
mmHg	Millimetres of Mercury
mmol	Millimoles
NaCl	Sodium Chloride
NIBP	Non-invasive blood pressure

PCO_2	Partial pressure of carbon dioxide
PO	*Per os*
PO_2	Partial pressure of oxygen
PP	Pulse pressure
PVR	Peripheral vascular resistance
Q	Blood flow
R	Correlation coefficient
SA	Sinoatrial
SAP	Systolic arterial pressure
SC	Subcutaneous
SCUE	Serviço de Cirurgia e Urgência de Equinos
SD	Standard deviation
SID	*Semel in die* (once a day)
sO_2	Oxygen saturation
SV	Stroke volume
TCO_2	Total carbon dioxide
TP	Total protein
µg	Microgram
UI	International units
ΔP	Pressure difference

I. Externships

1. Curricular externship

As a part of the final year's programme of the integrated master's degree in veterinary medicine, I performed the curricular externship at the Equine Surgery and Emergency Service (Serviço de Cirurgia e Urgência de Equinos, [SCUE]) of the veterinary faculty of Lisbon's University, under the guidance of Professor Luís Ressano Garcia Pardon Lamas and tutorship of Doctor Mariana de Carvalho Torres Magalhães, between 15th of September and 30th of November of 2019, making a total of two and a half months.

The SCUE is a referral service, part of the University of Lisbon Equine Hospital, with a varied caseload, but mostly attending gastrointestinal and orthopaedic emergencies, from all over Portugal. I had the opportunity to participate in several surgeries as an assistant surgeon, as well as in the anaesthesia induction, maintenance and recovery and, also, in all the processes associated to the patient's preparation in the surgery theatre (clipping, scrubbing and placing the urinary catheter), in both emergency and elective procedures, such as colic, arthroscopies, castrations, closure of the nephrosplenic space, tie-back, amongst others.

During this externship I was able to assist and follow numerous referral cases and consults, from orthopaedic and sports medicine to internal medicine, dentistry and reproduction. Furthermore, I joined in the hospital's daily routine throughout day and night shifts, performing several tasks including presentation and discussion of the cases of the interned patients with the team in the hospital rounds, monitoring the horses in the intensive care unit (ICU), administrating drugs, placing central venous catheters, nasogastric tubing, bandage replacement and helping in the imaging diagnosis and follow-ups and, admission, treatment and management of emergency cases. Moreover, I had the chance to work with donkeys and participate in foal care and management. All of which allowed me to acquire new theoretical and practical knowledges and develop clinical judgment.

During this externship I collected and analysed the data for the present study and in-between the extra-curricular externships I returned to SCUE every chance I get.

2. Extra-curricular externships

All together the extra-curricular externships allowed me to see and understand how other clinics, both veterinary educational hospital and private practices, have different ways to approach the most common issues in equine clinical practice, giving me an eye-opening experience and contributing greatly to my development as a future veterinarian.

2.1. Liège Veterinary University

This externship started at the University of Liège (Belgium) in the 1st of December of 2019 and lasted two weeks. During this time I was able to participate in surgeries and several orthopaedic consults, as well as, in the management of the interned horses. Moreover, I also participated in their Journal Club, in which I presented a recent article related to a specific case present in the hospital at that time.

2.2. De Morette Equine Clinic

As required by this clinic based in Asse (Belgium) this externship lasted two weeks, between the 12th and the 26th of January of 2020. During this period I was included in the daily routine of the hospital, consultations, surgeries, night duties and care for the hospitalized horses, and as this is a very busy clinic, I was able to see a great caseload, from internal medicine to sports medicine, including the admission, treatment and follow-up of several emergency cases. I performed several tasks under the interns' supervision such as drug administration, fluid therapy management, nasogastric tubing, bandage replacement, wound care, central venous catheter placement, among other tasks, which allowed me to gain self-confidence to perform the tasks required.

2.3. Rossdales Veterinary Surgeons

The externship in this Newmarket (United Kingdom) clinic started in the 1st of March and lasted until the 15th of March of 2020. As a known hospital for its veterinary surgeons, most part of the hospital extern student's day was spent in the surgical theatre, helping in the scrubbing, clipping and placement of the urinary catheter, and also scrubbing-in for several surgeries with different veterinary surgeons. All through this externship I participated in the inpatient examination and, also in the admission, treatment and management of surgical and medical emergencies, including trauma injuries and colic. This externship also contributed largely to my knowledge in neonatal foal care and management, including the placement of the central venous catheter and the nasogastric feeding tube and also the Madigan foal squeeze procedure.

Unfortunately, due to unexpected events, the remaining externships I've programmed for this year had to be cancelled.

II. Monography

1. Literature review

1.1. Cardiovascular system and hemodynamic parameters

The cardiovascular system is responsible for the distribution and delivery of oxygen and nutrients to cells and collection of carbon dioxide and other cell-waste products.

The heart is a perfect coordination between electrical impulses and muscular contraction. The electrical impulses are spontaneously generated in the sinoatrial (SA) node and then conducted throughout specialized conduction cells (internodal pathways), the atrioventricular (AV) node and the His-Purkinje system to the myocytes, culminating in the contraction of the cardiac muscle fibres (Muir & Hubbell, 2009; Doherty & Valverde, 2006). All the specialized cardiac fibres mentioned above have the ability to self-generate an action potential. Nevertheless, the SA node cells create these spontaneous action potentials faster, being, therefore, the site where the impulse starts in a normal heart (pacemaker) (Marr & Bowen, 2010; Cunningham, 2004).

This system is characterised by two interdependent circulations, pulmonary and systemic, each with its own unique features. The first one is the low-pressure part of the circulation and is responsible for the exchange of carbon dioxide and oxygen, while the last one works on high-pressure ensuring that the blood flow reaches the whole organism (Doherty & Valverde, 2006). The efficacy of this system is dependent mainly on three interconnected parameters: the blood flow, the peripheral vascular resistance and the blood pressure (Corley, 2004). The blood flow (Q) is directly influenced by the pressure difference (∆P) and inversely correlated with the peripheral vascular resistance (PVR), as evidenced by the Poiseuille's law of flow (Orsini & Divers, 2014):

$$Q = \frac{\Delta \mathrm{P}}{PVR}$$

Considering the above, the cardiovascular function can be clinically evaluated by a number of quantifiable components such as cardiac output (CO), heart rate (HR), stroke volume (SV) and blood pressure (BP) (see **Figure 1**).

The cardiac output is the volume of blood expelled by the left, or right, ventricle in one minute (L/min). It can be calculated multiplying the ventricular stroke volume (mL/beat) with the heart rate (beats per minute – bpm) (Muir & Hubbell, 2009; Reed, Bayly, & Sellon, 2018; Corley, 2004; Cunningham, 2004). In adult conscious healthy horses an adequate cardiac output is between 32 and 40L/min (Doherty & Valverde, 2006). Additionally, in order to allow the comparison of between species, the cardiac output (mL/min) can be devised by the body weight (Kg), obtaining the cardiac index (mL/Kg/min) (Corley, 2004). In adult conscious horses the cardiac index (CI) ranges from 70 to 90 mL/Kg/min (Doherty & Valverde, 2006).

$$CO = SV * HR$$

$$CI = \frac{CO}{body\ weight}$$

There are a wide range of techniques, both invasive and non-invasive, to determine the CO and their choice relies on the species and size of the patient, as well as the operator experience to perform them, since it can significantly change the data obtained. Regarding that, the three invasive methods commonly used are: the pulmonary artery thermodilution method, the lithium dilution method and the Fick method. The method of pulmonary artery thermodilution has the ability to measure the CO in adult horses using thermal energy (body temperature) as an indicator. It implies the placement of a catheter in the pulmonary artery and the injection of a cold isotonic solution directly in the right atrium. After that the CO is calculated as the area under the curve in a plot with the indicator against time (Shih, 2018). The lithium dilution is similar to the last one and uses a central catheter to inject lithium in the circulation and an arterial catheter for sample collecting. It is possible to use it during exercise and in anaesthetized foals (Marr & Bowen, 2010; Shih, 2018). The Fick method is one of the first methods described to measure the CO and obliges the evaluation of arterial and venous oxygen content and the respiratory gases by placing a catheter in the pulmonary artery and performing blood gas analysis (Marr & Bowen, 2010). Nevertheless, the CO can be measured non-invasively resorting to echocardiography, which itself can provide large information about the haemodynamic, structural and functional parameters of the heart, besides the CO. Despite having insignificant risk to the horse, it implies the presence of an experienced operator to avoid erroneous data collection (Shih, 2018).

Horses' heart is highly innervated by sympathetic and parasympathetic nervous fibres. The sympathetic nervous system is responsible for the rise of the heart rate, for example under exercise or fight-or-flight situations, releasing epinephrine and norepinephrine. Contrarily, the parasympathetic fibres have a distinctive vagal tone which is accountable for a particularly slow resting heart rate, when compared to other species (Doherty & Valverde, 2006; Marr & Bowen, 2010). The normal heart rate in a horse is between 24 and 40bpm. The electrical activity of the heart can be exhaustively assessed by auscultation with a stethoscope, electrocardiography or echocardiography allowing the evaluation of the rate of the heart beats and its components, as well as the existence of dysrhythmias (Marr & Bowen, 2010). The heart rate has greater influence in the cardiac output rather than the ventricular stroke volume, justified by the reduction of the diastole's time caused by an increased heart rate (tachycardia), leading to a compromised ventricles' filling capacity which, in turn, reduces the cardiac output (Doherty & Valverde, 2006).

The ventricular stroke volume is the blood expelled by the ventricles in one beat (mL/beat). It depends on the myocardial contractility, preload and afterload, and it's determined by the difference between the ventricular volume in the end of the diastole and in the end of the systole (Doherty & Valverde, 2006; Shih, 2018; Corley, 2004).

$$SV = (end - diastolic\ ventricular\ volume) - \ (end - systolic\ ventricular\ volume)$$

The myocardial contractility, also called inotropy, is the ability of the cardiac muscle fibres to contract, which in turn is dependent on the calcium concentration and its release to the sarcomere (Reed, Bayly, & Sellon, 2018). The preload is determined by the volume of blood in the left ventricle in the end of the diastole and is measurable as the maximum ventricular fibres length, which is not conceivable in living animals. As such, preload can be explained by the Frank-Starling principle that describes the mechanisms that maintain the harmony between the heart's force of contraction and venous return without extrinsic regulation, such as humoral or neural pathways (Doherty & Valverde, 2006; Jones & Lumb, 2015). Lastly, the afterload is the resistance against which the ventricle ejects the blood and can be indirectly estimated by measuring the arterial blood pressure (Doherty & Valverde, 2006; Marr & Bowen, 2010).

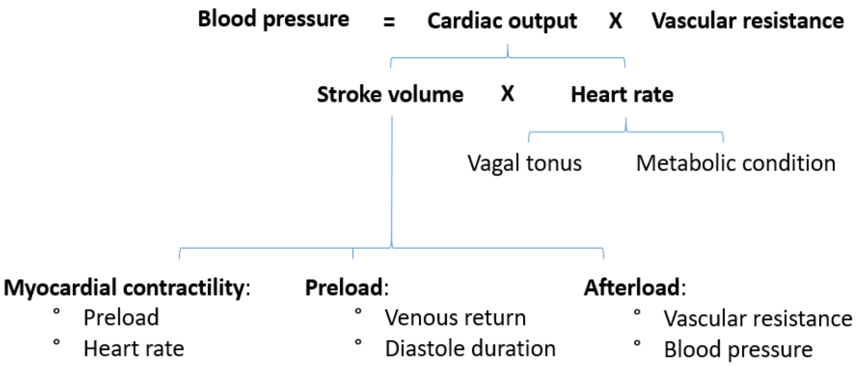

Figure 1 – Summary of some parameters influencing the cardiovascular function, such as blood pressure (BP), cardiac output (CO), stroke volume (SV) and heart rate (HR). Adapted from (Marr & Bowen, 2010).

The cardiovascular system in horses has a great capacity to modulate the different haemodynamic parameters referred above to preserve the normal tissue perfusion, and additionally, its interaction and coordination with the respiratory and urinary systems can be of upmost advantage. Despite that, once under extreme conditions, such as intense exercise or systemic diseases, this compensatory capacity can be exceeded, with major influence on the CO, mostly due to inadequate circulating volume which, in turn, causes a decrease of the preload and, consequently reduces stroke volume and afterload, impairing cardiovascular function (Corley, 2004).

The cardiac diseases such as anatomic malformation including valvar, myocardial or pericardial defects, functional impairment or other underlying cause, have an obvious effect on the cardiovascular function, which can be major or minor depending on the severity of the disorder (Reed, Bayly, & Sellon, 2018). Beyond that, it is also important to keep in mind the pericardium as well as the pleura, since an increased pressure inside the pericardium or the pleura may lead to a compromise in the diastole and, consequently the ventricular filling is affected (Reed, Bayly, & Sellon, 2018). Considering other systems, the horse's gastrointestinal tract is the foremost important when accounting for fluid loss, since bacterial endotoxins and ischaemia disrupt the integrity of the intestinal wall and result in a fluid movement to the intestinal lumen, causing dehydration. These events and the consequent decrease of peripheral vascular resistance promote a hypovolemic state, diminishing the preload and, therefore the stroke volume, compromising the correct functioning of the heart which can be life-threatening (Corley, 2004; Reed, Bayly, & Sellon, 2018).

1.2. Anaesthesia and the cardiovascular system

Anaesthesia can remarkably modify the cardiovascular function since most drugs used alter the preload, afterload, cardiac output, and heart's inotropy and chronotropy. These effects, coupled with the physiological and anatomical characteristics of the horse, make anaesthesia very challenging, which justifies the high mortality rate when compared to other species, approximately 1% in healthy horses and around 2% in sick horses undergoing emergency procedures (Johnston, Eastment, Wood, & Taylor, 2002; Dugdale & Taylor, 2016; Johnston, Talor, Holmess, & Wood, 1995; Johnston G. M., 2005). Thus, during anaesthesia it is essential to have a constant surveillance of the horse to guarantee an adequate physiologic body function and anaesthesia depth, as well as nociception relief and muscle relaxation (Doherty & Valverde, 2006; Taylor & Clarke, 2007). The cardiorespiratory monitoring is of upmost importance and helps the anaesthetist to predict and correct in good time changes that may compromise the survival or recovery of the horse (Shih, 2018; Heliczer, Lorelei, Casoni, & Navas de Solis, 2016).

Furthermore, the American Society of Anesthesiologists (ASA) created a classification system (see **Table 1**), used worldwide, based on the patient's pre-anaesthetic condition, co-morbidities and physical and haematological examination in order to be aware of the anaesthetic risks and post-op prognostic (American Society of Anesthesiologists, 2019; Association of Veterinary Anaesthetists, 2008).

Table 1- American Society of Anesthesiologists (ASA) classification system based on the pre-anaesthetic examination and co-morbidities of the horse, to assess the perioperative risks. Adapted from (American Society of Anesthesiologists, 2019).

Classification	Pre-anaesthetic condition and co-morbidities
ASA I	Healthy horse
ASA II	Healthy horse with moderate systemic disease e.g. mild anaemia, mild airway obstruction
ASA III	Horse with severe systemic disease e.g. severe airway obstruction
ASA IV	Horse with severe and life-threatening systemic disease e.g. intestinal volvulus
ASA V	Moribund horse with life expectation <24hours e.g. foal with uroperitoneum with marked metabolic imbalance
E	Emergency procedure e.g. colic

ASA, American Society of Anesthesiologists; E, Emergency; <, less than.

Monitoring the cardiovascular system in a horse under general anaesthesia informs the anaesthetist how well the body perfusion is, which itself depends on the cardiac output. However it isn’t practical to measure the cardiac output during elective surgical procedures, hence the evaluation is indirect through pulse, mucous membranes, electrocardiogram (ECG) and arterial blood pressure (the last is covered later in this work) (Taylor & Clarke, 2007).

The pulse can be evaluated in the peripheral circulation by pulse oximetry and by palpation of arteries that run more superficially, such as the facial artery, the transverse facial artery, the metacarpal or metatarsal arteries, the digital arteries or the coccygeal artery. The pulse is influenced by the heart’s contractility and stroke volume and depends on the difference between the systolic and diastolic blood pressure (pulse pressure) and when assessing it one should take into account the rate, strength and rhythm (Taylor & Clarke, 2007). A normal pulse rate range between 24-40bpm. A low pulse rate (bradycardia) indicates electrolyte imbalance, for example hypercalcemia or hyperkalemia, or heart blocks and, on the other hand, a high pulse rate (tachycardia) is associated to metabolic or systemic disorders, such as Cushing’s disease, colic, fever, anaemia, infection, shock, and moderate to severe pain (Cunningham, 2004; Marr & Bowen, 2010). A weak pulse (hypokinetic) results from a low cardiac output, hypovolemia or increased peripheral vascular resistance (vasoconstriction), resultant from septic shock, for instance. Contrariwise a strong pulse (hyperkinetic) points to an increased stroke volume (mostly due to congenital cardiac diseases). An irregular pulse can be a consequence of multiple disorders such as an electrolyte imbalance, metabolic acidosis, hypovolemia or increased peripheral vascular resistance (Doherty & Valverde, 2006; Marr & Bowen, 2010).

The mucous membranes monitoring is usually performed in the gums, and gives an idea of the peripheral tissue perfusion and oxygenation by assessing its humidity, capillary refill time and colour. The capillary refill time should be under two seconds, indicating a normal cardiac output thus, a delayed refill time is related to perfusion problems and low blood pressure and cardiac output. The mucous membrane colour evaluation is subjective nonetheless directs the thoughts towards certain perfusion or systemic issues, for example: pink (normal), pale pink (hypoperfusion), yellow (icteric), red (congestive) and blue (cyanotic or hypoxia) (Taylor & Clarke, 2007).

The ECG is an assessment of the electrophysiology of the heart and can show rhythm alterations (arrhythmias) as well as blocks on the heart's impulse conduction system. By placing the electrodes in certain points of the horse's body, the ECG detects the potential differences of the electrical fields and presents them as a wave with a positive or negative deflection according to the direction of the current of depolarization and the electrodes position. The magnitude of the deflection correlates to the quantity of depolarized myocardial tissue (Marr & Bowen, 2010). The positioning of the electrodes intends to create a triangle (Einthoven's triangle) in which the heart is the centre (see **Figure 2**), creating leads, i.e. a measurable potential difference between two electrodes, one negative and one positive. In the horse lead I is between the red (right arm, -) electrode and the yellow (left arm, +) electrode, the lead II between the red (right arm, -) electrode and the green (left foot, +), and lead III is between the yellow (left arm, -) electrode and the green (left foot, +) electrode (Marr & Bowen, 2010; Verheyen, et al., 2010). Usually the electrodes are positioned along the apex-base lead, that is, red (right arm) electrode is placed either at the top of the right scapula or in the low two thirds of the right jugular (lower neck), the yellow (left arm) electrode is placed at the cardiac apex, and the green electrode is positioned on the left side anywhere away from the heart, i.e. it doesn't have a specific position (Marr & Bowen, 2010; Mitchell, 2019). Mind that the colours of the referred electrodes correspond to the International Electrotechnical Commission (IEC) standard.

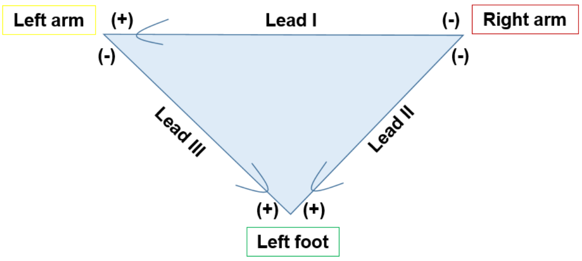

Figure 2 – Einthoven's triangle. Leads created by the positioning of a negative and a positive electrode on the patients' body: lead I between the red (right arm, -) electrode and the yellow (left arm, +) electrode, lead II between the red (right arm, -) electrode and the green (left foot, +), and lead III between the yellow (left arm, -) electrode and the green (left foot, +) electrode. The colours of the electrodes correspond to the International Electrotechnical Commission (IEC) standard.

The interpretation of an ECG trace must be careful and methodical. The electric impulse originated in the SA node, leads to the atria depolarization, which corresponds to the P wave in the ECG trace. The impulse is then delayed in the AV node originating a waiting complex without any deflection (PR interval). As the impulse continues, the ventricular depolarization occurs creating the QRS complex. The atrial repolarization occurs while the ventricular contraction is taking place and, as its repolarization impulse is weaker, the signal vanishes within the QRS complex. The ventricles' refractory period is represented by the ST interval in which no deflection is detected. The repolarization of the ventricles produces the T wave deflection (see **Figure 3**) (Marr & Bowen, 2010).

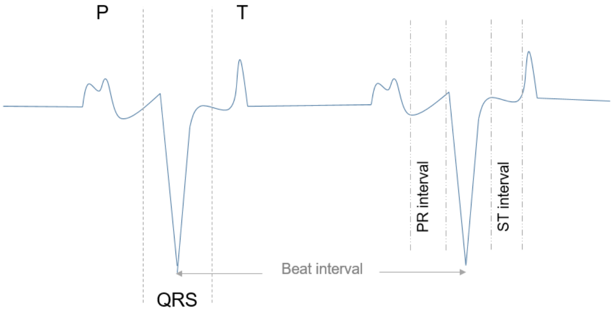

Figure 3 – Electrocardiogram (ECG) trace, with demonstration of the P wave produced by the atrial depolarization, the PR interval corresponding to the AV node impulse delay, the QRS complex created by the ventricular depolarization, the ST interval representing the ventricular refractory period, and the T deflection consistent with the ventricular repolarization. Adapted from (Marr & Bowen, 2010).

1.2.1. Anaesthetic drugs and its influence in the cardiovascular system

The drugs used in sedation, tranquilization and anaesthesia induction have wide-ranging effects, either directly or indirectly, on the cardiovascular system, influencing heart rate, cardiac output and systemic blood pressure (see **Table 2**) (Muir & Hubbell, 2009). Some of the drugs more commonly used in equine practice and its influence on the cardiovascular system will be described below.

Acepromazine is a phenothiazine drug that blocks the α_1-adrenergic receptors, decreasing the vascular tone (vasodilatation). This mechanism lessens the afterload as well as the preload and, consequently, reduces the heart's inotropy and cardiac output, therefore, decreasing the blood pressure, improving the blood perfusion and oxygenation of the peripheral tissues. Additionally it has antiarrhythmic properties. Regard that it must not be used in hypovolemic patients due to the substantial hypotension created (Taylor & Clarke, 2007; Doherty & Valverde, 2006). In low-doses, acepromazine is used via intramuscular approximately one hour prior to surgery as a cardioprotective agent, since reducing the myocardium's workload, decreases the risk of cardiac arrest in anaesthetised horses (Taylor & Clarke, 2007).

Additionally this drug smooths out the induction, maintenance and recovery of anaesthesia (Taylor & Clarke, 2007; Marr & Bowen, 2010).

The α_{2}-agonists, of which the most commonly used are xylazine, romifidine and detomidine, are sympathomimetic sedative agents responsible for the induction of bradycardia due to its effect on the baroreceptors pathways and on the SA node, increasing the vagal tone. These drugs cause vasoconstriction (increased peripheral vascular resistance) and transient hypertension followed by hypotension, and marked decreased of the cardiac output (Doherty & Valverde, 2006; Taylor & Clarke, 2007). The α_{2}-agonists use allows the reduction in the minimum alveolar concentration (MAC) of volatile drugs, especially if constant rate infusion (CRI) is given during general anaesthesia (Doherty & Valverde, 2006; Muir & Hubbell, 2009).

Opioids, such as butorphanol, are usually associated with α_{2}-agonists agents to sedate the horse (Muir & Hubbell, 2009). These drugs have a potent analgesic effect and a minimal effect on the cardiovascular system, including the cardiac output and blood pressure, nevertheless, are known to stimulate the vagal tone, slowing the heart rate (Riviere & Papich, 2018).

For the anaesthesia induction a combination of a muscle relaxant, usually a benzodiazepine, with a dissociative drug, such as ketamine, is used. Benzodiazepines, such as diazepam and midazolam, are muscle relaxants and promote the response to GABA, having insignificant cardiac effects (Taylor & Clarke, 2007). Ketamine increases the sympathetic nervous system activity and, indirectly, causes an increase in the heart's inotropy and chronotropy, which leads to the rise of the cardiac output and blood pressure (Doherty & Valverde, 2006; Muir & Hubbell, 2009). This drug is characterized by three main effects: catalepsy, amnesia and analgesia (Doherty & Valverde, 2006).

Volatile anaesthetics, like isoflurane, depend on the well function of both respiratory and cardiovascular systems to work, since a better alveolar perfusion leads to a greater anaesthetic absorption. Therefore, if the cardiac output is increased, the MAC is reduced, that is, it is necessary a smaller volatile drug's concentration to keep the horse anaesthetised (Doherty & Valverde, 2006). This group of drugs reduces the heart's inotropy, leading to a decreased stroke volume, cardiac output and heart rate. Simultaneously, these drugs diminish the peripheral vascular resistance (vasodilatation), hence occurring hypotension (Doherty & Valverde, 2006; Muir & Hubbell, 2009).

Catecholamines are short half-life sympathomimetic biologic amines. Depending on the receptor to which it links, different effects are expected: the β_{1}-adrenergic receptors are responsible for the increase of the myocardial contraction and heart's chronotropy, affecting directly the cardiac output and blood flow; the β_{2}-adrenergic receptors and α-adrenergic receptors have opposite effects on the vessels, the first mediates vasodilatation while the last one is responsible for vasoconstriction (Corley, 2004; Riviere & Papich, 2018). The use of catecholamines must be careful since it can have an arrhythmic effect (Corley, 2004). Dobutamine is a catecholamine frequently used during anaesthesia due to its strong affinity to the β_1-adrenergic receptors, hence increasing the cardiac output, in addition to its important effect as an inotrope, which results in the rise of the blood pressure, contradicting the hypovolemic effect of the volatile anaesthesia, and thus, perfusion and oxygen delivery to the peripheral tissues becomes more efficient (Corley, 2004; Muir & Hubbell, 2009).

Table 2 – Haemodynamic effects of the most commonly used drugs for tranquilization, sedation and anaesthesia induction and maintenance in horses.

Drug	Cardiac output	Heart's inotropy	Heart's chronotropy	Vascular tone	Blood pressure
Acepromazine	↓	↓	↓	↓	↓
α_2-agonists	↓	-	↓	↑→↓	↑→↓
Opioids	↓	↓	↓	-	↓
Ketamine	↑	↑	↑	-	↑
Benzodiazepines	-	-	-	-	-
Volatile agents	↓	↓	↓	↓	↓
Catecholamines	↑	↑	↑	↑	↑

↑, increase; ↓, decrease; →, followed by; -, minimal or insignificant effect.

In horses that undergo general anaesthesia, hypotension is a common issue that needs to be solved straightaway to avoid life-threatening complications. If the mean arterial blood pressure is less than 65mmHg a sequential procedure must be applied to restore the perfusion and the oxygen delivery to the tissues. Firstly, the main goals are to eliminate as much as possible the hypotensive agents in the body, which can be obtained by reducing the percentage of volatile anaesthetic, since it is an extremely hypotensive drug, and simultaneously, increase the cardiac output by increasing the preload through an upturn of the fluid therapy rate. If those procedures have none or little effect on the mean arterial pressure, pharmacological intervention is required, such as the use of vasoactive drugs, like dobutamine, and sequentially, hypertonic fluids (saline solution 7.5%) or even colloid fluids (Brown & Holmes, 1981; Corley, 2004). In some hospital practices dobutamine is given intravenously (IV) in constant rate infusion (CRI) in every surgery as part of the standard anaesthetic protocol, whilst in other hospitals dobutamine is only used when the mean arterial blood pressure is lower than 65mmHg.

1.3. Arterial blood pressure

The arterial blood pressure is defined as the product of cardiac output by peripheral vascular resistance (PVR), being an extremely useful haemodynamic parameter that reflects the blood flow to the organs and assesses indirectly the cardiovascular function and the tissular perfusion (Muir & Hubbell, 2009).

$$BP = CO * PVR$$

As blood pressure is highly dependent on several pathways and mechanisms that act together to assure a normal tissue perfusion (see **Figure 1**), a normal blood pressure is not always associated to haemodynamic homeostasis (Pinsky & Payen, 2005). For example, the arterial baroreceptors located at the aorta's arch and at the carotid artery's bifurcation are responsible for the balance between the parasympathetic and sympathetic stimulus, in response to the changes in the arterial blood pressure. Therefore, if a rise in the arterial blood pressure is detected by the baroreceptors, it leads to an enhance of the parasympathetic stimuli, which, consequently, inhibits the sympathetic tone, and results in the decrease of the heart rate, the cardiac output (negative inotropy) and the peripheral vascular resistance (vasodilatation) guaranteeing an adequate blood flow to the peripheral tissues (Muir & Hubbell, 2009). This means that, an adequate tissue perfusion is assured within a range of arterial blood pressure values. The mean arterial blood pressure relates better to the systemic circulation status and tissue perfusion, than systolic or diastolic arterial pressure (Pinsky & Payen, 2005; Corley, 2004). If the mean arterial blood pressure is below 65mmHg, i.e. hypotension, the blood flow to certain tissues, including brain, kidneys, and the coronary arteries is not guaranteed (Pinsky & Payen, 2005).

There is no consensus in the intervals considered normal for systolic, diastolic, and mean arterial blood pressure values (see **Table 3**), yet it is accepted that in horses anaesthetized the blood pressure is slightly lower than in awake standing horses due to the effect of the drugs administered for anaesthesia induction and maintenance (Taylor, 1981). In conscious and standing horses, the authors assume that, when using invasive blood pressure monitoring (IBP), the systolic arterial blood pressure (SAP) values range from 168mmHg to 120mmHg, for diastolic blood pressure (DAP) values are acceptable between 116mmHg and 70mmHg, and for mean arterial pressure (MAP) the interval is between 133mmHg and 94mmHg, whilst for non-invasive blood pressure methods (NIBP) the interval for SAP is 125mmHg and 95mmHg, for DAP ranges from 91mmHg to 54mmHg, and lastly for MAP is 89mmHg ± 14 (average ± standard deviation [SD]) (Shih, 2018; Magdesian, 2004; Fielding & Magdesian, 2015; Orsini & Divers, 2014; Reed, Bayly, & Sellon, 2018; Marr & Bowen, 2010). On the other hand, in horses under general anaesthesia using the invasive blood pressure measurement, the values for SAP are 106.6mmHg ± 8.5, for DAP are 59.7mmHg ± 5.3 and for MAP are 76.1 mmHg ± 5 (average ± standard deviation [SD]), whereas for NIBP the values are 103.3mmHg

± 10.8 for SAP, 59.6mmHg ± 10.1 for DAP and 75.7mmHg ± 8.6 for MAP (Heliczer, Lorelei, Casoni, & Navas de Solis, 2016; Reed, Bayly, & Sellon, 2018).

Table 3 – Summary and comparison of the systolic, diastolic and mean arterial blood pressure values considered normal, obtained with invasive (IBP) and non-invasive (NIBP) methods, for both standing conscious horses and horses under general anaesthesia, according to different references.

Method	**SAP** (mmHg)	**DAP** (mmHg)	**MAP** (mmHg)	Reference
Standing and conscious horses				
IBP	168 ± 6	116 ± 4	133 ± 4	(Parry, McCarthy, & Anderson, 1984)
	168 – 126	116 – 85	133 – 110	(Orsini & Divers, 2014) (Magdesian, 2004)
	142 ± 18	82 ± 12	106 ± 12	(Hurcombe & Scott, 2012)
	135 ± 15	90 ± 15	110 ± 15	(Shih, 2018)
			135 – 105	(Johnson, Garner, & Hutcheson, 1976)
NIBP	125 – 99	91 – 54		(Orsini & Divers, 2014)
	112 ± 17	77 ± 14	89 ± 14	(Parry, McCarthy, & Anderson, 1984)
	111.8 ± 13.3	67.7 ± 13.8	> 60	(Hurcombe & Scott, 2012) (Johnson, Garner, & Hutcheson, 1976) (Magdesian, 2004)
Anaesthetized horses				
IBP	106.6 ± 8.5	59.7 ± 5.3	76.1 ± 5	(Heliczer, Lorelei, Casoni, & Navas de Solis, 2016)
			> 60	(Hurcombe & Scott, 2012)
NIBP	103.3 ± 10.8	59.6 ± 10.1	75.7 ± 8.6	(Heliczer, Lorelei, Casoni, & Navas de Solis, 2016)

SAP, Systolic arterial pressure; DAP, Diastolic arterial pressure; MAP, Mean arterial pressure; IBP, Invasive blood pressure monitoring; NIBP, Non-invasive blood pressure monitoring; >, above; average ± standard deviation (SD).

1.3.1. Arterial blood pressure monitoring

The arterial blood pressure monitoring can be performed either invasively (or directly) or non-invasively (or indirectly), with different advantages and disadvantages for each one (Kurtz, Griffin, Bidani, Davisson, & Hall, 2005).

Nevertheless there are a number of factors that can influence the blood pressure values, such as size of the horse, breed, sex and age (Brown & Holmes, 1981). The size of the horse registered as the height difference from the place where the blood pressure is measured and the heart’s level, which can influence the data obtained due to hydrostatic pressure. In the same way that the size of the horse influences the blood pressure, the head position in a horse under general anaesthesia also influences the hydrostatic homeostasis, since if the head is lower than the heart there is more pressure detected in the carotid sinus and a negative feedback mechanism is activated to lower the blood pressure (Brown & Holmes, 1981).

Although not consensual, mares appear to have a slightly lower blood pressure, about 5 to 8mmHg in the systolic blood pressure and 4 to 7mmHg in the diastolic blood pressure, than stallions and geldings (Brown & Holmes, 1981).

In foals the non-invasive blood pressure measurement is very similar to the invasive blood pressure, since the thickness of the skin around the peripheral arteries is very thin, enhancing the accuracy of the values obtained, when comparing to adult horses (Giguère, Knowles, Valverde, Bucki, & Young, 2005; Brown & Holmes, 1981). In foals under one year old the blood pressure seems to be higher than in adult horses, and there's no significant difference in horses between 2 and 10 years old (Brown & Holmes, 1981).

1.3.1.1. Invasive arterial blood pressure measurement

The invasive arterial blood pressure measurement method provides a continuous monitoring of the blood pressure (Taylor, 1981). This technique is considered the gold-standard in horses that undergo general anaesthesia and consists in the catheterization of a peripheral artery (Shih, 2018). The arteries commonly used for catheterization are the facial artery, transverse facial artery and metatarsal or metacarpal arteries, and the chosen site takes into consideration if the pulse is easily palpated, even when the horse has low blood pressure (hypotension), as well as the surgical procedure to which the horse will be subjected, i.e. it has to be an easily accessible site (Shih, 2018; Doherty & Valverde, 2006).

To place the catheter there are different techniques, however the easiest and far most common is the slide-off technique in which the needle of the catheter approaches the artery with a 45º angle and once the blood appears on the tip of the catheter the operator places the catheter parallel to the artery and slides it off into the artery, ensuring that the blood keeps coming through and thus, that the tip of the catheter inside the artery it's free and not against its wall. After this the catheter is fixed to the horse with glue or tape to prevent it from getting out of place (see **Figure 4**). The catheter is then connected to a transducer through a fluid system (Taylor, 1981).

Figure 4 – Arterial catheter placed in the horse's facial artery.

A transducer is a system that converts a mechanical signal, in the case of blood pressure is a pulsatile signal, to an electrical one, that can be visualized in the multiparameter monitor as a pressure wave form. In order for this to work, it is necessary to have a continuous column of fluid, usually a saline fluid, connecting the transducer to the fluid (blood) in the patients' body. To have accurate readings the transducer has to be zeroed at the level of the heart, meaning that the transducer system sets the pressure sent to it as the atmospheric pressure. If the transducer is placed lower than the level of the heart, the blood pressure values will rise in millimetres of mercury (mmHg) correspondent to the centimetres (cm) of height difference to the heart level, and the other way around, rising the transducer will decrease the blood pressure values obtained.

The arterial catheterization allows the visualization of a pressure waveform that shows the systolic and the diastolic blood pressure and the pulse pressure (PP) which is the difference between the systolic and diastolic blood pressure (see **Figure 5**). The pulse wave correlates the stroke volume and the compliance of the arterial system. Therefore, a fast and abrupt decline of the wave suggests little peripheral vascular resistance to the blood flow (vasodilatation), and a slow and curved decline is associated to higher peripheral vascular resistance, i.e., vasoconstriction (Marr & Bowen, 2010). This is important to detect early any changes in the arterial blood pressure either hypotension or hypertension (Benes, et al., 2015).

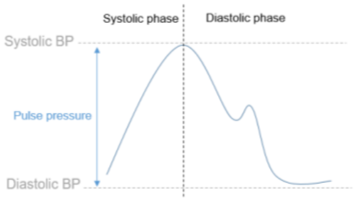

Figure 5 – Pressure wave visualized in the multiparameter monitor as a result of the transducer conversion of a pulsatile signal into an electrical signal. With the pressure wave is possible to see both systolic and diastolic blood pressure (BP), as well as the pulse pressure (which is the difference between the systolic BP and the diastolic BP).

Furthermore, the catheterization provides an easy access to arterial blood collection which is useful for blood gas analysis. The blood gas monitoring is a practical way to assess if the lungs are being well-perfused during the anaesthesia, since ventilation is highly dependent on the blood supply to the lungs and a poor perfusion can lead to hypoxaemia (Scheer, Perel, & Pfeiffer, 2002; Marr & Bowen, 2010).

There are some precautions that have to be considered along the process with this invasive technique: first and foremost, it is essential to do a local asepsis before placing the percutaneous catheter into the artery with a chlorhexidine solution followed by an alcohol solution, in order to avoid infections and other complications, secondly, during its use, regular flush with heparinized saline fluid must be done, to stop the clotting of the catheter's lumen, and lastly, immediately after removing the catheter, pressure should be done on the artery for a few minutes preventing the formation of an haematoma (Taylor, 1981).

Despite being the reference method to measure the arterial blood pressure, this technique has some issues that must be considered. Occasionally the catheterization of the artery can be a time consuming procedure, during which time the anaesthetist has no information about the horse's arterial blood pressure, hence the need of an trained operator to perform it. Beyond that, it can have some minor complications such as bleeding at the puncture site, haematoma, incorrect readings due to improper zeroing of the transducer, extremely long lines between the catheter and the transducer or air/thrombus in the system that can degrade the signal conversion decreasing the blood pressure values (Meidert & Saugel, 2018; Doherty & Valverde, 2006), or even major complications, e.g., carpal tunnel syndrome, trauma to the vessels or nerves, temporary occlusion of the artery, permanent ischaemia, local infection, sepsis, pseudo-aneurysm and thrombosis (Scheer, Perel, & Pfeiffer, 2002).

1.3.1.2. Non-invasive arterial blood pressure measurement

The non-invasive blood pressure monitoring measures the blood flow through an artery, and the methods used are divided into two subgroups: intermittent measuring devices, in which the values obtained are punctual, i.e., represent the blood pressure at a given moment, and continuous measuring devices that allow the making of a curve of values in a given time frame (Meidert & Saugel, 2018).

The intermittent measurement can be performed manually or automated (see **Figure 7**). In both the technique consists in the use of an inflatable cuff that is placed over a peripheral artery (usually the coccygeal artery or metacarpal/metatarsal artery), being manually or automatically inflated to a pressure greater than the systolic pressure to occlude the arterial flow in one body tip (tail or limbs). Manually the blood pressure detection is achieved either by palpation or auscultation of the artery distal to cuff. The palpation can be performed in a noisy environment but only gives the systolic blood pressure that is a result of the pulse returning to the artery, while the auscultation requires a silent environment to listen to the onset of the Korotkoff sounds using a stethoscope, where the first sound corresponds to the systolic blood pressure and, as the cuff deflates, its pressure equals the patient's pressure and the pulse sound becomes less intense, thus the last sound gives the diastolic blood pressure (Meidert & Saugel, 2018). The automated, or oscillometric, technique inflates the cuff until a predetermined pressure value to occlude the artery (see **Figure 6**). After this, the cuff is gradually deflated until the recommencement of flow throughout the artery produces changes in the blood flow resulting in a first pulse that is registered as the systolic blood pressure. As it continues to deflate the sensors detect the oscillations in the arterial vessels and the maximal oscillation registered corresponds to the mean blood pressure. The deflation of the cuff lasts until the sensors lose the ability to detect any pulse, and that is identified as the diastolic blood pressure (Taylor, 1981). Most oscillometric devices can be programmed to measure the arterial blood pressure intermittently with interval periods ranging between 1 and 480 minutes, but cannot provide a real-time pulse waveform.

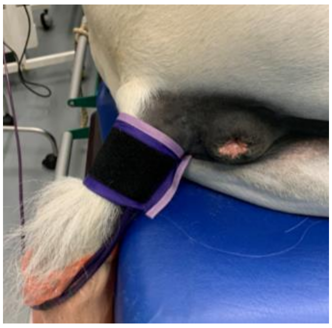

Figure 6 – Cuff placement in the tail for the non-invasive oscillometric technique.

The continuous measurement devices include the “volume clamp” method and the “arterial flattening tonometry” method (see **Figure 7**). The first one combines the use of a cuff and photodiode on a peripheral artery. The cuff pressure ensures that the artery diameter is constant (measured by the photodiode) in order to detect the pressure changes in the cuff that are subsequently displayed in a monitor (Meidert & Saugel, 2018). In the “arterial flattening tonometry” technique, as the name implies, the artery is flattened between a bone and a transducer which has the ability to read the pressure changes of the artery producing a pulse wave form visible in the monitor. Contrarily to the intermittent techniques, the continuous measurement of the blood pressure provides a real-time pulse waveform similar to the one obtained with the invasive blood pressure monitoring (Meidert & Saugel, 2018).

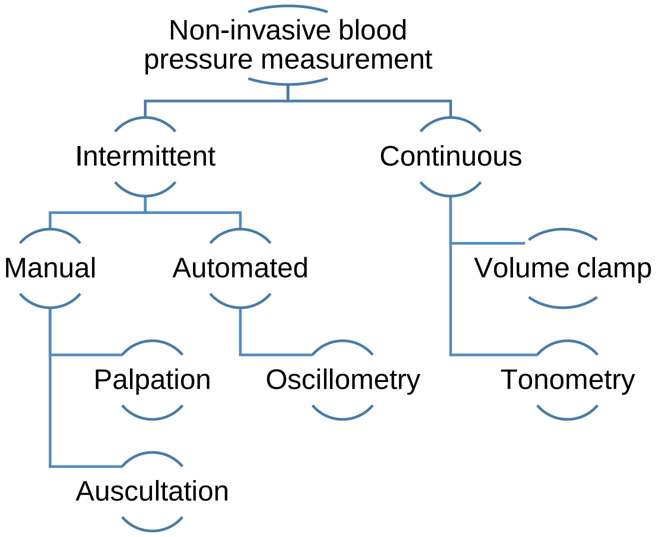

Figure 7 – Non-invasive blood pressure measurement methods. Adapted from (Meidert & Saugel, 2018).

To be useful in the clinical practice, the non-invasive methods for blood pressure monitoring must be practical and reliable (Taylor, 1981). The main advantage of these methods is that they can be used on both conscious and standing and anesthetized horses. Thus, some technical features must be regarded in both intermittent and continuous methods.

The greatest flaw of the intermittent methods is only providing punctual readings of the blood pressure. However other fragilities should be considered such as incorrect values if the cuff is not placed correctly or if the cuff is moved during the measurement (either due to patient's movements or someone touching the cuff), overestimation of the lower values and the underestimation of the higher values, and impossibility of placing the cuff due to the patient positioning associated to the surgical procedure (Meidert & Saugel, 2018; Doherty & Valverde, 2006). The auscultation and the palpation methods require an operator to obtain the blood pressure measurements (Branson, 1997), have low accuracy and lack some essential information, since either are unable to provide the MAP (Meidert & Saugel, 2018). With the oscillometric technique the width of the cuff must not be neglected as it has an important influence on the results obtained. If the cuff is too narrow the arterial blood pressure values are higher (overestimation), since the occluding pressure isn't enough and the systolic pulse returns too early. On the other hand, if the cuff size is too wide, the pulse takes longer time to return and the systolic pressure values are lower (underestimation) (Taylor, 1981; Reed, Bayly, & Sellon, 2018). The optimal cuff size is not consensual and also depends on the sensitivity of the machine used, as well as the manufacturer's instructions. Nevertheless, the most universally accepted is that the cuff size must be 30% or 40% of the tail's circumference (Doherty & Valverde, 2006), therefore a cuff with 9 cm of width should be suitable to most adult horses (Brown & Holmes, 1981). Concerning the cuff positioning it is important to consider that it is more efficient to place the cuff on the tail rather than the limbs, because most cuffs have a short length and slither off when inflated in the horse's members (Taylor, 1981).

Regarding the continuous methods they present high sensitivity to the horses' movements, and consequently, in conscious standing horses they can provide erroneous data (Meidert & Saugel, 2018). Moreover, it has been demonstrated that the continuous non-invasive blood pressure measurement has low accuracy and precision when compared to the reference method (invasive blood pressure), therefore it isn't reliable to consider it for clinical decisions (Kim, et al., 2014).

1.3.2. Accuracy and precision of the invasive and the non-invasive blood pressure measurements

As referred above, the electrocardiogram may be unchanged, whilst the cardiac output, and consequently the arterial blood pressure are deficient (Taylor, 1981). Therefore, it is of the upmost importance to have reliable cardiovascular monitoring methods. Considering this, and despite the continuous invasive blood pressure monitoring, the determination of the sensitivity and accuracy of non-invasive blood pressure measurement methods, is crucial so that they can be widely used outside the surgery context.

The blood pressure readings are more accurate when corrected to level of the heart (Taylor, 1981). Hence the height difference between the heart and the place where the arterial blood pressure is measured has to be considered due to hydrostatic pressure influences (Brown & Holmes, 1981). With the invasive arterial blood pressure (IBP), the transducer is placed at the level of the heart (usually the reference point is the tip of the scapula). On the other hand, for the non-invasive blood pressure (NIBP) measurements some authors defend that, in order to enhance the accuracy of the measurements obtained, it is necessary to apply a correction factor. It is possible to convert centimetres (cm) into millimetres of mercury (mmHg) dividing the height difference (measured in cm) by 1.36mmHg (13.6Kg/L is the specific gravity of mercury) (Lakhal, Ehrmann, & Boulain, 2017; Taylor, 1981). Other authors achieved the same goal assuming that each centimetre corresponds to 0.74mmHg (Tünsmeyer, Hopster, Feige, & Kästner, 2015), 0.75mmHg (Drynan, Schier, & Raisis, 2016; Yamaokaa, Flahertya, Pawsona, Scottb, & Auckburally, 2017) or 0.77mmHg (Heliczer, Lorelei, Casoni, & Navas de Solis, 2016; Reed, Bayly, & Sellon, 2018). If the cuff is placed below the heart's level the resultant value is subtracted of the non-invasive measurement, and if the cuff is placed above the level of the heart the value is added to the initial measurement (Taylor & Clarke, 2007). However, if the horse is on lateral recumbency the hydrostatic effects lose their influence on the values of the non-invasive arterial blood pressure (Brown & Holmes, 1981).

As regards the non-invasive oscillometric method, the mean arterial pressure (MAP) is obtained directly, while the systolic (SAP) and diastolic (DAP) pressures are obtained using algorithms predetermined by the monitor's manufactures. Therefore, the most accurate reading is the mean arterial blood pressure, followed by the systolic, since the blood flow underneath the cuff is stronger, and lastly the diastolic blood pressure, in which the cuff sensitivity to the blood flow changes is lower (Reed, Bayly, & Sellon, 2018; Meidert & Saugel, 2018).

When comparing the invasive and the non-invasive blood pressure data, it is expected for the systolic arterial pressure data obtained with the NIBP to be lower than the one collected with the IBP. This can be justified by the limited ability of the cuff to detect small flow changes that occur during the short period of time as the cuff deflates, and won't detect the arterial blood pressure until there is a substantial volume of blood flow beneath it (Brown & Holmes, 1981). Furthermore, the agreement between the techniques is higher in anaesthetized horses, since the movements in conscious horses can remarkably change the NIBP readings (Heliczer, Lorelei, Casoni, & Navas de Solis, 2016).

1.3.3. Clinical application

The arterial blood pressure measurement can be clinically useful for diagnosis, therapeutic monitoring and prognosis of various diseases (Taylor, 1981). To do so, the technique used to measure the arterial blood pressure non-invasively must be practical and easily applied either in conscious or anaesthetized horses (Taylor, 1981).

Horses in intensive care units often have systemic diseases and / or, either primary cardiovascular impairment, or secondary to an adjacent illness, that can diminish the tissue perfusion and consequently compromise the prognosis of the horse (Corley, 2004). For that reason, the arterial blood pressure is an easy way to evaluate the haemodynamic status, allowing a rapid and early intervention in case of a hypotension or hypertension (rare), since both can impair the function of the vital organs, compromising the patient’s life. Notice that hypotension is always pathological and is associated with unfavourable outcome, since it is the cause of hypoperfusion and ischaemia of vital organs, such as brain, renal and coronary arteries (Südfeld, et al., 2017; Benes, et al., 2015; Pinsky & Payen, 2005).

2. Aims

2.1. Overall goal and specific aims

The accuracy and precision of non-invasive blood pressure monitoring in horses is not yet well-defined. Consequently, this technique it's not being used to its full clinical potential.

This project's overall goal is to compare the blood pressure values obtained with a non-invasive method to those measured with the invasive method using the EDAN iM8 multiparameter monitor in horses presented for elective surgical procedures at the Equine Surgery and Emergency Service (Serviço de Cirurgia e Urgência de Equinos, [SCUE]) of the veterinary faculty of Lisbon's University, between September of 2019 and April of 2020.

The blood pressure measurements can help guide clinical and therapeutic procedures in critical-ill patients and foals. Considering the wide clinical potential of non-invasive blood pressure monitoring it is essential to determine the efficacy of this technique, since that in some circumstances, it's not possible to assess the blood pressure using an invasive method.

To do so, specific aims were outlined:

a. Register the horses' parameters: age, weight, tail's circumference, vertical height between the tail and heart levels.
b. Measure and register simultaneously the values for systolic, diastolic and mean blood pressure with a non-invasive oscillometric technique and the invasive gold-standard technique.
c. Statistically analyse the results obtained.

3. Methods

All measurements and procedures described in this chapter were optimized and systematically revised in order to minimize inter and intra-assay variability.

3.1. Study design & Patient selection

This is a prospective clinical study that investigates the accuracy and precision of NIBP and IBP measurements using EDAN iM8 VET monitor in anaesthetised adult horses.

Adult horses undergoing general anaesthesia for elective surgical procedures were enrolled in this study. Since no additional invasive procedures were performed beyond those that are part of the normal surgical and anaesthetic procedures of the mentioned hospital no further consent was required.

Health status of every individual was classified accordingly to the American Society of Anesthesiologists (ASA) (American Society of Anesthesiologists, 2019), based on the physical exam and both haematological and biochemistry results. Only horses with no history of cardiac diseases or other health problems, apart from the reason of the elective surgery (classification: ASA I) were involved in this study. Horses under one year old and ponies were excluded from this project because they did not meet the cuff size criteria used during the study. There was no exclusion criteria based on the weight, breed or gender.

3.2. Surgery

3.2.1. Patient preparation

Complete and thorough physical examination is required before every elective surgical procedure, as well as haematological, ionogram and serum chemistry analysis, including creatine kinase (CK), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), creatinine (Creat), blood urea nitrogen (BUN) and total protein (TP).

A 12 hour period of food-fasting and 8 hour water-fasting was imposed to diminish the risk of aspiration pneumonia or stomach rupture caused by impact trauma during induction or recovery from general anaesthesia (Doherty & Valverde, 2006). The mouth was flushed with water to avoid food residues to go into the airways when the horses were intubated.

A jugular catheter (intraflon2 80mm 12G, Vygon, France) was placed in every horse, with preference on the right jugular vein, except if the vein was damage by any reason (e.g. due to previous injections or longstanding jugular catheter placement) or if the surgical procedure required otherwise.

3.2.2. Medication pre and post-surgery

Anti-tetanic serum (Inmuser CT, Ovejero, Spain) 3000UI subcutaneously (SC) or intramuscularly (IM) was given to horses that were admitted to surgery without the tetanus vaccination protocol up-to-date.

Acepromazine (Calmivet, Vetoquinol, France) 0.04mg/Kg IM, was given to every horse 45 minutes to one hour before the induction of general anaesthesia.

Antibiotic therapy was performed in every horse according to the hospital's protocols: procaine penicillin (Depocilin, MSD Animal Health, Spain), 22000UI/Kg IM BID, starting before the surgical procedure, up to a maximum of five days post-op if necessary, and gentamicin (Gentasol, Labiana, Spain) 6.6mg/Kg IV SID, also starting before the surgery until 3 days post-op, if necessary. However, to one horse was administered marbofloxacin (Marbocyl, Vetoquinol, France) 2mg/Kg IV SID alone, and another horse was administered cefquinome (Ceffect, Bayer, Spain) 2 mg/Kg IM BID, instead of procaine penicillin, taking into consideration previous antibiotic sensitivity test results.

The horses were premedicated with anti-inflammatories. For orthopaedic surgeries phenylbutazone (Phenylarthrite, Vétoquinol, France) 4.4mg/Kg IV was administered before surgery and 2.2mg/Kg IV 12 hours after the first administration, and for castrations was given flunixin meglumine (Nixyvet, DFV Divasa-Farmavic, Spain) 1.1 mg/Kg IV BID. The protocol for all elective surgical procedures switches the anti-inflammatory to suxibuzone (Danilon, Esteve, France) 1.5g *per os* (PO) BID, 36 hours after surgery.

As recommended, all drugs used in the described protocols were given before sedation (Doherty & Valverde, 2006).

3.2.3. Anaesthesia protocol

The horses underwent the same anaesthesia protocol, except two, in which detomidine was replaced by romifidine.

Sedation was performed using detomidine (Domidine, Dechra, Spain) 0.01mg/Kg IV or romifidine (Sedivet, Boehringer Ingelheim, USA) 0.04mg/Kg IV, plus butorphanol (Dolorex, MSD Animal Health, Spain) 0.04mg/Kg IV, in the induction room. After the horse was profoundly sedated, general anaesthesia induction was performed with diazepam (Diazedor, Richter pharma, Spain) 0.05mg/Kg IV and ketamine (Ketamidor, Richter pharma, Spain) 2.2mg/Kg IV. As soon as the horse recumbent the orotracheal intubation was performed with a 24-26mm endotracheal tube. Subsequently, the horse was hoisted with straps, placed in the operating table according to the surgical procedure and surgeon's preference and then connected to the large animal anaesthesia machine (TitanXL, DRE veterinary, USA).

Anaesthesia was maintained in a closed circle system with oxygen (4-6L/min) mixed with isoflurane (IsoFlo, Zoetis, United Kingdom) with controlled ventilation. The horses were ventilated with a peak pressure of 30 cmH_2O, a tidal volume of 15mL/Kg and the respiratory rate was adapted to the patients' needs ranging between 5-8/minute. The horses with the anaesthetic protocol that included romifidine for sedation, received a constant rate infusion (CRI) of romifidine 40µg/Kg/h during surgery, as required.

Anaesthesia monitoring equipment were set in place for continuous overseeing of the horse's parameters and displayed in a multiparameter monitor (EDAN iM8 VET, China) including electrocardiogram (ECG) for continuous monitoring of horses heart rate (HR), capnography to measure the end-tidal carbon dioxide ($ETCO_2$), pulse oximetry for continuous non-invasive calculation of oxygen saturation (sO_2), and arterial pressure measurements.

If the horse showed signs of superficialization of the anaesthesia a bolus administration of ketamine (Ketamidor, Richter pharma, Spain) 0.55mg/Kg IV was given, with exception on the last 30 minutes of surgery. In that case xylazine (Rompun, Bayer, Spain) 0.3-0.6mg/Kg IV, was given instead.

Fluidtherapy was performed in every horse with Ringer's solution (LacRinger, Braun, Germany) and in some cases sodium chloride solution (NaCl 0.9%, Braun, Germany) to correct some acid-base imbalance. A dobutamine solution (Dobutamina, Generis, Portugal) 0.25 – 0.5µg/Kg/minute IV, was administered intraoperatively in constant rate infusion (CRI) to prevent hypotension or if the mean arterial blood pressure value was below 65mmHg, as required.

Arterial blood gas analyses were performed with an iSTAT machine (iSTAT1, Abbott, USA) using CG4+ cartridge ($CG4^+$, Abbott) every 30 minutes after the surgery started to evaluate the acid-base status and ventilation. The cartridges used provide information about pH, partial pressure of carbon dioxide (PCO_2) and of oxygen (PO_2) (mmHg), base excess (BE) (mmol/L), bicarbonate (HCO_3) (mmol/L), end-tidal carbon dioxide (TCO_2) (mmol/L), oxygen saturation (sO_2) (%) and blood lactate (mmol/L).

At the end of each anaesthesia the horse was hoisted back to the recovery room and extubated when the swallow reflex returned.

3.3. Study protocol: Blood pressure measurement methods

In all horses' invasive (standard procedure) and non-invasive blood pressure monitoring was performed and recorded simultaneously.

After clipping and aseptic preparation, a catheter (introcan-W 20G 1¼", Braun, Germany) was used to cannulate percutaneously the facial or the facial transverse artery and connected to the multiparameter monitoring equipment (EDAN iM8 VET, USA) through a saline fluid-filled non-expandable extension line. The pressure transducer was placed and zeroed at the heart's level, having as a reference point the tip of the right scapula. The arterial blood pressure was continuously recorded and the arterial catheter was flushed with heparinized fluid (3000IU/L) (Heparina sódica, Braun, Portugal; NaCl 0.9%, Braun, Germany) every 10 minutes.

The non-invasive arterial blood pressure measurements were obtained by an oscillometric technique. A cuff was placed around the unclipped horse's tail, near its base, with the sensors centred with the median coccygeal artery. The width of the cuff was between 30% and 40% of the tail's circumference. As soon as the cuff was correctly placed the readings started and were programed to be automatically performed every minute during the entire anaesthesia and displayed in the same monitor as the invasive blood pressure measurements (EDAN iM8 VET, USA). The maximum pressure to inflate the cuff was predetermined on the referred monitor and set at 200mmHg. Each non-invasive reading took between 40-60 seconds. If the cuff is moved or touched during the measurement time, an interference in the reading is recorded and the values fail to appear on the monitor. In such event the equipment would only redo the blood pressure measurement at the next scheduled time.

The data collection started immediately after the arterial catheter was placed and connected to the monitor and throughout the entire procedure until the end of the anaesthesia.

3.4. Data & statistical analysis

The data collected for both invasive (IBP) and the non-invasive (NIBP) arterial blood pressure measurements were introduced in a datasheet and separated into three columns with the systolic (SAP), the diastolic (DAP) and the mean (MAP) blood pressure values.

To perform the statistical analysis three major groups were considered: the first one with the paired readings all together, a second group with a subdivision according to the patient's recumbency during the surgical procedure (dorsal or left lateral recumbency), and a third group considering the values of the invasive mean arterial blood pressure (considered as the reference): hypotension (when MAP is ≤65mmHg), normotension (if MAP is between 65mmHg and 90mmHg) and hypertension (when MAP >90mmHg).

To evaluate the correlation between the invasive and the non-invasive blood pressure for systolic, diastolic and mean blood pressure measurements the Pearson correlation coefficient (R) was calculated.

To compare the invasive (reference method) and the non-invasive (alternative method) systolic, diastolic and mean arterial blood pressure measurements was used the Bland-Altman method of agreement between the reference method of measurement and an alternative one, with multiple observations per individual (Bland & Altman, 1999; 2007). The bias was calculated as the mean difference between the invasive and non-invasive techniques for systolic, diastolic and mean arterial blood pressure measurements. To interpret the results, notice that a negative bias corresponds to an overestimation of the invasive blood pressure measurements by the non-invasive technique and, in turn, a positive result indicates an underestimation of the invasive blood pressure measurements. The 95% limits of agreement of the differences between the invasive and the non-invasive blood pressure measurements are calculated and are obtained as the mean difference (bias) ± (1.96 x standard deviation (SD) of the bias) mmHg (Bland & Altman, 1999; 2007). Thereafter, the Bland-Altman plots of the differences between the IBP and the NIBP against the mean of each pair of readings were drawn, including the lines representing the bias ± 1.96 x SD for the SAP, DAP and MAP, using a commercial statistics software (GraphPad Prism 5, GraphPad Software, Inc., CA, USA).

The validation of the non-invasive blood pressure method was assessed accordingly to the American College of Veterinary Internal Medicine (ACVIM) Hypertension Consensus Panel (AHCP) and Veterinary Blood Pressure Society (VBPS) recommendations for dogs and cats (Brown, et al., 2007). Therefore, the non-invasive blood pressure measurement method is considered acceptable if the study includes more than 8 subjects, the mean difference (bias) between the invasive and non-invasive techniques is ≤10mmHg and the standard deviation (precision) is ≤15mmHg and the correlation coefficient (R) between the values obtained with both techniques is ≥0.9, amongst other criteria (Brown, et al., 2007). The interpretation of such criteria must, however, ensure that account is taken for the fact that they are based on studies for dogs and cats, and not for horses.

4. Results

4.1. Patients & surgery

A total of 11 horses admitted at SCUE of the veterinary faculty of Lisbon's University requiring general anaesthesia for elective surgical procedures were enrolled in this study, of which only two were mares. Every horse's health status was classified as ASA I accordingly to the American Society of Anesthesiologists (American Society of Anesthesiologists, 2019). The horses' age ranged between 1 and 13 years old (8 ± 3.82years [average ± standard deviation]) and the weight between 350 and 600kg (514 ± 71.76Kg).

There were seven orthopaedic surgical procedures, including four arthroscopies, two surgeries for desmotomy and fasciotomy of the deep branch of the plantar lateral nerve and one surgery to remove plate and screws. Five horses were submitted to castration (one horse had an orthopaedic surgery and a castration). Of all surgical procedures only two were performed in left lateral recumbency and the remaining nine in dorsal recumbency. The surgery time ranged between 58 and 270 minutes (115.91 ± 63.01 minutes).

Every horse, at some point, required the use of dobutamine intraoperatively in order to maintain the mean arterial blood pressure value above 65mmHg, except the horses in which romifidine was included in the anaesthesia protocol.

4.2. Blood pressure measurement data

In this study, a total of 533 paired readings from the invasive and the non-invasive techniques of systolic, diastolic and mean arterial blood pressure were obtained from the 11 horses.

The site for the placement of the arterial catheter depended on the horse's position. For the horses on dorsal recumbency all had the catheter on the facial artery, either left or right, and for the horses on left lateral recumbency, one had the catheter on the transverse facial artery and the other on the facial artery.

For the oscillometric method, in every horse, the cuff was placed around the unclipped tail, near its base, with the sensors centred with the median coccygeal artery. This method was programmed to measure the blood pressure every minute during the entire surgery time, starting as soon as the invasive method was correctly placed. At some time points, due to external interference in the cuff while the measurement was occurring, the measurement's reading time was automatically extended to try to read the blood pressure, even so, if this method fail to detect the pressure pulses, the monitor would show the error messages "Cuff interference" or "Time out", and the equipment did the blood pressure measurement at the next scheduled time. The tail's circumference ranged from 20 to 30cm, and the mean ratio between the width of the cuff and the tail's circumference was 39.9%, which is in accordance with the manufacturer's instructions.

4.3. Descriptive statistics & Bland-Altman analysis

In order to assess the accuracy of the paired readings obtained in our study, the descriptive statistics and the Bland-Altman analysis are presented separately into three groups: the readings all together, a group considering the horses' recumbency (dorsal and left lateral) and other group considering the blood pressure categories: hypotension (when the invasive (reference technique) measurement of MAP is ≤65mmHg), normotension (if MAP is between 65 and 90mmHg) and hypertension (when MAP >90mmHg).

4.3.1. For all the paired readings

The average and standard deviation (SD) values of the readings of invasive and non-invasive blood pressure measurements obtained simultaneously in a multiparameter monitor (EDAN iM8 VET), as well as the Bland-Altman analysis for the paired readings including the mean difference (bias), the bias's standard deviation, the upper and lower 95% limits of agreement, and the Pearson correlation coefficient (R), are summed in the **Table 4**.

Table 4 – Descriptive statistics, including the mean and standard deviation (SD) of all the paired readings for invasive and non-invasive measurements, and Bland-Altman analysis with the bias, bias's standard deviation, upper and lower 95% limit of agreement and the Pearson correlation coefficient (R) for systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP).

Statistical analysis	Arterial blood pressure		
	SAP	**DAP**	**MAP**
Number of paired readings	533	533	533
Invasive mean ± SD (mmHg)	109 ± 17.3	71 ± 14.3	84 ± 14.5
Non-invasive mean ± SD (mmHg)	106 ± 17.5	65 ± 13.5	82 ± 15.4
Bias (mmHg)	3.2	5.7	1.7
SD of bias (mmHg)	17	12	13
Upper limit of agreement (mmHg)	36	29	27
Lower limit of agreement (mmHg)	-30	-17	-23
Correlation coefficient (R)	0.53	0.64	0.64

The Bland-Altman plots of agreement between the IBP and the NIBP, with multiple observations per individual, for SAP, DAP and MAP are shown in **Figure 8**. The bias and the bias's SD were 3.2 ± 17mmHg for SAP, 5.7 ± 12mmHg for DAP and 1.7 ± 13mmHg for MAP (see **Table 4**). The upper and lower limits of agreement were 36 and –30mmHg, 29 and –17mmHg and 27 and –23mmHg, for SAP, DAP and MAP, respectively. The Pearson correlation coefficients (R) were 0.53 for SAP and 0.64 for DAP and MAP. The correlation plots are presented in Appendix 2.

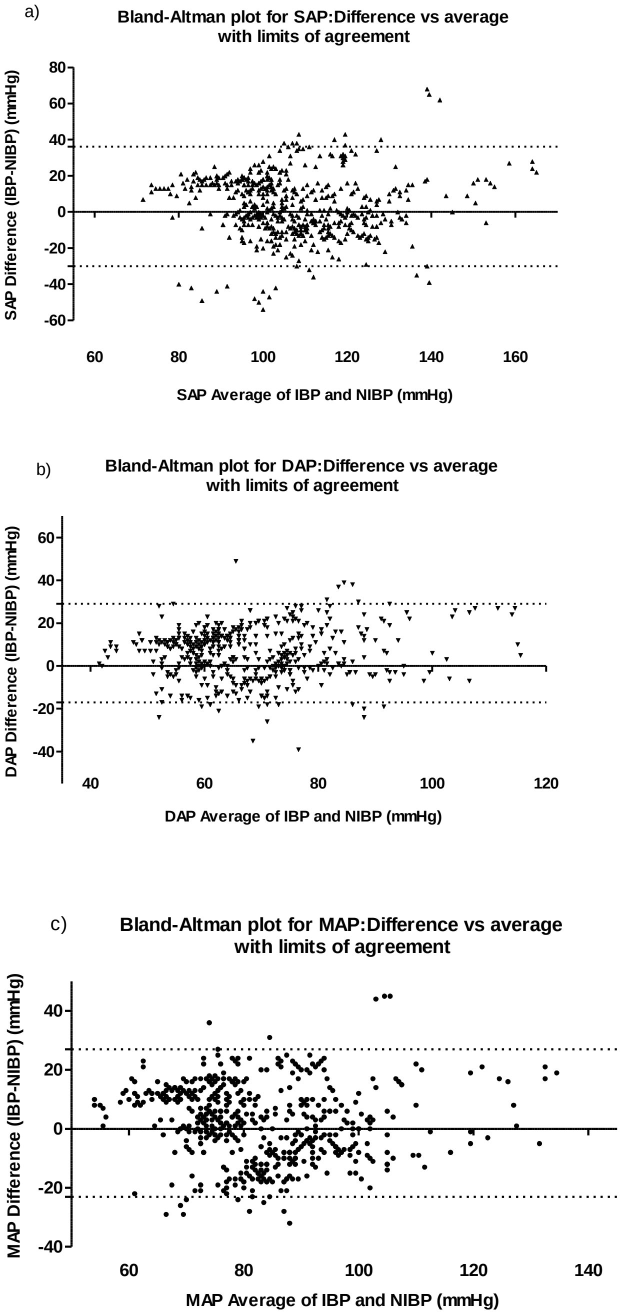

Figure 8 – Bland-Altman plots for the paired readings of the blood pressure measurements to show the agreement between the invasive (IBP) and non-invasive (NIBP) methods for the **a)** systolic blood pressure (SAP), **b)** diastolic blood pressure (DAP) and **c)** mean blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP). The upper and lower lines in each plot represent the limits of agreement between the two methods.

4.3.2. Considering the horses’ recumbency

When analysing the horse’s data considering their recumbency there were 142 paired readings for the left lateral recumbency and 391 for the dorsal recumbency. The data analysis performed included the average and standard deviation (SD) values for the readings of invasive and non-invasive blood pressure measurements obtained simultaneously in a multiparameter monitor (EDAN iM8 VET), as well as the Bland-Altman analysis for the paired readings including the mean difference (bias), the bias’s standard deviation, the upper and lower 95% limits of agreement, and the correlation coefficient (R), and are presented separately in the **Table 5**.

Table 5 - Descriptive statistics, including the mean and standard deviation (SD) of all the paired readings for invasive (IBP) and non-invasive (NIBP) measurements, and Bland-Altman analysis with the bias, bias’s standard deviation, upper and lower 95% limit of agreement and the Pearson correlation coefficient (R) for systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP).

Statistical analysis	Arterial blood pressure		
	SAP	DAP	MAP
Left lateral recumbency			
Number of paired readings	142	142	142
Invasive mean ± SD (mmHg)	110 ± 17.7	67 ± 11.0	81 ± 12.9
Non-invasive mean ± SD (mmHg)	88 ± 10.0	53 ± 6.4	66 ± 7.9
Bias (mmHg)	22	14	15
SD of bias (mmHg)	10	6.2	6.8
Upper limit of agreement (mmHg)	42	26	29
Lower limit of agreement (mmHg)	2.1	1.7	2.1
Correlation coefficient (R)	0.87	0.87	0.9
Dorsal recumbency			
Number of paired readings	391	391	391
Invasive mean ± SD (mmHg)	109 ± 17.2	73 ± 15.0	85 ± 14.9
Non-invasive mean ± SD (mmHg)	112 ± 14.8	70 ± 12.5	88 ± 13.0
Bias (mmHg)	-3.6	2.8	-3.3
SD of bias (mmHg)	13	12	11
Upper limit of agreement (mmHg)	23	26	18
Lower limit of agreement (mmHg)	-30	-20	-24
Correlation coefficient (R)	0.66	0.64	0.72

The bias and the SD of bias were 22 ± 10mmHg for SAP, 14 ± 6.2mmHg for DAP and 15 ± 6.8mmHg for MAP for the horses in left lateral recumbency and –3.6 ± 13mmHg for SAP, 2.8 ± 12mmHg for DAP and –3.3 ± 11mmHg for MAP for the horses in dorsal recumbency. The 95% limits of agreement for the horses in left lateral recumbency were from 2.1 to 42mmHg for SAP, from 1.7 to 26mmHg for DAP and from 2.1 to 29mmHg for MAP, while for the horses in dorsal recumbency were from -30 to 23mmHg for SAP, from -20 to 26mmHg for DAP and from -24 to 18mmHg for MAP. The Pearson correlation coefficient (R) for the horses in left lateral recumbency were 0.87 for SAP and DAP and 0.9 for MAP, and for the horses in dorsal recumbency were 0.66, 0.64 and 0.72 for SAP, DAP and MAP, respectively (see **Table 5**). The Bland-Altman plots of agreement between the IBP and the NIBP, with multiple observations per individual, for SAP, DAP and MAP are shown separately for the horses in left lateral recumbency (see **Figure 9**) and for the horses in dorsal recumbency (see **Figure 10**). The correlation plots are presented in Appendix 2.

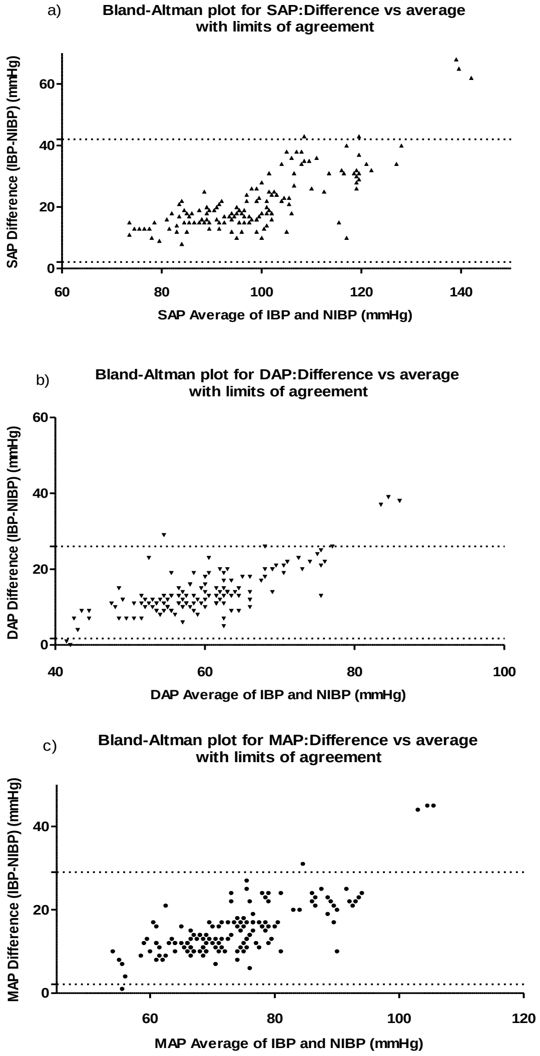

Figure 9 - Bland-Altman plots for the paired readings of the blood pressure measurements to show the agreement between the invasive and non-invasive methods for the **a)** systolic blood pressure (SAP), **b)** diastolic blood pressure (DAP) and **c)** mean blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP), for the horses in left lateral recumbency. The upper and lower lines in each plot represent the limits of agreement between the two methods.

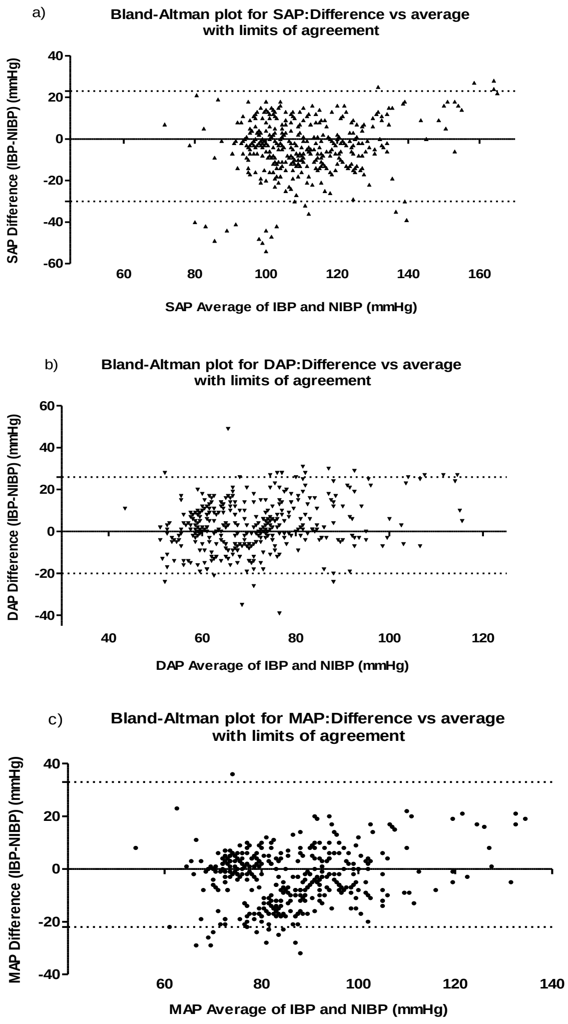

Figure 10 - Bland-Altman plots for the paired readings of the blood pressure measurements to show the agreement between the invasive and non-invasive methods for the **a)** systolic blood pressure (SAP), **b)** diastolic blood pressure (DAP) and **c)** mean blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP), for the horses in dorsal recumbency. The upper and lower lines in each plot represent the limits of agreement between the two methods.

4.3.3. Considering the blood pressure group

The data obtained was also divided into three groups according to the values of the invasive mean arterial blood pressure (considered to be the reference). Therefore 24 paired readings were obtained for the hypotensive group (MAP ≤65mmH), 359 paired readings for the normotensive group (MAP between 65 and 90mmHg) and 150 paired readings for the hypertensive group (MAP >90mmHg). The statistical analysis was similar to the one performed for all the groups referred above and included the average and standard deviation (SD) values for the readings of invasive (IBP) and non-invasive (NIBP) blood pressure measurements obtained simultaneously in a multiparameter monitor (EDAN iM8 VET), the Bland-Altman analysis for the paired readings including the mean difference (bias), the bias's standard deviation, the upper and lower 95% limits of agreement, and the Pearson correlation coefficient (R), and are presented separately in the **Table 6**.

Table 6 - Descriptive statistics, including the mean and standard deviation (SD) of all the paired readings for invasive and non-invasive measurements, and Bland-Altman analysis with the bias, bias's standard deviation, upper and lower 95% limit of agreement and the Pearson correlation coefficient (R) for systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure measurements in anaesthetised adult horses obtained with an arterial catheter (IBP) and an oscillometric method (NIBP).

Statistical analysis	Arterial blood pressure		
	SAP	DAP	MAP
Hypotension (≤65mmHg)			
Number of paired readings	24	24	24
Invasive mean ± SD (mmHg)	82 ± 10.7	49 ± 4.3	60 ± 4.3
Non-invasive mean ± SD (mmHg)	90 ± 17	52 ± 10.3	67 ± 13.5
Bias (mmHg)	-7.9	-3.5	-7.4
SD of bias (mmHg)	22	11	15
Upper limit of agreement (mmHg)	36	18	22
Lower limit of agreement (mmHg)	-52	-25	-37
Correlation coefficient (R)	-0.29	0.05	-0.18
Normotension (65-90mmHg)			
Number of paired readings	359	359	359
Invasive mean ± SD (mmHg)	103 ± 9.1	65 ± 6.7	78 ± 6.2
Non-invasive mean ± SD (mmHg)	101 ± 14	61 ± 10.1	77.5 ± 12.1
Bias (mmHg)	2.5	3.9	0.31
SD of bias (mmHg)	16	10	12
Upper limit of agreement (mmHg)	33	24	24
Lower limit of agreement (mmHg)	-28	-17	-23
Correlation coefficient (R)	0.15	0.29	0.29
Hypertension (>90mmHg)			
Number of paired readings	150	150	150
Invasive mean ± SD (mmHg)	129 ± 16.1	89 ± 11.4	102 ± 11.7
Non-invasive mean ± SD (mmHg)	122 ±14.7	77 ± 13.3	96 ± 13.7
Bias (mmHg)	6.9	12	6.3
SD of bias (mmHg)	18	12	13
Upper limit of agreement (mmHg)	43	36	32
Lower limit of agreement (mmHg)	-29	-13	-19
Correlation coefficient (R)	0.30	0.50	0.49

The bias, the bias’s SD and the 95% limits of agreement were -7.9 ± 22 (from -52 to 36) mmHg for SAP, -3.5 ± 11 (from -25 to 18) mmHg for DAP and -7.4 ± 15 (from -37 to 22) mmHg for MAP for the readings in the hypotension group, 2.5 ± 16 (from -28 to 33) mmHg for SAP, 3.9 ± 10 (from -17 to 24) mmHg for DAP and 0.31 ± 12 (from -23 to 24) mmHg for MAP for the normotensive readings and, in the hypertensive group the results were 6.9 ± 18 (from -29 to 43) mmHg for SAP, 12 ± 12 (from -13 to 36) mmHg for DAP and 6.3 ± 13 (from -19 to 32) mmHg for MAP. The Pearson correlation coefficient (R) for all the groups was very poor (see **Table 6**). The correlation plots and Bland-Altman plots of agreement between the IBP and the NIBP, with multiple observations per individual, for SAP, DAP and MAP, are shown separately for the hypotensive, normotensive and hypertensive groups in the Appendix 2 and 3, respectively.

5. Discussion

The invasive blood pressure measurement method is defined as the gold-standard in horses. However, its use is not always possible, and a practical and reliable alternative method must be found. We investigated whether the oscillometric non-invasive method for measuring blood pressure has a good correlation to the invasive (gold-standard) method in healthy horses that undergo general anaesthesia for elective surgeries, using the EDAN iM8 VET multiparameter monitor. Our results showed that, for all the paired readings, MAP had the lower value of bias (1.7mmHg), while SAP and DAP had 3.2mmHg and 5.7mmHg, respectively, meaning that MAP is the most accurate reading of all three (SAP, DAP and MAP), as expected according to what is described in the literature. Despite having good bias (≤10mmHG), the precision (SD of bias) was low for SAP (17mmHg) and the correlation coefficient was low for SAP, DAP and MAP, and therefore did not meet the validation criteria recommended by the ACVIM (Brown, et al., 2007). Though, the interpretation of these validation criteria must be made with caution, since its extrapolation for horses has not been yet done.

In order to test the hypothesis that horses position on the surgical table as well as the BP range (hypo-, normo- and hypertensive), might influence the results we separated our data according to this variables.

Data analysis of the readings in different recumbencies showed that the bias for horses in left lateral recumbency was significantly higher (22mmHg, 14mmHg and 15mmHg for SAP, DAP and MAP, respectively) when compared to the values obtained in the horses in dorsal recumbency (-3.6mmHg for SAP, 2.8mmHg for DAP and -3.3mmHg for MAP). However, the SD of bias for all those readings was ≤15mmHg. The data obtained from the horses in left lateral recumbency had greater correlation (0.87 for SAP and DAP, and 0.9 for MAP) than the ones in dorsal recumbency, that showed correlation coefficients of 0.66 for SAP, 0.64 for DAP and 0.72 for MAP, which is understandable, since the hydrostatic forces in left lateral recumbency have little or no effect on the blood pressure values. Notice that, in dorsal recumbency, the horse’s tail is below the heart’s position, hence the hydrostatic forces are lower when compared to the readings of the IBP (in which transducer is placed at the level of the heart, therefore the readings are already corrected when displayed on the monitor) and it’s expected to have consistently lower values of blood pressure registered in the oscillometric method in comparison to the invasive one. Therefore, to adjust the values of NIBP, some correction factors have been proposed in order to contemplate the hydrostatic pressure that arises from the height difference between the level of heart and the tail. Notwithstanding, in some cases, the correction factor can be discarded on grounds that the error introduced by the positioning of the cuff is negligible/small (Hatz, Hartnack, Kümmerle, Hässig, & Bettschart-

Wolfensberger, 2015). In this study, the mean height's difference from the tail to the heart of the horses that were on dorsal recumbency was 43cm, which corresponds to an average increase of 32mmHg of the non-invasive blood pressure. Nevertheless, as the results obtained for the horses in dorsal recumbency where not consistently lower than the ones obtained with the invasive method, applying a correction factor would not be wise.

When datasets were split according to the blood pressure range, of all three groups (hypotensive, normotensive and hypertensive), the bias and precision showed better results for the normotensive group, as expected, followed by the hypertensive group, and, lastly, by the hypotensive group. Furthermore, the bias was negative (-7.9mmHg for SAP, -3.5mmHg for DAP and -7.4mmHg for MAP) for the results of the hypotensive group (≤65mmHg), i.e. there's an overestimation of the invasive blood pressure measurements by the non-invasive method, which is logical since the oscillometric technique has limited ability to detect pulse pressure when the blood flow is weak, due to poor peripheral perfusion, presenting higher values than the real ones. The precision (SD of bias) revealed to be worst in SAP for all the three groups. The correlation coefficients for these analysis were very low.

The data presented here cannot be directly compared to the results found in the literature, since the studies evaluated have different designs, using different arteries for both IBP and NIBP, applying or not the correction factors to the non-invasive measurements and including standing and conscious horses and anaesthetized ones, amongst other variants. Nevertheless, we find our results relevant since they highlight some of the limitations that the use of non-invasive blood pressure measurement methods have when considering them for clinically important decisions.

The cuff size must not be neglected, since it can induce major errors in the data obtained and, in this project we found it to be 40% of the tail's circumference, which is in agreement with the manufacturer's recommendations.

The number of horses enrolled in this project was the major setback, as the hospital has a great caseload of emergencies (surgical and medical) and, despite our efforts, and due to unexpected events, it was not possible to gather a bigger sample. We believe that a bigger sample would have helped clarify our results. However, the number of paired readings obtained throughout this study was similar to the ones found in literature, which allowed the statistical analysis thereof. Other possible limitation to this study is the involvement of different anaesthetists, which can lead to operator-related errors and increase the inter-patient, variance. However, considering the hospital´s management and logistics, the anaesthesia wasn't conducted by the same person in all cases.

Overall, with this work it was possible to confirm our hypothesis that the non-invasive blood pressure measurement method using the EDAN iM8 VET multiparametric monitor, despite being less accurate than the invasive technique, is an important tool to assess the patient’s condition and would not lead to dangerous clinical decision. The mean arterial blood pressure obtained with the non-invasive method showed a good correlation to the invasive blood pressure, in adult horses under general anaesthesia.

Combined together, the results presented here, although preliminary, are very promising in redirecting the therapeutic monitoring for horses.

6. Conclusions

The work presented here is an important step towards determining the accuracy and precision of the non-invasive blood pressure measurements in adult horses under general anaesthesia, using the EDAN iM8 VET multiparametric monitor, as a reliable method to be used in horses, both in surgery and, in therapeutic monitoring for critically-ill patients.

We were able to assess the correlation between the invasive and the non-invasive methods to measure the blood pressure, in three different ways: the readings all together, the readings separated by the horse's recumbency and by the horse's blood pressure range.

It is now possible to infer that, despite being less accurate than the invasive (gold-standard) method, the non-invasive blood pressure measurement method, using the EDAN iM8 VET multiparameter monitor, is reliable for the use in healthy anaesthetized horses. Moreover, we showed that the horses in left lateral recumbency have a better correlation than the horses in dorsal recumbency.

Adding to the fact that these results may lead to the creation of a more specific tool for the diagnosis and clinical monitoring of horses, the determination of the accuracy and precision of the non-invasive blood pressure measurement method would allow the possibility of using this method for therapeutic guidance in critically-ill patients and would not lead to harmful or life-threatening clinical decisions.

7. Future work

The work presented here is still preliminary and further studies are needed. The determination of the accuracy and precision of the non-invasive method to measure the blood pressure is crucial to its implementation and use in critical care patients. Furthermore, measuring the non-invasive blood pressure in adult horses, as well as in foals, with cardiovascular impairment either primary or secondary to colic, hypovolemic shock, endotoxemia, among other causes, can help to better monitor and guide the therapeutic approaches in each case.

During this project's development it was not possible to gather a bigger sample, since SCUE is a referral hospital with a large emergency caseload, and a smaller quantity elective surgeries. A bigger sample would make our results more reliable. Nevertheless, in future work we intend to successfully performed this task and, maybe, include patients with cardiovascular imbalances, such as horses with colic, to assess the sensitivity of the non-invasive blood pressure method under extreme conditions.

Additionally, it would also be interesting to measure the non-invasive blood pressure in standing conscious horses and assess if repeated measurements in the same horse for a predetermined time frame can influence the results obtained for the blood pressure as the horse gets acquaintance to the procedure performed.

The use of the tool assessed in (or following) this project may be decisive in the implementation of new diagnostic and therapeutic strategies leading to a personalized and more efficient medical care of horses, either in hospital, or in ambulatory practice.

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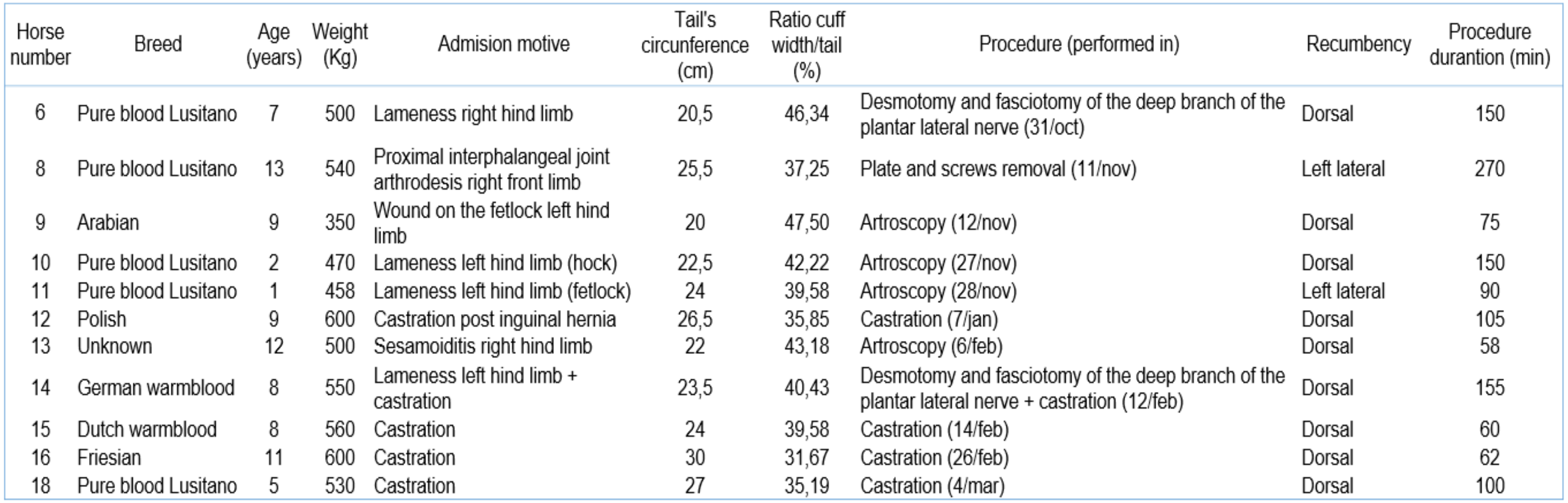
9. Appendix

9.1. Appendix 1 – Horses' data list

A general data collection was carried out for each horse at admission and during the procedure (see table below).



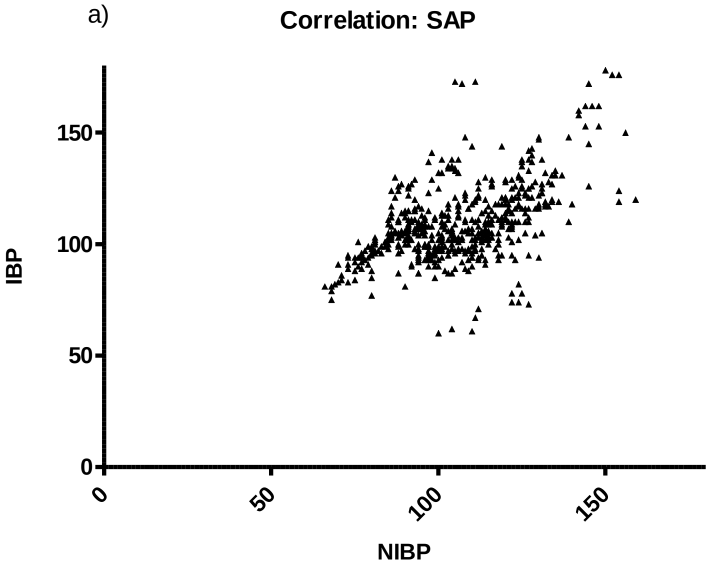
Horse number	Breed	Age (years)	Weight (Kg)	Admision motive	Tail's circumference (cm)	Ratio cuff width/tail (%)	Procedure (performed in)	Recumbency	Procedure durantion (min)
6	Pure blood Lusitano	7	500	Lameness right hind limb	20,5	46,34	Desmotomy and fasciotomy of the deep branch of the plantar lateral nerve (31/oct)	Dorsal	150
8	Pure blood Lusitano	13	540	Proximal interphalangeal joint arthrodesis right front limb	25,5	37,25	Plate and screws removal (11/nov)	Left lateral	270
9	Arabian	9	350	Wound on the fetlock left hind limb	20	47,50	Artroscopy (12/nov)	Dorsal	75
10	Pure blood Lusitano	2	470	Lameness left hind limb (hock)	22,5	42,22	Artroscopy (27/nov)	Dorsal	150
11	Pure blood Lusitano	1	458	Lameness left hind limb (fetlock)	24	39,58	Artroscopy (28/nov)	Left lateral	90
12	Polish	9	600	Castration post inguinal hernia	26,5	35,85	Castration (7/jan)	Dorsal	105
13	Unknown	12	500	Sesamoiditis right hind limb	22	43,18	Artroscopy (6/feb)	Dorsal	58
14	German warmblood	8	550	Lameness left hind limb + castration	23,5	40,43	Desmotomy and fasciotomy of the deep branch of the plantar lateral nerve + castration (12/feb)	Dorsal	155
15	Dutch warmblood	8	560	Castration	24	39,58	Castration (14/feb)	Dorsal	60
16	Friesian	11	600	Castration	30	31,67	Castration (26/feb)	Dorsal	62
18	Pure blood Lusitano	5	530	Castration	27	35,19	Castration (4/mar)	Dorsal	100

9.2. Appendix 2 – Correlation plots

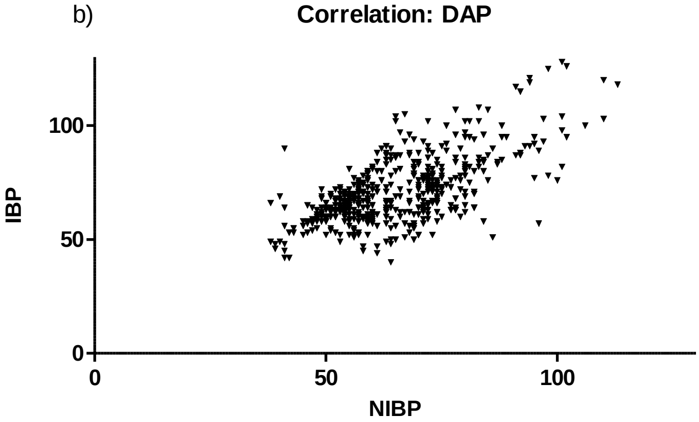
Correlation plots between the IBP and the NIBP values were made for SAP, DAP and MAP.

9.2.1. For all the paired readings

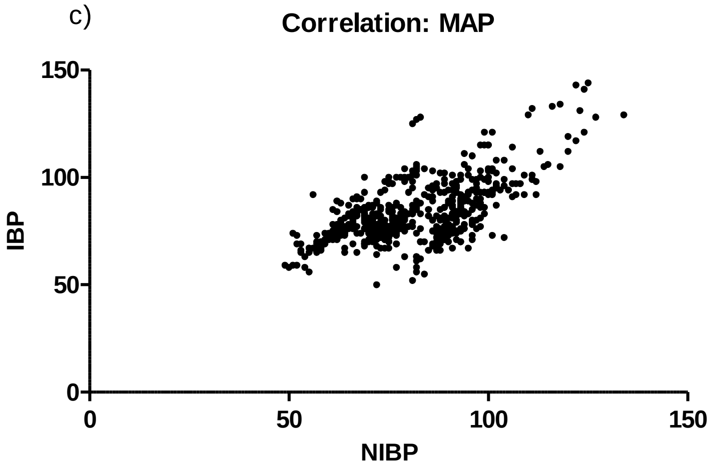
a)



b)



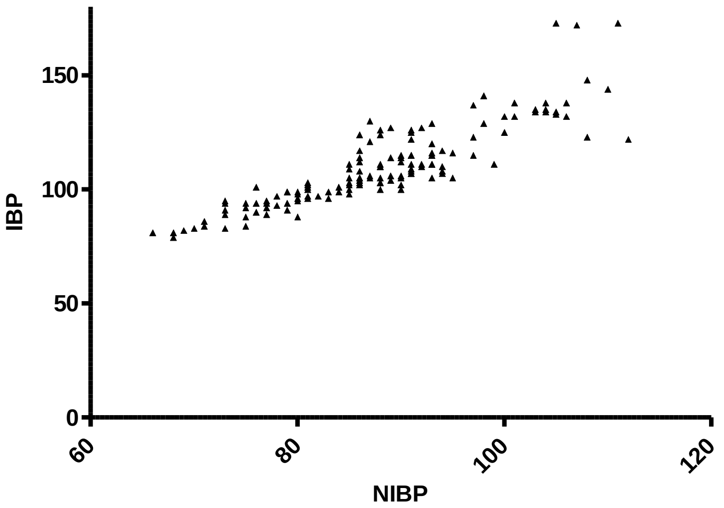
c)



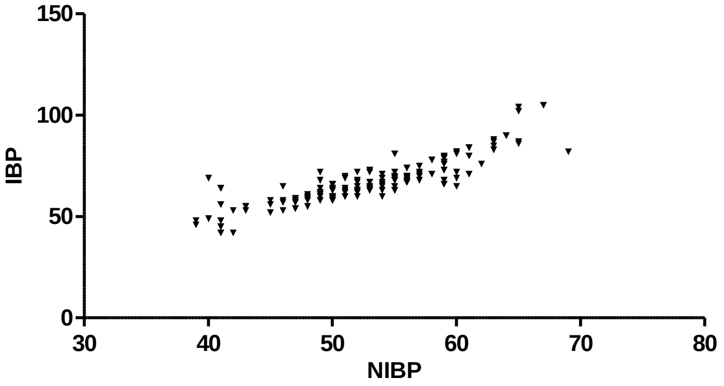
9.2.2. Considering the horses’ recumbency

9.2.2.1. Horses in left lateral recumbency

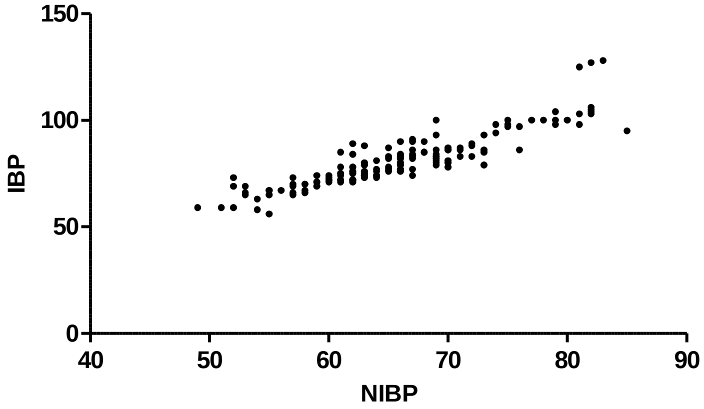
a) **Correlation: SAP - Lateral recumbency**



b) **Correlation: DAP - Lateral recumbency**

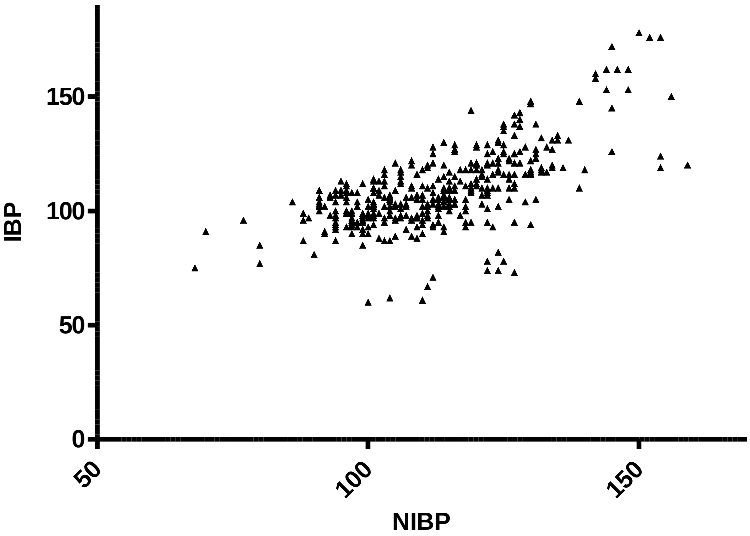


c) **Correlation: MAP - Lateral recumbency**

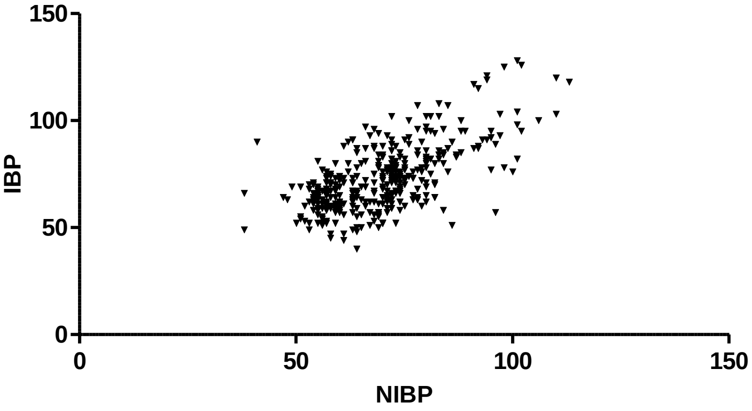


9.2.2.2. Horses in dorsal recumbency

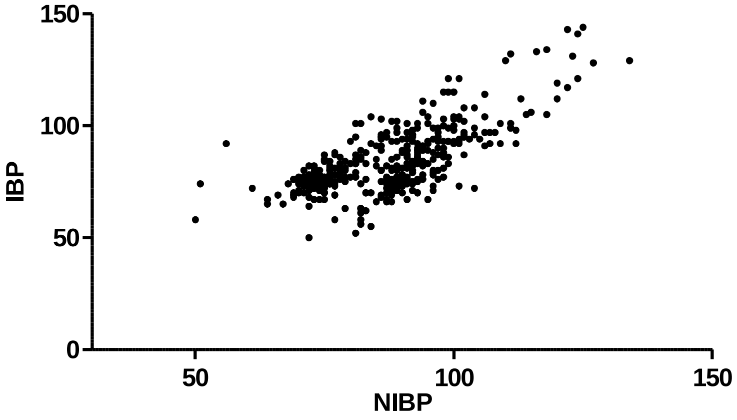
a) **Correlation: SAP - Dorsal recumbency**



b) **Correlation: DAP - Dorsal recumbency**

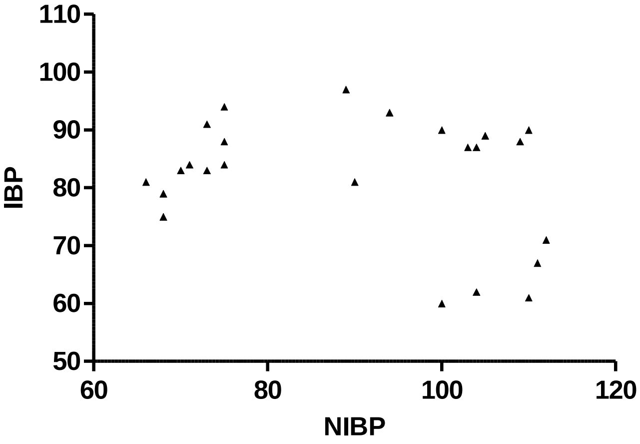


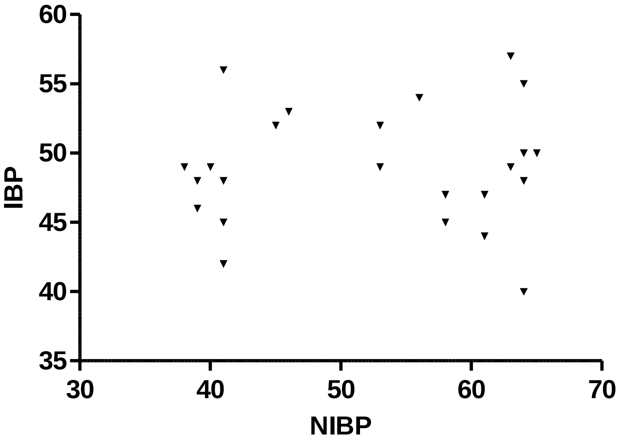
c) **Correlation: MAP - Dorsal recumbency**

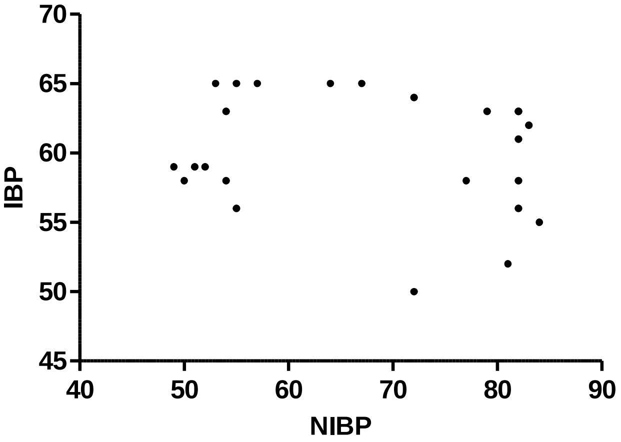


9.2.3. Considering the blood pressure group

9.2.3.1. Mean blood pressure (IBP) ≤ 65mmHg

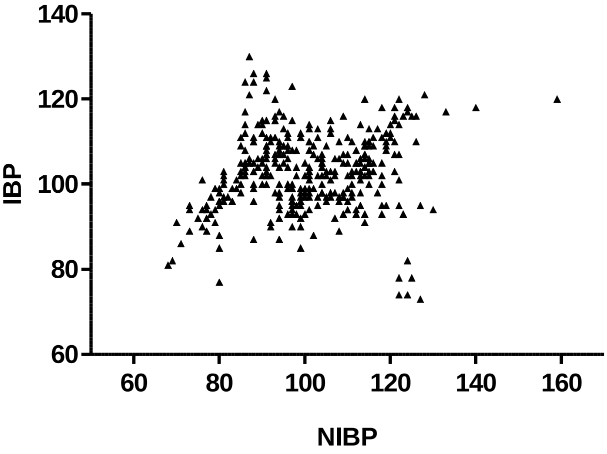

a) **Correlation: SAP <65mmHg**


b) **Correlation: DAP <65mmHg**

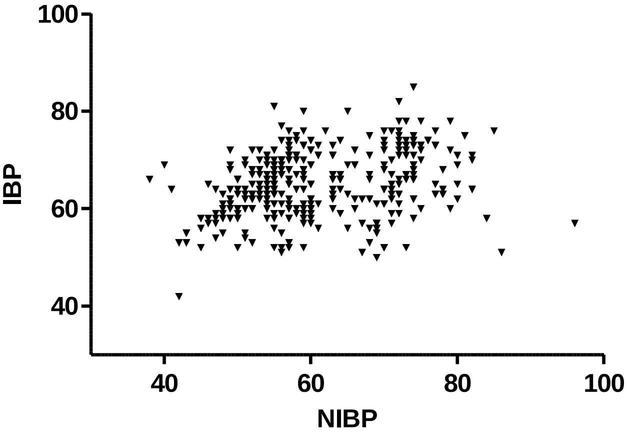

c) **Correlation: MAP <65mmHg**

9.2.3.2. Mean blood pressure (IBP) between 65mmHg and 90mmHg

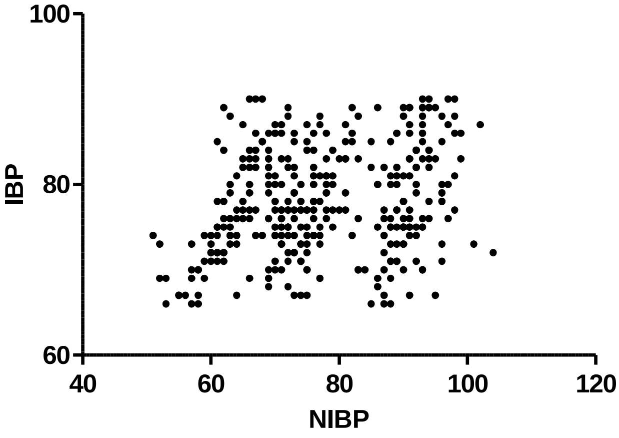
a) **Correlation: SAP - between 65-90mmHg**



b) **Correlation: DAP - between 65-90mmHg**

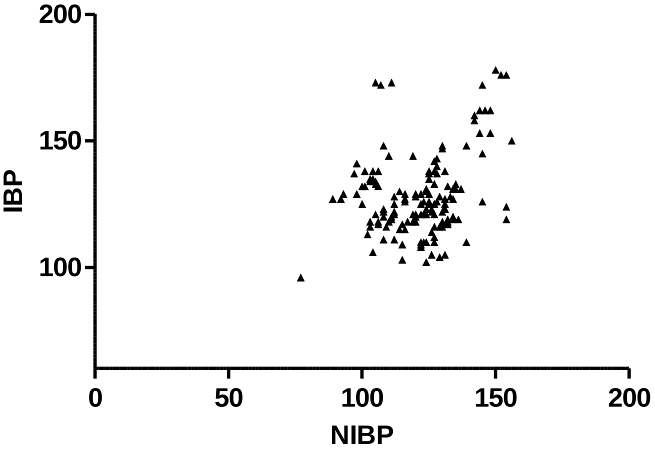


c) **Correlation: MAP - between 65-90mmHg**

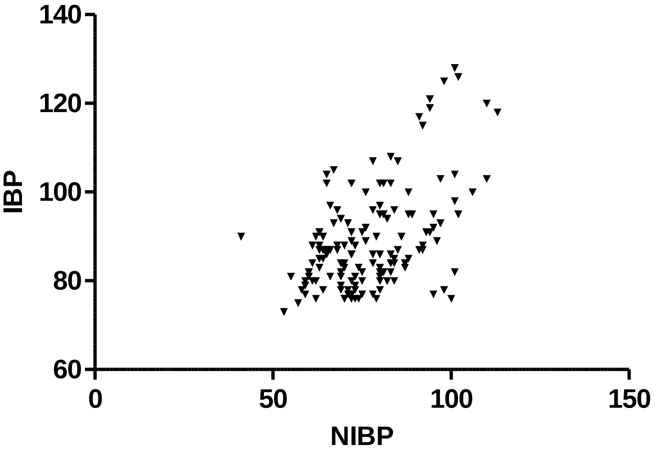


9.2.3.3. Mean blood pressure (IBP) >90mmHg

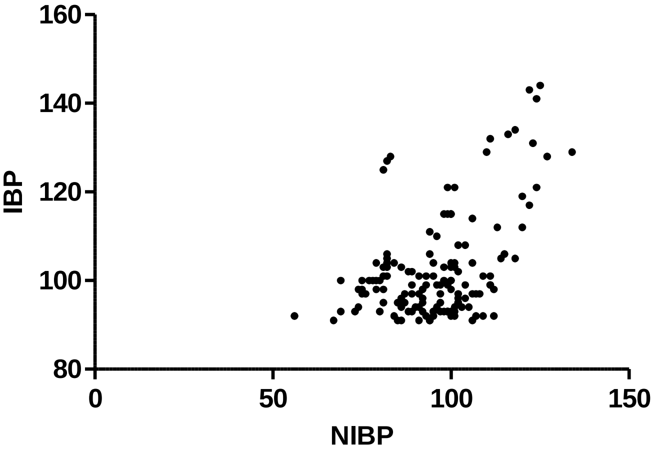
a) **Correlation SAP >90mmHg**



b) **Correlation: DAP >90mmHg**



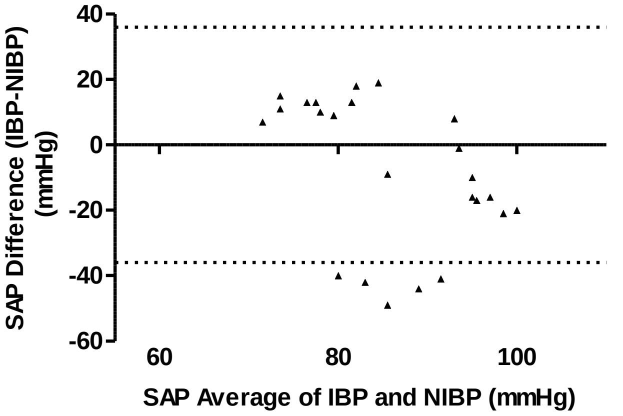
c) **Correlation: MAP >90mmHg**



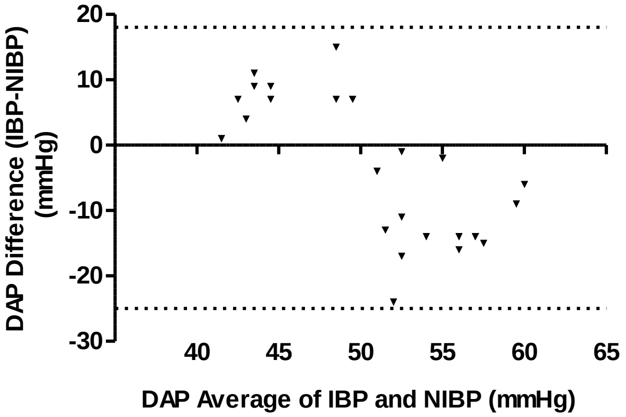
9.3. Appendix 3 – Bland-Altman plots considering the blood pressure group

9.3.1. Mean blood pressure (IBP) ≤ 65mmHg

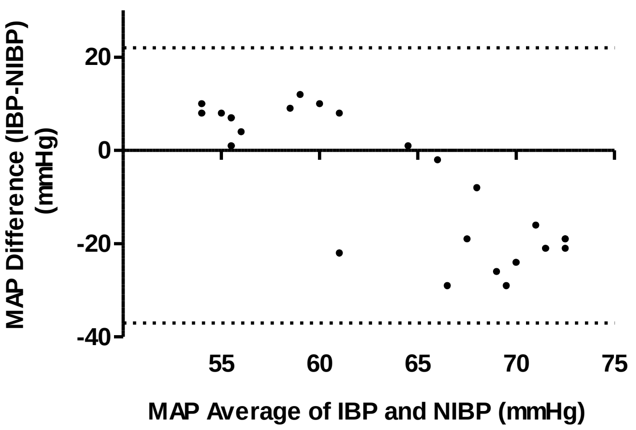
a) **Bland-Altman plot for SAP:Difference vs average with limits of agreement**



b) **Bland-Altman plot for DAP:Difference vs average with limits of agreement**

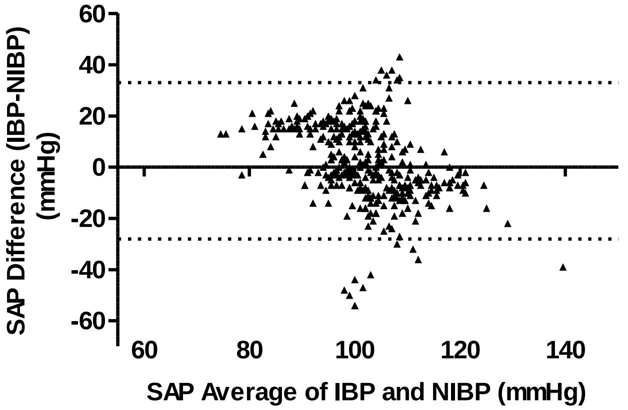


c) **Bland-Altman plot for MAP:Difference vs average with limits of agreement**

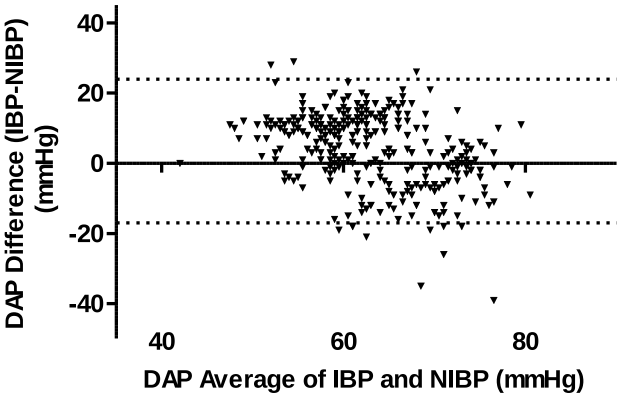


9.3.2. Mean blood pressure (IBP) between 65mmHg and 90mmHg

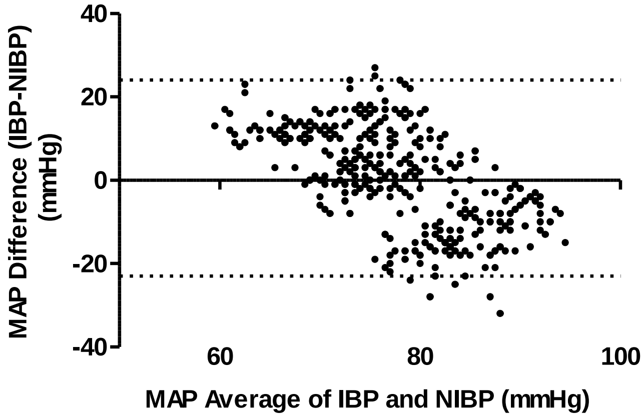
a) **Bland-Altman plot for SAP:Difference vs average with limits of agreement**



b) **Bland-Altman plot for DAP:Difference vs average with limits of agreement**

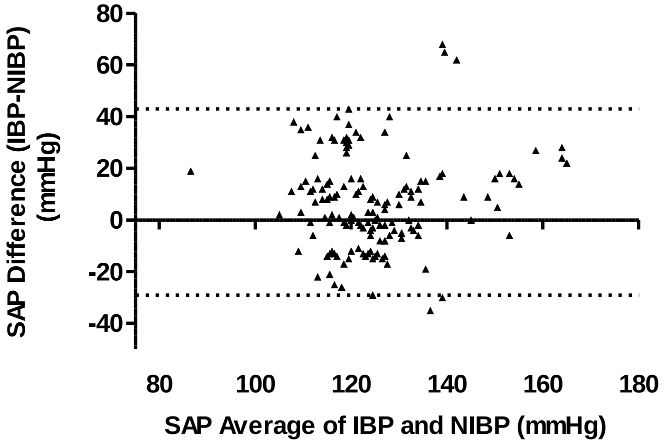


c) **Bland-Altman plot for MAP:Difference vs average with limits of agreement**

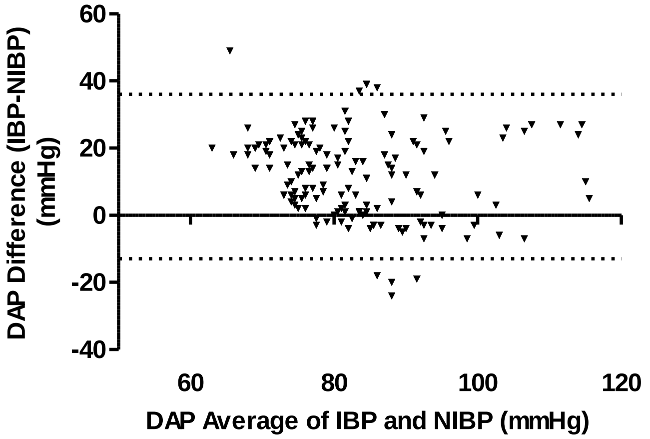


9.3.3. Mean blood pressure (IBP) >90mmHg

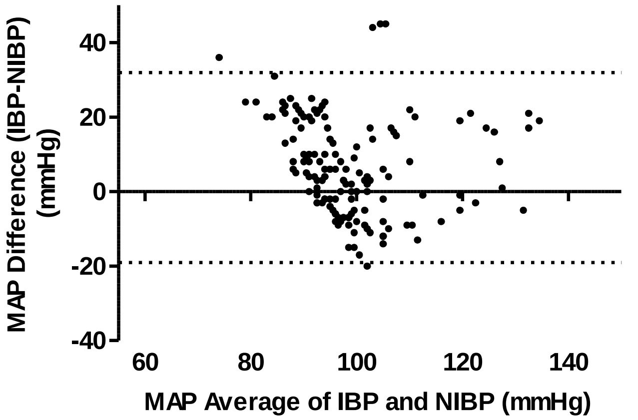
a) **Bland-Altman plot for SAP:Difference vs average with limits of agreement**



b) **Bland-Altman plot for DAP:Difference vs average with limits of agreement**



c) **Bland-Altman plot for MAP:Difference vs average with limits of agreement**

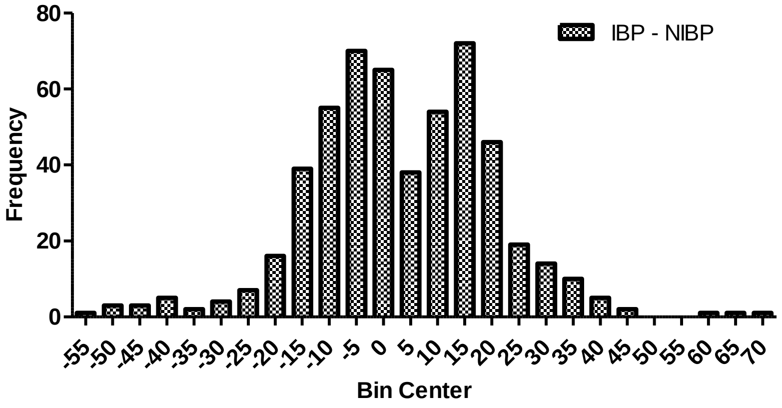


9.4. Appendix 4 – Histogram plots

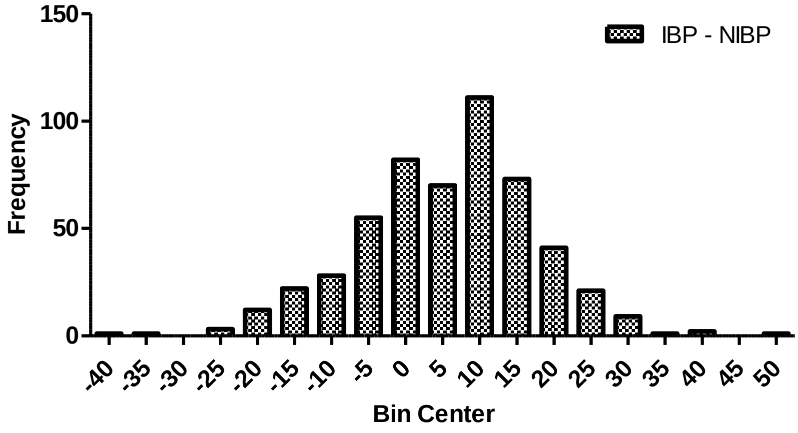
Histograms with the difference between the IBP and the NIBP values were made for SAP, DAP and MAP.

9.4.1. For all the paired readings

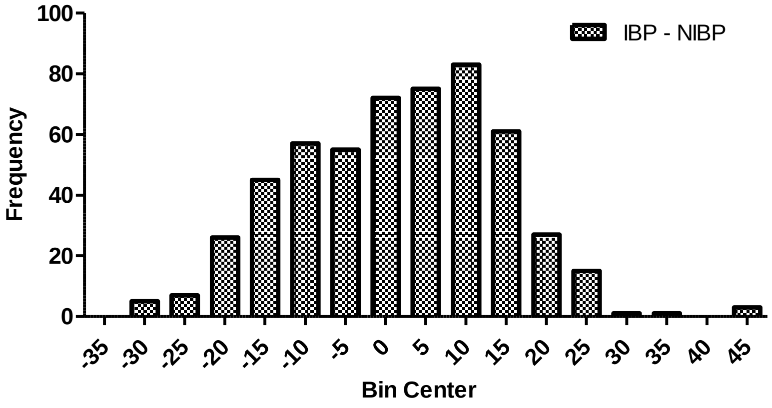
a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**



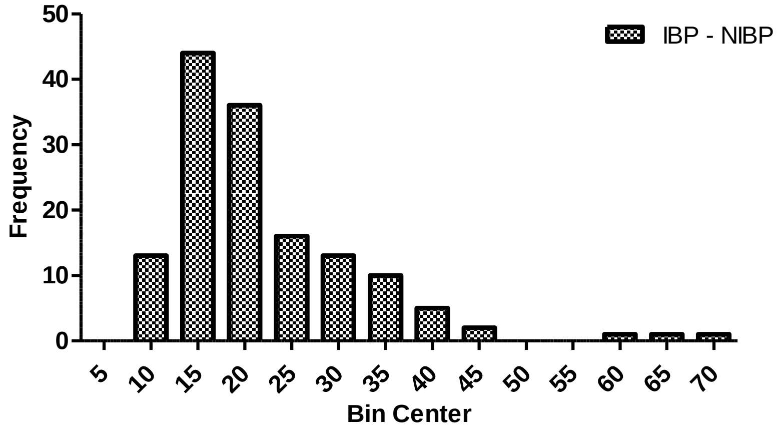
c) **Histogram of Bland-Altman of MAP:Freq. dist.**



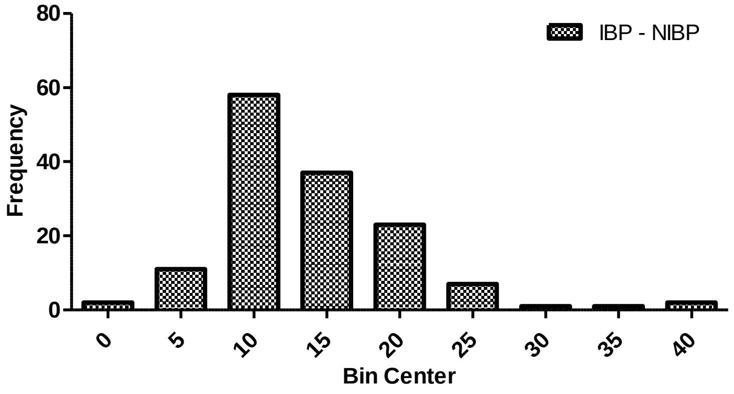
9.4.2. Considering the horses' recumbency

9.4.2.1. Horses in left lateral recumbency

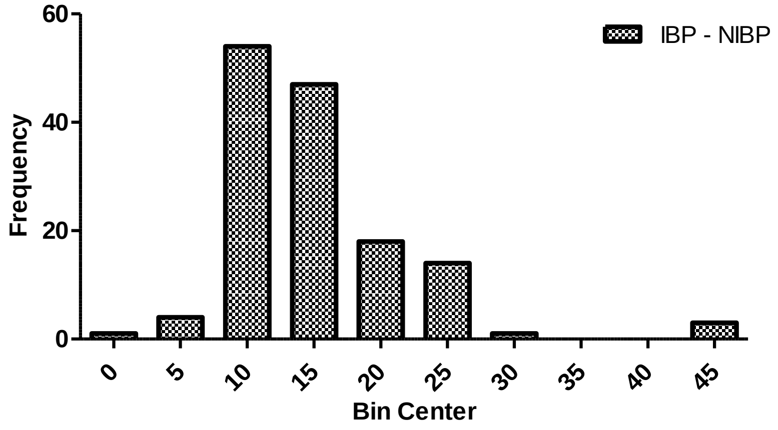
a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**

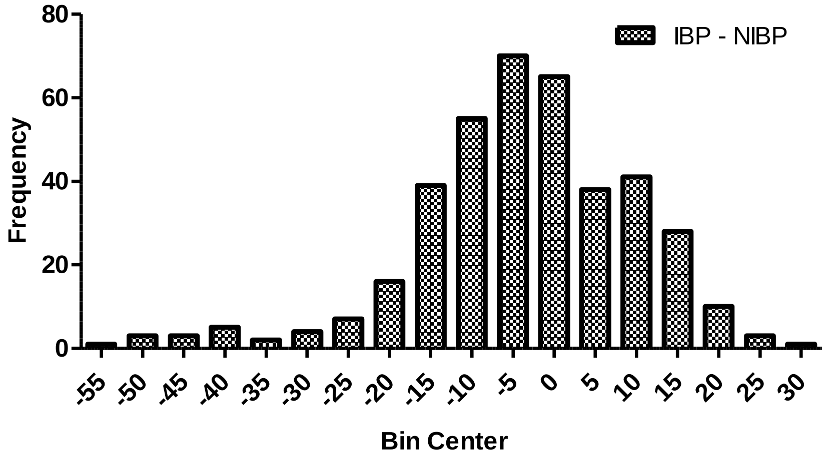


c) **Histogram of Bland-Altman of MAP:Freq. dist.**

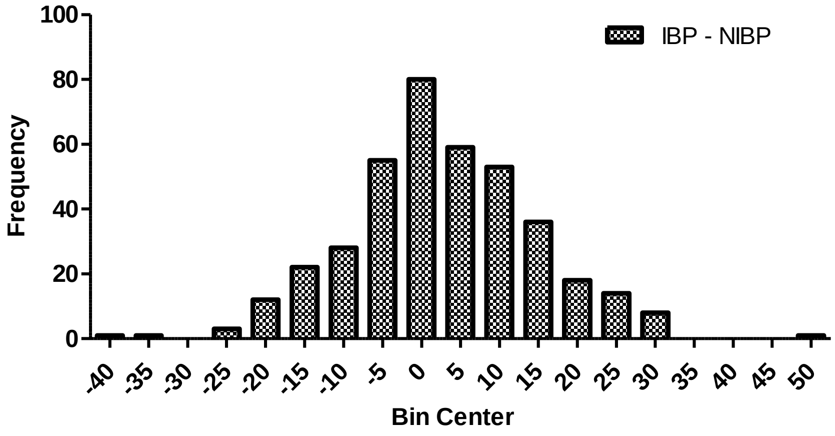


9.4.2.2. Horses in dorsal recumbency

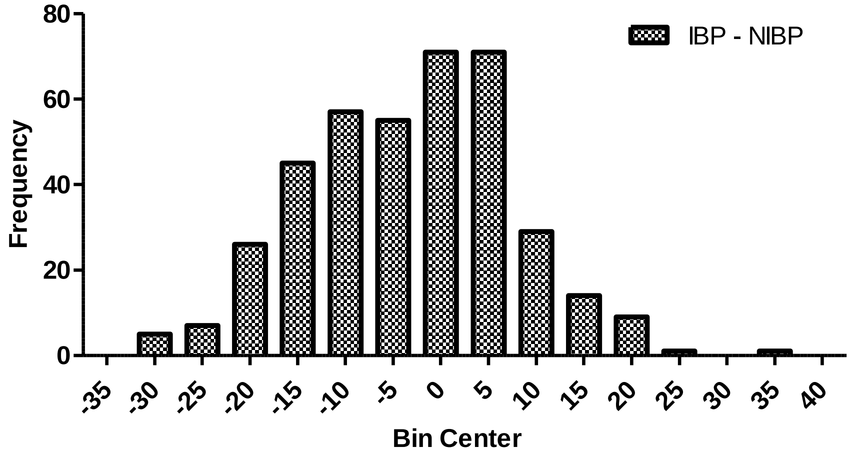
a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**



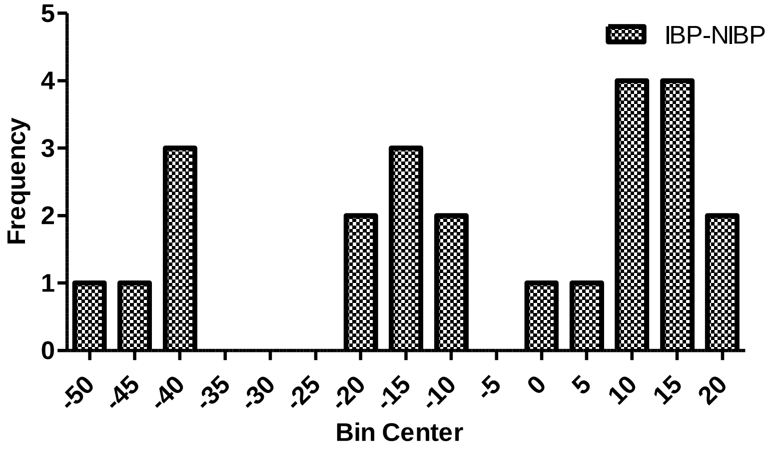
c) **Histogram of Bland-Altman of MAP:Freq. dist.**



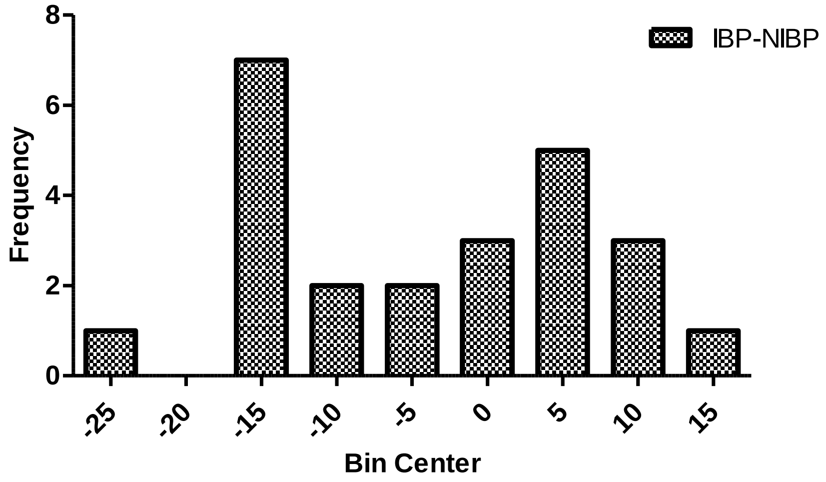
9.4.3. Considering the blood pressure group

9.4.3.1. Mean blood pressure (IBP) ≤ 65mmHg

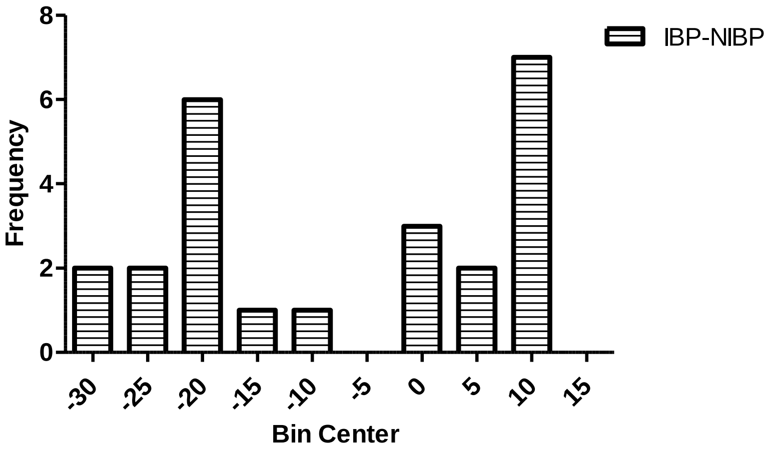
a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**

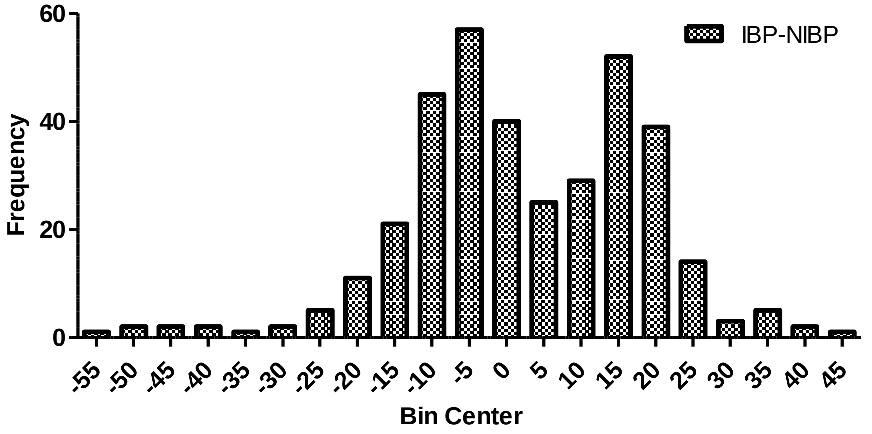


c) **Histogram of Bland-Altman of MAP:Freq. dist.**

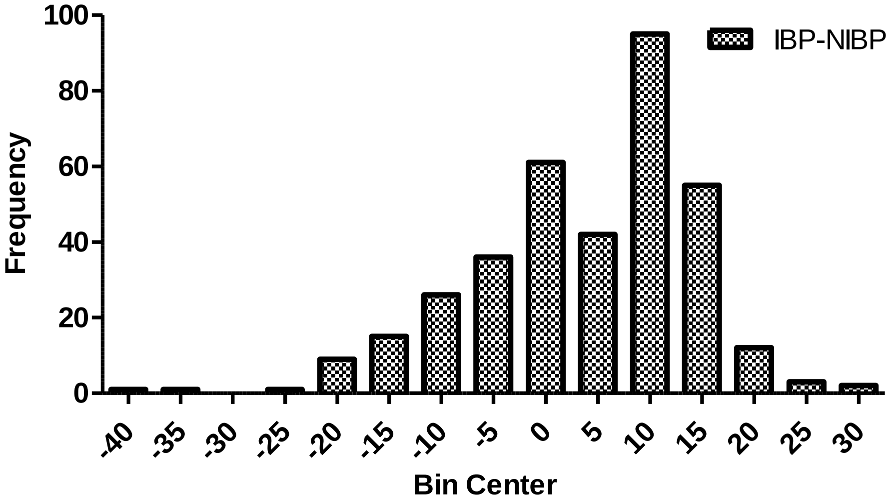


9.4.3.2. Mean blood pressure (IBP) between 65mmHg and 90mmHg

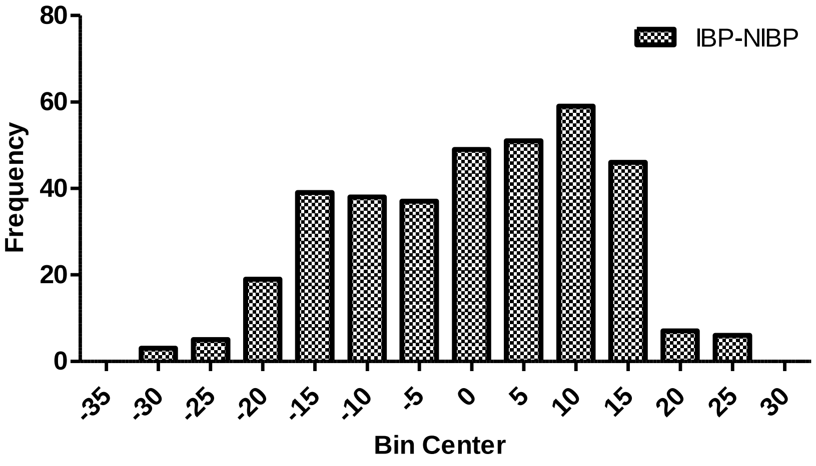
a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**

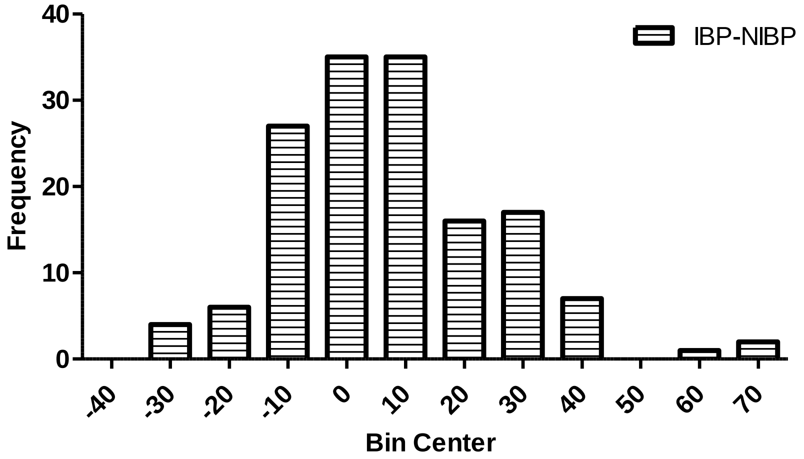


c) **Histogram of Bland-Altman of MAP:Freq. dist.**

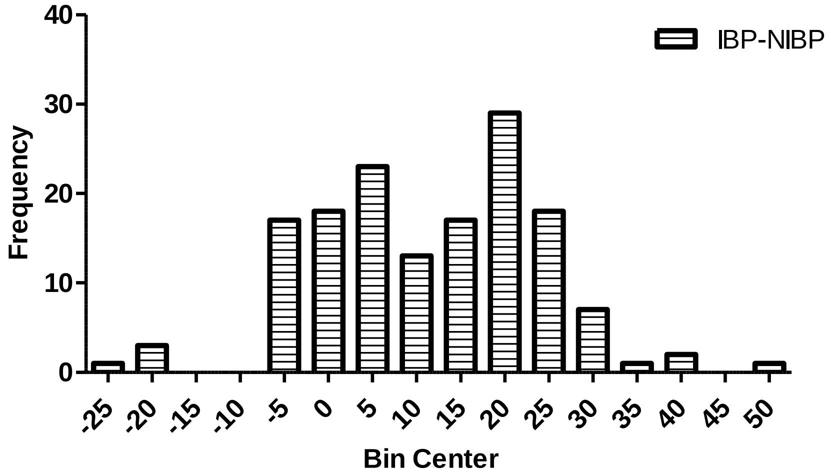


9.4.3.3. Mean blood pressure (IBP) >90mmHg

a) **Histogram of Bland-Altman of SAP:Freq. dist.**



b) **Histogram of Bland-Altman of DAP:Freq. dist.**



c) **Histogram of Bland-Altman of MAP:Freq. dist.**