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Comparison of modified oscillometric device (PetMAP) with invasive blood pressure in anesthetized pigs undergoing MRI

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1. INTRODUCTION

Monitoring blood pressure (BP) is highly important in managing patients undergoing general anesthesia since hypotension is one of the most frequent complications in anaesthetised animals (Almeida et al., 2014). Hypotension is defined as a mean arterial pressure (MAP) of lower than 60mmHg and SAP lower than 80mmHg and is a state in which adequate perfusion of vital organs can not be guaranteed (Grimm et al., 2015). Intraoperative hypotension has the potential to cause an ischemia–reperfusion injury which may manifest as dysfunction of any vital organ. Among the most sensitive organs to be affected in this way are the kidneys and the heart (Love et al., 2006, Walsh et al., 2013). Moreover, data from the Perioperative Ischemia Evaluation Trial in human medicine demonstrated that hypotension was the most likely factor for postoperative death (Deveraux et al., 2008). Thus, precise detection of hypotension can faciliate quick anaesthetic intervention and therefore decrease morbidity and mortality of the patients. High quality data also enables re-evaluation of anaesthetic protocolls and asessment of the effects of administered drugs (Almeida et al., 2014).

Invasive blood pressure (IBP) monitoring can be seen as the current gold standard for measuring blood pressure in real time, as it provides high accuracy and instantaneous measurements (Bosiack et al, 2010, MacFarlane et al., 2010). However, it can be technically challenging to set up and therefore time consuming, as it requires a monitoring system and precise insertion of the catheter into a peripheral artery (Almeida et al., 2014, Seliskar et al., 2013). Therefore, IBP measurements are usually not used as a standard method of BP monitoring in clinical routine but rather for cardio-vascular instable patients or research. Non-invasive blood pressure (NIBP) methods, like Doppler-Ultrasonography or oscillometric devices are used routinely during general anaesthesia (GA). These devices are easy to use, non-invasive, portable, inexpensive and reusable (Piel, 2008). Unfortunately they are generally considered less precise than IBP measurements (e.g. Love et al., 2006; Piel, 2008; Almeida et al., 2014, Calesso et al., 2018, Skleding & Valverde, 2020). Many studies over the last years were performed on this topic, trying to validate new, easy to use NIBP devices that promise to deliver reliable data (e.g. Calesso et al., 2018, Cerejo et al., 2017, Almeida et al., 2014).

PetMAP™ (Ramsey Medical, Inc. And CardioCommand, Inc., USA), a portable oscillometric device, showed some promising results in studies with dogs and cats (e.g. Calesso et al., 2018, Cerejo et al., 2017). Unfortunately, PetMAP ist not classified as *MRI safe* or *MRI conditional*, as it is known to constitute a threat in all MRI settings (petMAP graphic II Operator's Manual, Reddy et al., 2012). Because of the magnetic field of the MRI any ferromagnetic items inside the range of the force of attraction will be pulled towards the core of the magnet and can become hazardous projectiles (Reddy et al., 2012). This is the reason why, frequently due to a lack of MRI compatible equipment, patients are sparsely monitored during the imaging procedure. However, the PetMAP used with 7m extension line, would allow it's use outside of the MRI and would therefore make it feasable in this environment.

In this study, we focus on pigs because of their importance in research. Due to morphological parallels of pigs and humans, the animals are often used as a translational model to learn more about human physiology and pathology (Fil et al., 2021). Measuring the blood pressure with petMAP graphic II on anesthetized pigs has not yet been validated with an invasive method generally nor with extensions.

The aim of this present study is to compare agreement and trending ability of the PetMAP graphic II with 7m extension line with direct blood pressure measurements in anaesthetised pigs undergoing MRI.
We hypothesised that modified PetMAP graphic II with extension line would deliver valid measurements, according to the Association for the Advancement of Medical Istrumentation (AAMI) (Stergiou et al., 2018) and the American College of Veterinary Internal Medicine (ACVIM) (Brown et al., 2007) standards, when compared to invasive blood pressure measurements in anaesthetised pigs.

2. LITERATURE OVERVIEW

2.1. Invasive- and non-invasive blood pressure measurement

Cardiac output (CO) is defined as the volume of blood that is pushed into the systemic circulation by the heart in one minute and is the basis for haemodynamic stability and oxygen delivery (Mellema, 2016). It can be estimated via various techniques like indicator dilution, transthoracic bioimpedance or other pulse contour analyses (Grimm et al., 2015). Unfortunately, those techniques are unpractical for standard clinical practice and therefore mainly used in research settings or human medicine (Briganti et al., 2018). Hence, to estimate the state of circulation sufficiency parameters correlated to CO are measured in the veterinary practice, e.g. blood pressure.

2.1.1. Definitions

BP is often referred to as the *fourth vital sign* in humans. In addition to temperature, respiratory rate and pulse, it provides an overview of the patients well being and body functionality (Love et al., 2006). Many books and papers have been published about this topic. The following pages give an overview of the key mechanisms concerning this topic and are paraphrased out of Grimm et al., 2015, and Love et al., 2006, if not marked otherwise.

Blood pressure is influenced by three key mechanisms: Vascular tone, cardiac output and blood volume. A body in a normotensive state can distribute enough blood and therefore enough oxygen to vital organs and makes it possible to dispose waste products. Normotension is considered as a mean arterial pressure (MAP) >60mmHg and <100mmHg, respectively (Almeida et al., 2014 and Sierra et al., 2015). Grimm et al., 2015 describes normal MAP values for horses, sheep and goats as 70-100mmHg, while the range for dogs and cats is 80-120mmHg, respectively. MAP values between 60 and 90mmHg are described as normotensive for pigs (Rieß et al., 2016).

Hypotension is defined as a MAP lower than 60 and SAP lower than 80mmHg in any species and is a state in which adequate perfusion of vital organs can not be guaranteed (Sedgwick et al., 2021; Grimm et al., 2015). It can be caused by haemorrhage, hypovolemia, myocardial damage, cardiac arrhythmia, anaphylaxis, autonomic disbalance, sepsis (endotoxemia) and various other diseases (Steagall, 2015). But also iatrogenic causes like general anesthesia through medication-induced vasodilatation and/or cardiac depression can induce potentially life-threatening decreases of BP. Autoregulation of blood pressure via the vital organs heart, brain, and kidney is the ability of the body to compensate for systemic arterial pressure changes. This protective mechanism provides constant perfusion at the range of different blood pressures. Different organ systems use different autoregulatory mechanisms like renin-angiotensin-aldosteron system (RAAS) in the kidney, and myogenic and metabolic control in the brain, heart and kidney. Differences in blood pressure, blood volume or metabolic products are detected by number of different receptors which start a series of compensating mechanisms. For example, in RAAS system, the cells that sense a sodium concentration are in the *macula densa,* a group of modified epithelial cells of the kidney, and result in renin release and therefore activation of RAAS. This protective mechanisam is functional at a range of blood pressure between 60 and 150 mmHg. Outside of this range as in case of severe hypotension – MAP under 60mmHg – perfusion of vital organs cannot be guaranteed anymore Therefore, hypotension is dangerous and may cause severe and permanent damages if not treated correctly and immediately.

Acute hypertension is less common than hypotension in veterinary patients (Sierra et al., 2015). During general anesthesia, a patient is considered hypertensive if it shows a MAP >140 or SAP >180mmHg (Grimm et al., 2015). Rieß et al., (2016) consider anesthetised pigs hypertensive if they show a MAP of >90mmHg. Various interactions between endocrine, renal, vascular and nervous systems can increase BP. Essential or primary hypotension, elevated blood pressure without any obvious cause is the most frequent form in humans. Veterinary patients often develop hypertension secundary to endocrinopathies like renal diseases, hyperthyroidism or hyperadrenocorticism. Especially eyes, brain and kidney are sensitive to sustained hypertension. Acute blindness due to retinal detachment is one of the most common clinical presentations of hypertension in cats. Other causes of hypertension are pain, sympathetic stimulation, infusion of high volumes or the application of vasoactive medication.

2.1.2. Methods of blood pressure evaluation

Blood pressure evaluation can be subdivided into two major groups, direct and indirect measurement techniques.

- **Invasive blood pressure** (IBP) **measurement** is considered the gold standard in blood pressure evaluation. The technique is based on the insertion of a catheter directly into an artery and connecting it to a transducer system. This system will be further explained in more detail.
- **Non invasive blood pressure (NIBP) measurement** can be obtained via various noninvasive methods. All of them are based on restricting blood flow in the underlying superficial artery with the inflatable cuff which is placed around a limb or tail. Different techniques are then used to detect blood flow during slow release of the cuff:
    - **Doppler Ultrasonography** uses a shift in frequency of waves to achieve measurements.
    - **Photoplethysmography** detects arterial volume through transmission of ultrared light. Various studies over the last years tested accuracy of those noninvasive techniques, comparing them to the gold standard invasive BP (IBP) (e.g. Calesso et al., 2018, Cerejo et al., 2017, Almeida et al., 2014).
    - **Oscillometric devices** work by detecting oscillations inside the cuff. In the following, the IBP measurement method and the oscillometric non-invasive BP (NIBP) measurement method are described in more detail as they were used in the course of this study.

Invasive blood pressure measurement

IBP monitoring refers to techniques that involve direct access to the arterial system in order to obtain the measurement. The measuring system contains a cannula, column of pressurized saline, transducer at the level of the patient's heart, microprocessor, amplifier and display unit. The pressure from the artery is transmitted through the fluid column to the thin diaphragm in the transducer. The movement of the diaphragm caused by arterial pressure is detected by a strain gaugue. As the diaphragm is stretched, wires in the transducer also stretch and their electrical resistance changes. The resistance signal is converted to a pressure signal by calibration. The signal from the transducer is then amplified and displayed as continuous waveform.

In veterinary medicine, usually the lack of compliance of the patient necessitates sedation or general anesthesia to ensure immobility and safety. The dorsal metatarsal artery or femoral artery are most commonly used for placement of a catheter in dogs and cats, depending on the size of the patient. The lingual, carotid or auricular artery, or any other accessible artery can be used as well, if necessary. A study in pigs (Bass et al., 2009) found that auricular and femoral arteries deliver similar results for IBP evaluation in these animals. Sterile preparation of the puncture site is necessary before insertion to ensure minimal complications. Clipping of the hair and sterilisation with alcohol or iodine solution is sufficient. Usually an 18 to 24-gauge sterile catheter is used. Palpation of the pulse is helpful but may be impossible in severely hypovolaemic or hypotensive patients. The insertion technique should be similar to venous catheterization and follow the same direction as the artery at an angle of approximately 45°, however it requires some skill. Successful placement is indicated by pulsatile and prompt blood flow through the needle. In case of misplacement into the vein or outside of any vessel, the procedure has to be repeated.

After successful advancement into the vessel and removal of the stylet, an extension line is connected to minimize movment and displacement at the insertion point. Flushing with 1 to 2 ml of (heparinised) saline solution ensures patency of the catheter (the use of heparinised solution has been controversial). It then should be secured with adhesive tape. It is recommended to label the arterial catheter as such to prevent confusion with a venous catheter and therefore misinjection. After catheterization and fixation a tubing system with the pressure transducer can be connected. Tubing is primed with (heparinized) saline solution and the transducer needs to be placed at the same level as the heart. This avoids measurement errors concerning hydrostatic pressure differences due to gravity. The zeroing of the transducer to atmospheric pressure should be periodically performed. Therefore, a stopcock at the level of the heart is opened between the transducer and the atmosphere and closed towards the patient and the zeroing is done by the monitor. Measurement erros will be discussed in more detail.

Another method of IBP measurement uses an aneroid manometer, which only provides an analog MAP reading, but no arterial pressure wave. Also, telemetry has been described and used in research settings. This method uses radio signals emitted by an indwelling catheter which allows for continuous readings in conscious animals. To prevent clotting of the artery, the catheter should be flushed frequently with (heparinized) saline solution and checked for air bubbles.

Technical problems which influence IBP measurements are listed here:

Calibration errors – The IBP device is calibrated via one–point calibration by zeroing transducer to atmospheric pressure. The gauge pressure, pressure above atmospheric is beeing measured. However, dispite calibration, drift of zero and gain can occure over time.

Transducer height - The transducer must be placed at the level of the patient's right atrium. 7,5 mmHg as an error equivalent have to be added or substracted for each 10 cm deviation in height.

Natural frequency and resonance: Resonant frequency and damping are parameters that must be within certain limits to allow optimal measurments without deviations. The resonant frequency of a measuring system is the natural frequency where a measuring medium vibrates at the highest amplitude. It is important for the natural frequency of the arterial transducer to be significantly different from the frequency of the arterial wave or else it could amplify the signal. The natural frequency should be 6-10 times that of the heart rate (Grimm et al., 2015).

Amplitude reduction ratio is the height of ½ cycle devided by the height of the previous ½ cycle and should ideally be low (0.1-0.4) (Figure 1) while the resonant frequency should ideally be high. **Frequency response**: arterial pressure wave form is complex sine wave. Fourier analysis allowes this complex wave form to be broken down into a series of simple waves of different amplitudes and frequencies.

Damping is the tendency of an object to resist oscillating. Overdamping underestimates SAP, overestimates DAP but MAP remains the same (e.g. air bubbles, blood clots or unsuitable tubing). The BP trace is therefore „flattened“ (Figure 2). **Underdamping** leads to the opposite effect (Figure 2): SAP values are calculated as too high and diastolic values as too low.

The complications of IBP measurements are cannula disconnection leading to blood loss, arterial thrombosis and ischemia distal to the cannula, dependent on the collateral vascularization, location and species, infection. Also, inadvertent injection of drugs into the artery can cause vascular occlusion and ischemia. Arterial lines should be clearly labelled and color- coded.

After removal of the catheter, the puncture site should be compressed firmly to avoid hemorrhage or haematoma formation.

Figure 1. Normal resonant frequency. The waveline returns to the baseline after 2 oscillations. The amplitude reduction ratio is calculated by dividing the height of ½ cycle by the height of the previous ½ cycle. One whole cycle is defined by the distance from peak to peak or through to through. (from Grimm et al., 2015, p 93).

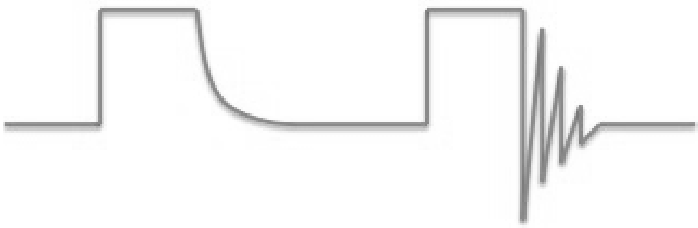


Figure 2. Results of a dynamic pressure response test. This test determines the rate at which oscillations come to a rest and can be used to evaluate over- and underdamping. The wave on the left is overdamped: The waveline returns to the baseline without any further deflections. The second wave on the right is underdamped: The waveline shows more than two cicles of oscillations before returning to the baseline (from Grimm et al., 2015, p 93).

The main **advantages** of IBP measurement are that it is more accurate than non-invasive techniques, continuity of measurement in real time, and that it is not affected by heart rate or rhythm. Additional parameters like arterial blood gases can be measured and the continuous arterial wave form is visible. **Disadvantages** are the time consuming and possibly challenging installation, possible complications (listed above) and the higher price compared to other techniques.

Oscillometric non-invasive BP measurement

Oscillometric non-invasive BP measurement is based on the principle of an oscillotonometer, where the cuff has occluding and sensing function. The system includes a cuff, a pneumatic pump, a bleed valve, a transducer, a processor and a display monitor. A pneumatic pump occludes the artery in the limb and a bleed valve slowly starts to deflate the cuff. As the cuff deflates, the transducer detects the flow of the blood under under the cuff. At systolic blood pressure there is a sudden increase in oscillations. At mean arterial pressure there is a maximal amplitude and at diastolic pressure there is sudden decrease in oscilltions. The processor with a built-in algorithm, then relates the change of oscillations/pressure transients to the blood pressure. Some systems measure SAP, DAP and MAP (high definition oscillometric devices) but the majority of systems, eg. PETMap, mesure only MAP, and values of SAP and DAP are calculated through the manufacturer's species-specific algorithms. These readings are then displayed on the monitor.

An inflatable cuff is usually placed around the metacarpus or metatarsus or around the base of the tail. A mark on the cuff indicates how the cuff should be placed in relation to the underlying artery. Cuff-width is highly important as a wrong size causes deviation of measurements. Most studies recommend the width of the cuff to be approximately 40% of the circumference of the limb. If the cuff is too big the actual BP is underestimated. If the cuff is too small, results are reversed and the actual BP is overestimated. The airhose should not be kinked and ideally be placed at heart level. The cuff needs to be placed at the heart level or if not possible it needs to be compensated for the difference in height: for every 10 cm above or below the heart 7,5 mmHg needs to be added or substracted, respectively (Ehrenwerth & Eisenkraft, 1993). Just like in IBP settings, this prevents measurement errors through the influence of hydrostatic pressure because of gravity. Connection to the oscillometric device and configuration of the monitor facilitates readings.

Periodic fluctuations (oscillations) are produced by the arterial walls during inflation and deflation of the cuff. During the deflation period, three changing points of the frequency of oscillation can be observed: Systolic arterial pressure (SAP) is indicated by a rapid increase of oscillation. The maximum is reached at the mean arterial pressure (MAP). Rapid decrease of oscillation indicates the diastolic arterial pressure (DAP). In conventional oscillometric devices, usually only MAP is measured as the maximal oscillation of pressure, the algorithm

calculates SAP and DAP values. High Definition Oscillometry (HDO) provides not only more precise data about blood pressure, as all three values are measured, but also visualises the pulse waves on the monitor. This allows an extensive overview over additional important parameters like stroke volume, systemic vascular resistance, rhythm and dysrhythmia (Egner, 2015).
Several manufacturers offer different oscillometric devices. In this study PetMAP graphic II, developed by Ramsey Medical Inc., manufactured by CardioCommand, Inc., was used.

The main **advantages** of NIBP measurements are the easy and quick setup that does not require sedation or general anesthesia and the continuous readings. **Disadvantages** are that NIBP measurements are less accurate than IBP measurements which was stated in many studies about dogs and cats (e.g. Almeida et al., 2014; Seliskar et al., 2013; Cerejo et al., 2017). Gladczak et al., 2013, conducted a study with a sphygmomanometer with an automated cuff on pigs and came to the same conclusion. Measurements are affected by heart rate and rythm, movement, obesity, and presence of hair coat.

Advantages and disadvantages of IBP and NIBP equipment must be compared before installation for every individual patient. Pigs are often used reasearch animals and may differ from animals in clinical settings. Compliance of awake animals is important, as well as injuries, cardiovascular status or the need for arterial blood samples.

2.2. Requirements for MRI *safe* and MRI *conditional* equipment

MRI imaging is commonly used in evaluation of central nervous diseases, orbital and nasal disorders, oncology, cardiovascular problems and planning of soft tissue surgery. This is due to the ability of MRI to present a particularly good view of soft tissue (Gilbert et al., 2010). Increasingly, research and other fields of medicine utilize this technology.
MRI relies on the interactions between two types of magnetic fields. Manipulation of frequency induces slight changes of energy levels in hydrogen nuclei inside the body. These are found in tissues of higher water content and can be detected and localized (Reddy et al., 2012).

During scanning, any movement will cause profound aberration of the final images. Therefore, in veterinary medicine, the patient will commonly be either sedated or undergoing general anesthesia. Unfortunately, anesthesia in an MRI environment is connected with numerous safety concerns like limited access to the patient and need for special equipment that has to be MRI-safe or MRI-conditional. As a consequence of the continuously generated magnetic field, any ferromagnetic items inside the range of the force of attraction will be pulled towards the core of the magnet and can become hazardous projectiles. Used equipment must therefore meet certain criteria to ensure safety of the patient and medical staff.

The Medicines and Healthcare products Regulatory Agency (MHRA) updated the safety guidance in 2014. Devices are categorised into three groups, MRI *safe,* MRI *conditional* and MRI *unsafe*. MRI *safe* equipment is, as the name indicates it, safe to use, as it poses no additional hazards in a ferromagnetic environment. However, it is not guaranteed that the devices functionality is unaffected. It is preferable to only use MRI *safe* devices. MRI *conditional* equipment, on the other hand, is only safe to use under certain circumstances. Various parameters like spatial gradient, limits on static field strength, specific absorption rate, radiofrequency fields or other configurations of the scanner or the device itself need to be adjusted before the device may be used. A device that was evaluated under one condition may not be safe to use under another, for example at a higher magnetic field strength. MRI *unsafe* equipment poses hazards in every setting and must not be used. (Wilson et al., 2010; MHRA, 2014).

The operator's manual of petMAP graphic II states that it is „not intended for use on patients being imaged with an MRI device since the petMAP device contains magnetically active materials and could result in injury if used too close to an operating MRI" (petMAP graphic II Operator's manual 2013-2014). The use of prolongation tubes, which do not contain ferromagnetic elements, makes it possible to place the device outside of the critical MRI environment (Faraday cage).

The problems associated with anesthesia for MRI

The MRI is performed in diagnostic areas which are very often remote and isolated and can be critical in emergency situations when trained and professional help is needed. It is a cold and noisy environment. Due to the noisy magnets, earplugs must be used and the patient needs to be covered to minimize the risk of hypothermia. Once the patient is in the scanner, access is limited. This is why reliable monitoring is so important. Anaesthetic equipment as mentioned above, has to be special "MRI safe" or conditional and the clinican has to be familiar with the equipment, which is often different from that on surgical wards. ECG (Electrocardiogram) pads leads are short to minimize the risk of magnetically induced currents within them, which can lead to burns. Depending on the equipment MRI conditional of not, the anaesthetic machine is inside or outside of the faraday cage. A long or very long circle system is used which brings additional problems with rebreathing leading to hypercapnia and respiratory acidosis.

2.3. Validation of new blood pressure measurement techniques

Validation and testing of blood pressure measuring devices began in the 1980s. Since then, numerous protocols have been published by e.g. the British Hypertension Society (BHS), the European Society of Hypertension (EHS) or the German Hypertension League. Currently, the guidelines by the American College of Veterinary Internal Medicine (ACVIM) and the Association for the Advancement of Medical Instrumentation (AAMI) are the most current and also most used for the validation of blood pressure measuring devices in veterinary medicine.

2.3.1. Guidelines by ACVIM

As mentioned, IBP is considered the gold standard of blood pressure measurement techniques. New methods have to be evaluated and compared to this gold standard to ensure the precision and repeatability of produced data.

The American College of Veterinary Internal Medicine (ACVIM) published the consensus statement addressing the requirements for validation of BP measuring devices in 2007 (Brown et al., 2007). New ACVIM guidelines on treatment of hypotension from 2018 (Acierno et al.,

2018) do not further address this topic. Thus, the 2007 guidelines are still valid in veterinary medicine. Consensus statements provide veterinarians with guidelines for veterinary practice and research. The ACVIM consensus statements criteria of validation are based on those of the Association for the Advancement of Medical Instrumentation (AAMI). AAMI provides criteria for devices that are intended for use in people which is a factor that has to be kept in mind. Further, it is important to notice that in human medicine new equipment is not validated against IBP monitoring (as is common in veterinary medicine) but against the auscultatory technique. This facilitates the comparison of two methods for conscious individuals, which is not always possible or reliable in veterinary medicine. Interstingly, British Hypertensive Society is not recommending the comparison of indirect methods to direct intraarterial BP, since systolic and diastolic arterial BP values obtained by the direct techniques are different from the measurements obtained by indirect methods (Skelding & Valverde, 2020a&b). This seems to be due to considerable beat to beat variation in BP, which is not reflected by indirect readings. Blood pressure simultaneously measured directly and indirectly from the same artery can have random discrepancies as great as 24 mmHg for SAP and 16 mmHg for DAP (O'Brien et al., 1993).

Indirect measuring of blood pressure is considered usually more challenging in conscious animals than it is in humans because of a lack of compliance in animals as well as "white coat" hypertension (stress-induced increase in BP). Most devices that have been validated in the past therefore were used on anaesthetised animals. Devices that are validated in one setting may be inappropriate for others; e.g. validation for unconscious dogs does not imply validation for conscious dogs or unconscious cats. Also, there have to be extra validation-processes for systolic and diastolic blood pressure measurements. To our knowledge petMAP graphic II is not validated for the use in anesthetized pigs.

The ACVIM guidelines from 2007 stated various recommendations for the use of NIBP devices in small animals. In our thesis, we applied those rules for pigs:

In order to get precise and reproducible measurements and minimise errors, a standard procedure should be followed. Ideally, the environment should be quiet and calm, the patient should not be nervous or excited, if awake; otherwise the patient should be sedated. Ventral or lateral recumbency is preferred to limit the distance between heartbase and cuff. Cuff-width should be around 40% of the limbs or tails circumference. Deviations can be minimized if the procedure is performed by the same operator. The first one or two measurements should be discarded as they are more susceptible for errors. A minimum of three, but preferably 5-7 consistent, consecutive measurements should be protocolled. Statistical analysis and comparison of the paired databases is performed afterwards. A system is considered validated by the ACVIM if the following criteria are met:

- The study group contains at least 8 animals if comparison with a direct measurement method is conducted; comparison with an already validated NIBP device requires a subject database of 25 or more;
- The NIBP measurements of SAP and DAP each don't show a mean difference higher than 10mmHg to the paired IBP measurements; standard deviation has to be ≤15mmHg;
- Correlation between paired IBP and NIBP measurements must be ≤0,9 for both SAP and for DAP each
- 80% of all results for each indirect SAP and indirect DAP must lie within 20mmHg of IBP measurements; and 50% within 10mmHg.

Periods of hyper and hypotension are not required by ACVIM guidelines. However, a new device needs to be evaluated in wide range of blood pressure measurments and especially in hypo and hypertension. In the AAMI guidelines these periods are defined as mentioned below and included in the evaluation. Additionally, although not required criteria by ACVIM guidelines for validation of the new devices, MAP measurements are included to ACVIM guidelines in this thesis.

2.3.2. Guidelines by AAMI

The Association for the Advancement of Medical Instrumentation (AAMI) posted a more current statement in 2018 in collaboration with the European Society of Hypertension (ESH) and International Organisation for Standardization (ISO) (AAMI/ESH/ISO Collaboration Statement, 2018; Stergiou et al., 2018). The statement is based on the criteria for humans, but can also be used for other species. So far, no study with pigs was validated with AAMI guidelines. It has to be kept in mind though, as stated above, that it is harder to evaluate BP in conscious animals than in conscious humans. Several criteria for optimal data collection were stated to provide a comparable standard for blood pressure device evaluation. The average of three readings should be compared against a reference method, in this case invasive BP measurement. A minimal study group of 85 subjects is required. If the device provides more than one cuff size, a set number of subjects have to be tested for each cuff. For general population studies at least 30% male and 30% female participants should be included. All subjects should be older than 12 – in other words, no small children should be involved. Listed requirements on the range of blood pressure that should be included into evaluation are: at least 5% of the readings are required to be ≤60mmHg and 20% ≥160mmHg. This provides better understanding of the device's precision in hypertensive or hypotensive states. Special population studies are to be included after a positive validation process of the general population. Special populations involve various states or diseases that are stated in the document. AAMI/ESH/ISO recommend sequential BP measurements rather than simultaneous recordings. (R_1-T_1-R_2-T_2-R_3-T_3-R_4. R: Reference, T:Test). Data should be presented in standardized Bland-Altmann scatter plots and absolute BP differences between 5,10 and 15 mmHg should be presented and evaluated.

The consensus in this statement by AAMI/ESH/ISO is that a device may be accepted

- „if its estimated probability of a tolerable error (≤10mmHg) is at least 85%" (AAMI/ESH/ISO Collaboration Statement. J Hypertens. 2018 Mar; 36(3): 472-478**).**

Another guideline by AAMI from 2009 (ANSI/AAMI/ISO 81060-2, 2009) states that

- a mean bias of ≤ 5mmHg with
- a SD of ≤ 8mmHg is required for a NIBP device compared to the gold standard.

2.3.3. Literature

PetMAP graphic II has been tested in various studies in different species over the last years. Vachon et al. (2014) tested its accuracy in both conscious and unconscious dogs compared to IBP. In this study, blood pressure was generally underestimated by the non-invasive method during anesthesia (SAP: -6.1mmHg ± 10.4mmHg; MAP: -2.9mmHg ± 9.3mmHg; DAP: -6.9mmHg ± 6.7mmHg), while it was overestimated in conscious dogs for MAP and DAP measurements. SAP was underestimated in conscious animals. In that study, all the ACVIM criteria (Bias and SD, and 10 and 20mmHg ranges) except the correlation (>0,9), were reached for SAP and DAP. The MAP values didn't reach the criteria by ACVIM except for bias and SD. The study from Muir et al (2008) also found a slight underestimation of blood pressure measured by PetMAP graphic II during anesthesia in dogs. (Bias ± SD; SAP: -1.64mmHg ± 11.9mmHg; MAP: -6.16mmHg ± 8.2mmHg; DAP: -6.1mmHg ± 7.7mmHg). A generally acceptable accordance during normotension in anaesthetised dogs was stated nonetheless in both studies. Muir reached the ACVIM criteria for bias and standard deviation for all three parameters, SAP, MAP and DAP with this device. Acierno et al. (2013) stated a generally bad accordance of NIBP mesurements to the invasive method in anestethized dogs. The SAP values showed a mean bias of 9.9mmHg with limits of agreement of 73.7 to -53.9; MAP showed a bias of -8.9 and LOA of 23.3 to -41.2; DAP showed a mean bias of -6.3 and LOA of 28.2 to 40.8). And as reported in a recent dissertation by Piel (2018) measurements of petMAP graphic II did not succide to reach the criteria stated by ACVIM during normotension but reached all the criteria for SAP, MAP and DAP in hypotensive states.

Various other studies were conducted with other models of petMAP, e.g. petMAP graphic (I) or petMAP classic in cats and dogs with very variable results, e.g. Seliskar et al. (2013); Almeida et al. (2014); Cerejo et al. (2017). The MAP and DAP reached the ACVIM standards for ±20mmHg and ±10mmHg percentages, while SAP did not fulfill the criteria in the study by Seliskar et al. (2013). In the study from Almeida et al. (2013) it was found that SAP at the left thoracic limb and MAP at the right pelvic limb met all the ACVIM criteria except for the correlation. DAP values did not meet the criteria and neither did SAP at the right pelvic limb or MAP at the left thoracic limb. PetMAP graphic in cats reached the criteria for MAP by ACVIM and even by AAMI for MAP and DAP but not for SAP in the recent study of Cerejo et al. (2017).

Studies in pigs using other NIBP devices and neonatal or children size cuffs (Gladczak et al., 2013; Chow et al., 1999) reported promising results. Gladczak et al., found that the tested oscillometric device, child size Critikon Dura-Cuf – GE Healthcare, Waukesha WI was able to provide reliable results for normotensive pigs in surgical settings. Chow et al., 1999, created phases of induced hypotension and hypertension with another neonatal cuff and found that results overall were within the 95% confidence interval and NIBP therefore can be used as a good substitute to IBP measurements.

3. MATERIALS AND METHODS

3.1. Study group

This study is a prospective, experimental comparative study. Data were collected from 24 female, intact Landrasse pigs. The pigs were anesthetized twice for the main experiment (n=48). The first anesthesia and MRI was performed with animals at the five weeks of age when the pigs weiged 9.0±1.3kg (mean ± SD). The second procedure was conducted with the same animals seven weeks later, at the age of twelve weeks, when the pigs weighed 37.5±3.4kg. All pigs were evaluated healthy according to their medical history and by visual check before anesthesia and were considered ASA 1 patients according to the American Society of Anesthesiologists classification. The animals were owned by the University of Veterinary Medicine Vienna, Austria, being part of a primary study evaluating MRI in pigs. The primary study was approved by the Federal Ministry for Education, Science and Research of the Republic of Austria (protocol number BMBWFW-68.205/0079-V/3b/2019). All animals (n=24) from the non-related primary study were included.

Data sets from animals in which invasive blood pressure measurements were not conducted due to unsuccesfull placing of the arterial line, or if data were missing because of the problems with the arterial catheter during anesthesia were excluded from the analysis. Sample size calculation was not conducted prior to the study as the number of animals was predefined by the primary study. All experiments were performed and data collected from October to December 2019 at the University of Veterinary Medicine Vienna, Austria. Randomisation was coordinated by the primary study. All experiments were done in standardized manner as described in the experimental procedures.

The following description of the procedure applies to both experiments, at five weeks and at twelve weeks, as they were carried out in the same way and order.

3.2. Experimental procedures

3.2.1. Anaesthetic protocol

Animals were not necessarily fasted before the procedure. The pigs were premedicated with azaperone (Azaperon, Stresnil®, Lilly Deutschland GmbH, Germany) 12 mg/kg intramuscularly (IM) and xylazin (Xylazin, Rompun®, Provet AG, Switzerland) 2 mg/kg intramuscularly (IM). Twenty minutes after premedication, or as soon as sedated enough, an intravenous catheter (Vasofix®safety 22G, Braun, Germany) was inserted into either the right or left ear into the auricular vein for drug administration and for fluid therapy. Used fluid was sterofundin (Sterofundin ISO Ecoflac Plus, B. Braun Melsungen AG, Germany) with a flow of 5 ml/kg/h during the duration of the procedure. Anesthesia was induced with ketamine (Ketamine, Narketan®, Vetoquinol, France) 5-7.5 mg/kg intravenously (IV), followed by a bolus of 100 mg ketamine if needed to achieve sufficient depth of anesthesia. Lidocaine (Lidocaine, Xylocain® 20%, AstraZeneca GmbH, Germany) was sprayed onto the larynx to facilitate orotracheal intubation. The endotracheal tube was inserted and the cuff was inflated with a cuffator to 30 mmHg. The pigs were then positioned inside the MRI in ventral recumbency. The endotracheal tube was connected to a circuit system connected and anaesthetic machine (Leon mri, Löwenstein Medical SE & Co. KG, Germany). Anesthesia was maintained with isoflurane in 100% oxygen and animals were thereafter instrumented. Multiparameter Monitors (MRI Patient Monitor Model IP5, Phillips, Germany) were used to measure: ECG, endtidal CO_2 (EtCO2), respiratory rate, oxygen saturation (SpO_2), exspired and inspired oxygen and isoflurane concentration, and temperature. Depth of anesthesia was evaluated clinically as long as the patient was accessible. All animals were ventilated with pressure (12-20 cmH2O) or volume-controlled ventilation (tidal volume of 10 – 12 ml/kg) to reach normocapnia.

3.2.2. NIBP instrumentation

NIBP readings were obtained with petMAP graphic II (Ramsey Medical, Inc. And CardioCommand, Inc., USA). The blood pressure cuff was placed on the pelvic limb at the height of the metatarsus. Cuffsize was chosen according to the manufacturer's instructions: the cuffs width was approximately 40 % of the limb's circumference. The cuffs were always placed by the same anaesthetist in order to minimize bias. For the connection to the cuff (within the magnetic field) the multiple (n=7) connected pressure tubings (Pressure Tubing 100cm, Mert Medical Pte., Singapore), were used, as displayed in Figure 3. This modification of the extension tubing was connected to the monitor's air hose and then to the monitor. The cuff sites were at the same level as the right atrium of the heart because of the positioning of the animals. The device was activated in the non-optimized mode and the first reading was disguarded. The non-optimized mode was chosen according to the manufacturer recommendations as dog- and cat-mode use species-specific algorithms. The petMAP device was placed outside of the MRI in safe distance outside of the Faraday cage during the procedure.

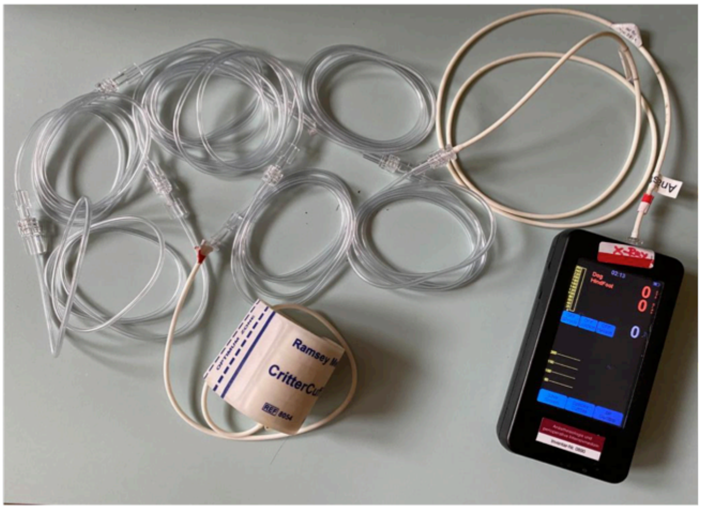


Figure 3. Demonstration of NIBP instrumentation: An oscillometric device for blood pressure measurement, petMAP graphic II, was connected to seven metres (n=7) of clear extension lines and then to the cuff. This makes it possible to place the non-MRI-compatible device outside of the MRI environment.

3.2.3. IBP instrumentation

IBP measurements required, as mentioned, the insertion of an arterial cannula. The medial tarsal artery was used for placement. The skin in the area was cleaned from coarse dirt with warm water and soap. The area was then clipped with sterile single use razor. The site was sterilized with alcohol. The puncture site was chosen contralateral to the cuff site at the height of the metatarsus. A 22-gauge sterile catheter (Kruuse Venocan Plus IV Catheter 22G, Kruuse, Denmark) was used to insert into the artery. Successful placement of the catheter was confirmed by pulsatile and prompt blood flow through the needle. After advancement into the vessel and removal of the stylet, a fluid-filled pressure transducer system integrating a flush system was connected. A 0.9 % sodium chloride solution was periodically fused to flush the catheter to maintain its patency. Arterial pressure was sensed by an attached transducer, which was placed at the level of the right atrium of the heart. Calibration of the monitor (MRI Patient Monitor Model IP5, Phillips, Germany) was performed prior to study. The calibration of the IBP measurement system (zeroing) was performed before each anesthesia as descibed in Grimm et al., 2015. The signal quality was evaluated prior and during the procedure as already described in chapter 2.1. The natural frequency of the transducer system that we used is 40 Hz, and the arterial wave pressure had a frequency of 1- 2 Hz (the animal's heart frequency is 60 – 120 bpm), wich is significantely different from the transducer. The tubes were checked constantly for air bubbles, which were removed from the system if necessary.

Systolic, diastolic and mean pressure recordings were obtained every 5 minutes simultaneously from the IBP and NIBP devices for the duration of the MRI scanning procedure by one anaesthetist. As mentioned, usually, due to the more time-consuming set up of IBP monitoring, the first few readings of petMAP were not paired with an IBP measurement, as it took time to set up. Only paired data for IBP and NIBP were included in further analysis.

3.3. Statistical methods

Data were tested for distribution, technical and biological variance, and Bland-Altman and 4-quadrant plots were produced. Furthermore, data were compared to the guidelines of the American College of Veterinary Internal Medicine ACVIM (Brown et al., 2007) and the Association for the Advancement of Medical Istrumentation AAMI (AAMI/ESH/ISO 2018 and 2009) (chapter 2.3.2).

The two methods used to estimate blood pressure, NIBP and IBP, were compared as follows: Technical and biological variation were calculated separately for both methods for all three parameters, SAP, MAP and DAP (Table 1). The technical variances V_I of the invasive and V_N of the non-invasive method, are likely almost uncorrelated, as the two methods are technically very different, while the covariance between the two methods likely reflects the biological variance V_B. Furthermore, the variance of the difference of the two measures reflects nearly exclusively the technical variation, while the variance of the mean of the methods reflects mainly the biological variation with minor contributions from the technical variances.

Indeed, with the above-stated assumptions the variance of the differences of the two methods corresponds to the sum of their variances minus twice their covariance:

$$(V_I + V_B) + (V_N + V_B) - 2V_B = V_I + V_N \quad (1)$$

The variance of the mean of two methods corresponds to:

$$\left(\frac{(V_I+V_B)+(V_N+V_B)+2V_B}{4}\right) = V_B + \frac{V_I}{4} + \frac{V_N}{4} \quad (2)$$

	BP_IBP	BP_NIBP
BP_IBP	$V_B + V_I$	V_B
BP_NIBP	V_B	$V_B + V_N$

Table 1. Formula for the calculation of variances and covariances. Biological variation: V_B. Technical variation of the invasive measurement technique: V_I. Technical variation of the non-invasive measurement technique: V_N

The Bland-Altmann method was used as a statistical method to compare two different measuring systems, a new (S_1) and an established one (S_2). In this technique, the difference in the results of the two methods are plotted against the mean of each method. In the cartesian coordinate system the diagram is hence described by the graph

$$S\,(x,y) = \left(\frac{S_1 + S_2}{2}, (S_1 - S_2)\right). \quad (3)$$

Three horizontal lines indicate

(1) Bias (the mean difference between two methods)
(2) Bias + 1.96 x standard deviation (SD) of the difference between two methods and
(3) Bias – 1.96 x standard deviation (SD) of the difference between two methods.

(2) and (3) represent the 95% limits of agreement (LOA), meaning that 95% of the differences are expected to lie within the range between both limits. In the AAMI/ESH/ISO 2018 statement, the use of a standardized Bland-Altmann plot is advised for ease of evaluation. Horizontal lines are drawn from 15 to -15 mmHg, every 5 mmHg. And the ranges of the x- and y-axes are prescribed. This provides easy evaluation conditions. In this thesis, the standardized version described by AAMI/ESH/ISO in 2018 and a modified version was displayed.

Furthermore, data were presented graphically with four-quadrant plots. These can be used to evaluate the ability of a new measurement system to measure changes in blood pressure when compared to a reference method (Saugel et al., 2015). Differences in subsequent measurements taken by the reference method (in this case IBP) are plotted on the x-axis, and those taken by the studied method (NIBP) on the y-axis. If both IBP and NIBP show an increase of blood pressure, the value will lie in the upper right quadrant of the plot; if both methods show a decrease of blood pressure, the value will lie in the bottom left quadrant. These two quadrants therefore indicate similar trends of measurements. If both methods deliver the same value, it will lie on the 45-degree line. Discordant measurements on the other hand will lie in the other two quadrants (upper-left and down-right). Four-quadrant plots therefore are very useful in evaluating trends – which is very important for the clinical use. If there is little to no change in either method, values will lie close to the center, which is rather uninformative. Therefore, a central region, in our case plus or minus 5mmHg for both measurements, is excluded from these considerations.

4. RESULTS

4.1. Data and Distribution

Data from all 24 pigs, weighing 9.0 ± 1.3kg at the age of five weeks (n=24) and 37.5 ± 3.4kg at the age of twelve weeks (n=24) were enrolled in the study. An arterial catheter was successfully placed in every pig (n=48). The mean anesthesia time from induction to the completion of the last measurement varied between 35 - 120min with a mean of 82min ± 12.4 SD, depending on the duration of the MRI scanning procedure and set up. For the experiment at the age of five weeks a cuff size of #3.5 was used in 21 of 24 cases, cuff size #3 in the remaining three. For the experiment at the age of twelve weeks only size #5.5 was used. Usually, the first readings of petMAP were not paired with an IBP measurement due to the time needed to place an arterial cannula during the set up of the IBP measurement system. This resulted in a mean of 13 paired blood pressure sets per anesthesia that were available per patient (every 5 min). In total 618 paired measurements for SAP and 617 for MAP and DAP were collected. 19 PetMAP and 44 IBP measurements were missing. Missing PetMAP readings were either not noted or the PetMAP did not display the measurement or the timing of the measurement was wrong. Missing IBP measurements were due to a loss of patency or loss of the arterial cannula. Table 2 shows the ranges of measured bloodpressure.

	IBP Min In mmHg	IBP Max In mmHg	NIBP Min In mmHg	NIBP Max In mmHg
SAP	55	129	55	173
MAP	41	94	31	146
DAP	19	78	15	31

Table 2: Ranges of measurements from invasively (IBP) and non-invasively (NIBP) measured blood pressure.

Assumptions for linear models are that variances do not scale with means and that the residuals are normally distributed. Small deviations from these assumptions were evident by unequal variances (see below) and other tests for normality. Transformation, like taking the log or the square root, unfortunately did not increase the fit; therefore untransformed data were used. Since linear models are robust to minor violations of assumptions, and also because the deviations were instructive we present the results of linear model analyses.

4.2. Variance and Covariance analysis

Variance and covariance were calculated individually for SAP, MAP and DAP like in table 1. The results are presented in table 3 (a, b, c) and descried below.

Variance and covariance for SAP (Table 3a)

For SAP variances and covariances were generally higher than for MAP or DAP. We interpret the covariance of SAP_i and SAP_n, the invasively non-invasively measured SAP respectively, as the biological variation, V_B. This was estimated to be V_B=137.34. Therefore, the technical variation of IBP, V_I, was estimated to be 220.03-137.34=82.69. And the technical variation of the PetMAP device was estimated to be 226.68-137.34=89.34. Obviously, the technical variation of the invasively measured SAP, SAP_i, is quite high and only 5% better than that of SAP_n.

Variance and covariance for MAP (Table 3b)

Biological variation V_B was estimated to be 113.59, slightly smaller than for SAP. Technical variation of MAP_i was estimated to be 118.45-113.59=4.86, only 4.27% higher than the biological variance. Hence, the technical variance of the MAPi was practically negligible. The technical variation of the non-invasively acquired MAP, MAP_n, was estimated to be 182.09-113.59=68.5, with 60% more than half the biological variation. These extreme differences in the technical variability between the two methods (IBP almost no and NIBP rather strong technical variation), needs to be accounted for when interpreting the Bland-Altmann plots. Indeed, the mean and the difference between the two methods, will be correlated positively or negatively, depending on which variable is substracted, due to this difference high technical variability of MAP_n and low technical variability of MAP_i.

Variance and covariance for DAP (Table 3c)

DAP values also showed a low technical variation of IBP. Biological variation was estimated to be 96.41, technical variation of DAP_i was estimated to be 94.28-96.41=-2.13 and of DAP_n to be 205.08-96.41=108.67. Hence, the technical variation of DAP_i is again nearly negligible. The technical variation of the non-invasive device on the other hand is as high as the variance of DAP_n and 112.7% higher than the biological variation. V_B of DAP is lower than of MAP and SAP.

	SAP_i	SAP_n
SAP_i	220.03	137.34
SAP_n	137.34	226.68

A

	MAP_i	MAP_n
MAP_i	118.45	113.59
MAP_n	113.59	182.09

B

	DAP_i	DAP_n
DAP_i	94.28	96.41
DAP_n	96.41	205.08

C

Table 3 a, b, c. Variances and Covariances SAP (a), MAP (b) and DAP (c) for assessing biological and technical variation of two blood pressure measurement methods (invasive vs. non-invasive)

4.3. Linear regression models

A linear model and two factorial models for individual and time, was used to partition the variance (Figure 4). Note that some technical parameters, e.g. the cuff size or placement stay constant during a session. The variability of the original NIBP values was quite high. (Figure 4, A, C, E). For SAP, most data points were between 60 and 120mmHg; for MAP between 40 and 100mmHg and for DAP between 20 and 80mmHg.

The regression slopes were relatively steep, indicating accordance between the two methods, likely due to the shared biological variability. Plots of the residuals for SAP, MAP and DAP, after removal of the variation among individuals and between time points, showed lower variability, generally within the range of ±20mmHg (Figure 4 B, D and F, respectively). Only in the case of SAP, the residuals showed a higher correlation ($\rho_r = 0.62$) than the original data ($\rho_o = 0.78$) and for DAP the residuals showed a lower correlation ($\rho_r = 0.53$) than the original data ($\rho_o = 0.73$). This indicates that for SAP the high technical variation, which is similar between the measurement systems, is removed relative to the biological variation, whereas this is reversed with MAP and DAP. For SAP, the technical variation is similar in IBP and NIBP, while MAP and DAP show a higher technical variation in NIBP measurements.

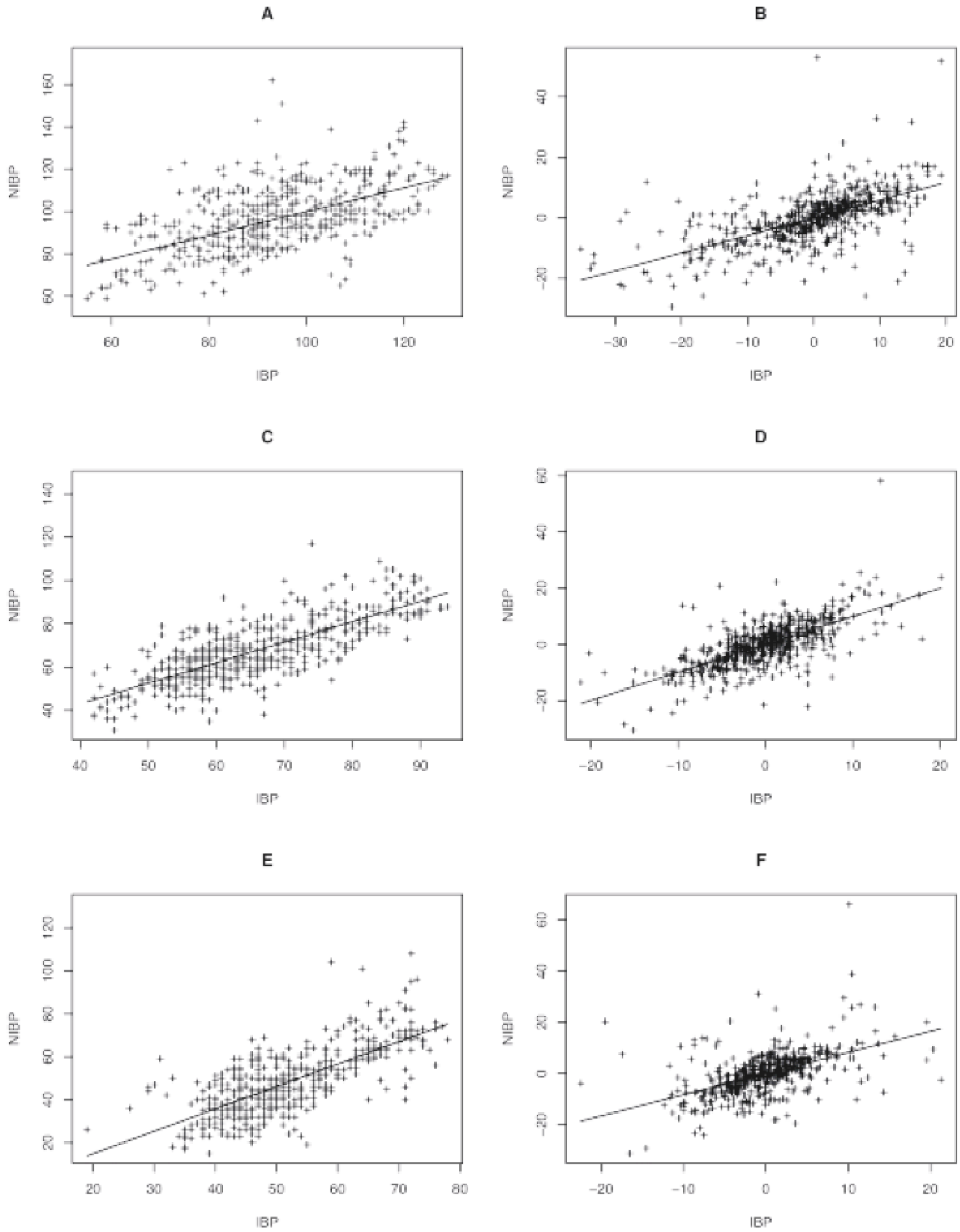


Figure 4: Linear models for assessing the relationship between invasive blood pressure measurements (x-axis) vs. non-invasive blood pressure measurments (y-axis) for SAP (A, B), MAP (B, C) and DAP (E, F). The plots on the left side (A, C, E) show a two-factorial model: individual and time; on the right side (B, D, F) represent same linear models after removal of technical variation.

4.4. Bland Altmann analysis

Bland-Altman plots were calculated as shown in Figure 5. Many data points were outside of the range of AAMI standards while about half of the plot area was empty (Figure 3A, C, E). Hence, Bland-Altmann with adjusted ranges are presented as well (Figure 3B, D, F). Means and 95% limits of agreement (LOA) were added to the plots for easier evaluation.

Representation of SAP measurements with the Bland-Altmann plot showed wide technical variation of data (Figure 5, A and B). 54% of paired measurements showed a difference of at most ±10mmHg, 32% of values of at most ±5mmHg and 87% of at most ±20mmHg. But the rest 13% showed a difference of more than ±20mmHg. Values of means and differences showed only a small correlation of $\rho = 0.02$ for SAP measurements.

Representation of MAP measurements with the Bland-Altmann plot showed narrower technical variation of data (Figure 5, C and D). In 78%, the differences between the methods were within ±10mmHg, with 51% showing only a small deviation of ±5mmHg. Nearly all differences (97%) were within the ±20mmHg. Deviations outside ±20mmHg showed a pattern: generally lower blood pressure values showed negative differences towards -30mmHg, while data indicating higher blood pressure showed more deviations towards +30mmHg. Correspondingly, values of means and differences showed a correlation of 0.30 for MAP. This is likely due to the higher variation of NIBP, as spurious low values of NIBP decrease both the mean and the difference.

Representation of DAP measurements with the Bland-Altmann plot showed quite a wide distribution of the calculated values (Figure 5, D and E). Most of the differences between the methods (67%) were within the ±10mmHg interval, 35% within the ±5mmHg and 95% within the ±20mmHg interval. Altogether 28/618 (4,5%) values showed a difference of more than 20mmHg. Similar to MAP, the lower BP values showed more deviations towards -30mmHg (underestimation), the higher values towards +30mmHg (overestimation) and means and differences showed a correlation of 0.47. Again, this is likely due to the higher technical variation of NIBP, spurious low values of NIBP decreased both the mean and the difference. All three measurements, SAP, MAP and DAP showed a very small bias of under 5mmHg.

The LOA help for easier evaluation of the BA plots and were displayed in table 4. The means of all 3 values, SAP, MAP and DAP are relatively close to zero. This means that calculated differences were equally distributed towards both ends of the range.

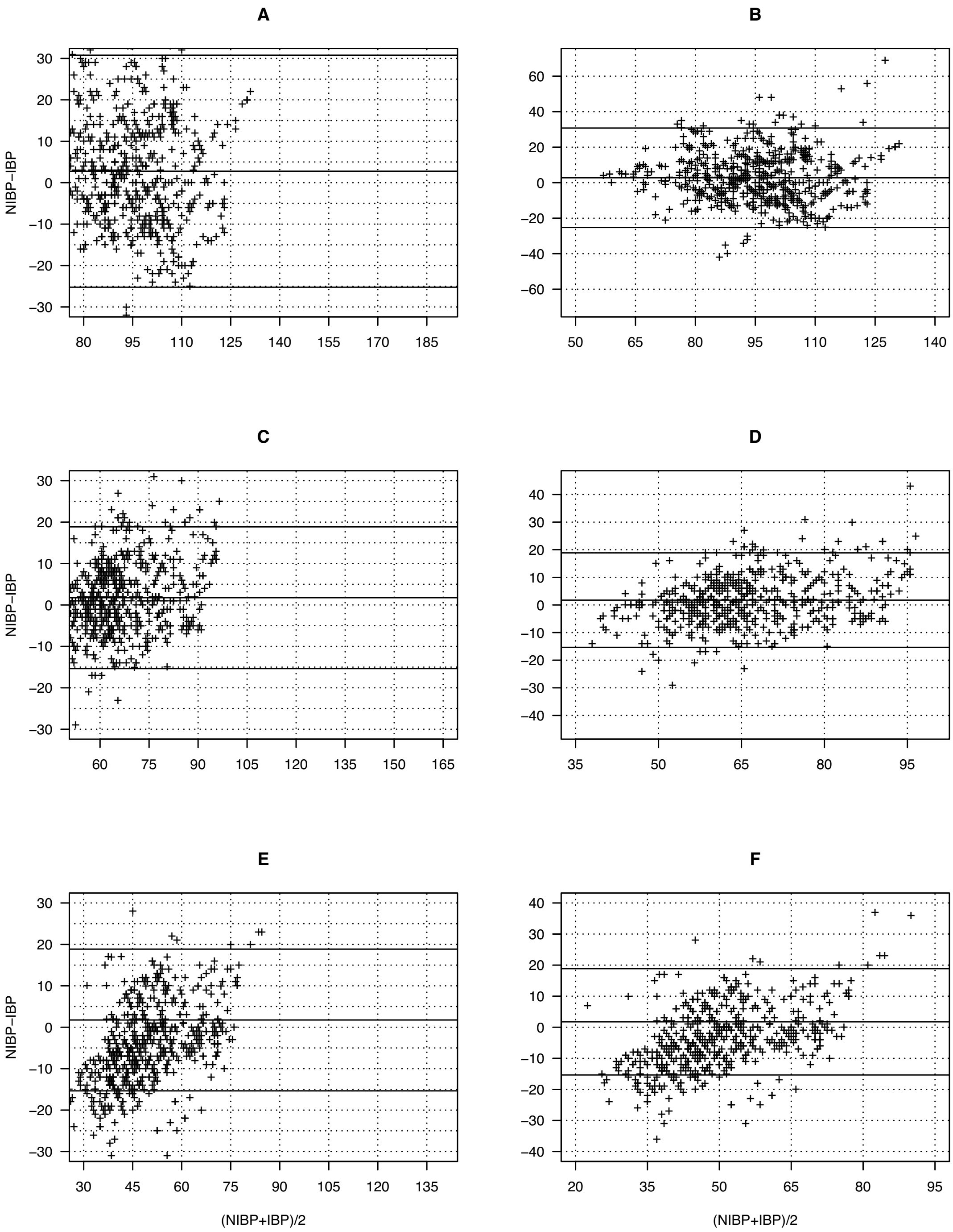


Figure 5.

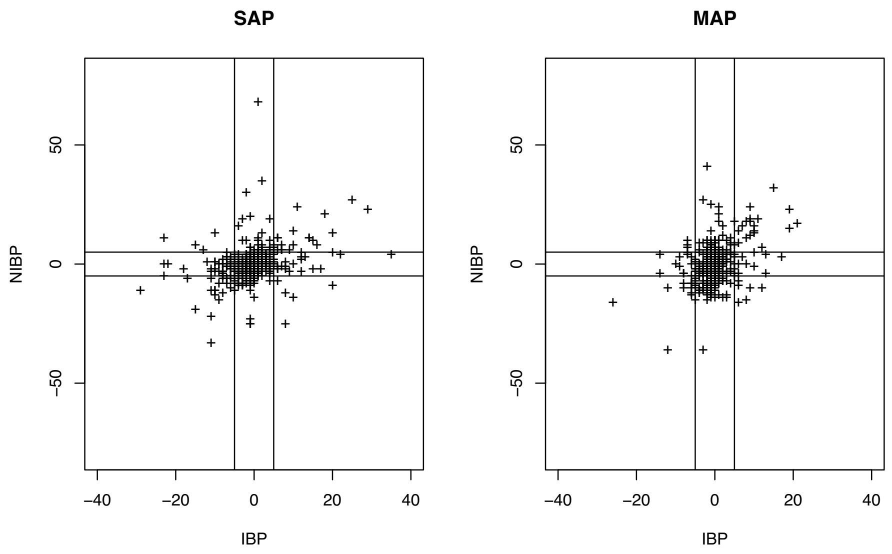
Bland-Altmann (BA) plots for assessing the relationship between blood pressure measured by petMAP, an oscillometric device, and blood pressure measured invasively each for SAP (A, B), MAP (C, D) and DAP (E, F). Presentation of the data as recommended by AAMI via Bland-Altmann plot were used on the left side (A, C, E). The same data presented by adjusting the x- and y achsis (B, D, F) fitted better our data set. Bias and 95% Limits of Agreement (LOA) are indicated by three horizontal lines.

	Mean	Mean + 1.96*SD	Mean – 1.96*SD
SAP	2.78	30.77	-25.22
MAP	1.75	18.86	-15.35
DAP	-3.76	15.93	-23.46

Table 4. Limits of agreement for SAP, MAP and DAP. The 95% LOA describe the interval in which 95% of the differences between two values lie.

4.5. Four quadrant plots

Data represented with **four-quadrant plots** for SAP, MAP and DAP (Figure 6). All three plots for SAP, MAP and DAP showed most data within the uninformative exclusion zone of plus or minus 5mmHg. Generally, the rest of the data except for a few outliers were in the upper-right and bottom-left quadrants confirming some trending between methods for all three measured variables (SAP, MAP and DAP).



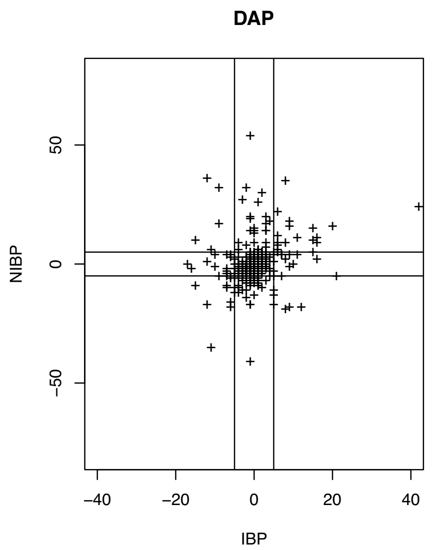


Figure 6. 4-Quadrant Plots for assessing the relationship between changes of BP measured invasively vs non-invasively each for SAP, MAP and DAP. Values in the bottom left and top right quadrant indicate good trending ability of the NIBP device. All three values show quite low trending ability.

4.6. Comparison to the guidelines

Lastly, the methods were compared according to the **guidelines by the American College of Veterinary Internal Medicine (ACVIM) (Brown et al., 2007) and the Association for the Advancement of Medical Instrumentation (AAMI) (Stergiou et al., 2018)** (Table 5 and 6, respectively).

For SAP, MAP and DAP most ACVIM criteria were met.

SAP

The difference of SAP_n minus SAP_i values was 2.78 ± 14.29 SD (ACVIM requires a mean difference of ≤10mmHg and SD ≤15mmHg). The correlation between SAP_i and SAP_n was 0.57, and **thus did not reach the standards of >0.9.** Of the SAP_n values 86.7% were found within ±20mmHg of the reference method IBP and 54.2% were found within ±10mmHg - note that the guidelines require 80% and 50%, respectively.

MAP

The difference of MAP_n minus $SMAP_i$ values was 1.75 ± 8.73 SD (ACVIM requires a mean difference of ≤10mmHg and SD ≤15mmHg). The correlation between MAP_i and MAP_n was 0.78, and **thus did not reach the standards of >0.9.** Of the MAP_n values 96.9% were found within ±20mmHg of the reference method IBP and 78.6% were found within ±10mmHg.

DAP

The difference of DAP_n minus DAP_i values was 3.76 ± 10.05mmHg SD. Correlation between IBP and NIBP was only 0.73 and **hence did not meet the requirement of 0.9.** Of the DAP_n values 95% lie within 20mmHg of the paired DAP_i value, and 67% within the ±10mmHg interval.

Concordance to AAMI guidelines (Table 6)

The guidelines for validation set by AAMI 2018 recommend a proportion of more than 85% for NIBP to be within ≤10mmHg of the paired IBP measurement. In the present study only 67% of the measurements were found within this interval. The 2009 guidelines by AAMI (ANSI/AAMI/ISO 81060-2, 2009) also require a mean bias of ≤5mmHg and standard deviation of ≤ 8mmHg of paired SAP and DAP. As described above, the mean differences

(IBP-NIBP) of the paired SAP, MAP and DAP measurements were 2.75mmHg, 1.75mmHg and 3.47mmHg with standard deviations of 14.3mmHg, 8.73mmHg and 10.0mmHg, respectively.

	Number of animals	Bias	SD	Correlation	<10mmHg in %	<20mmHg in %
ACVIM criteria	8	≤10	≤15	≥0,9	≥50	≥80
SAP		2.75	14.29	0.57	54.2	86.7
MAP	12/24	1.75	8.73	0.78	78.6	96.9
DAP		3.47	10.05	0.73	67	95

	Number of animals	Bias	SD	Correlation	<10mmHg in %	<20mmHg in %
AAMI criteria	85	≤5	≤8	No criteria	≥85	No criteria
SAP		2.75	14.29	0.57	54.2	86.7
MAP	12/12	1.75	8.73	0,78	78.6	96.9
DAP		3.47	10.05	0.73	67	95

Table 5 and 6. Summary of the data analysis and concordance to ACVIM and AAMI guidelines of oscillometric (petMAP graphic II) device compared to invasive blood pressure measument in anesthetized pigs undergoing MRI. SD, standard deviation.

5. DISCUSSION

In this study, 617 measurements were used to validate modified petMAP graphic II with 7m extension lines against invasive blood pressure measurements in anesthetized pigs undergoing MRI. The modified petMAP graphic II could fullfil the majority of the validation criteria of the ACVIM guidelines and showed a sufficient ability to follow trends with invasive blood pressure measurements.

Validation of new devices or slightly modified old devices, as in this case, to measure blood pressure (BP) stems from the need of the clinicians to assess blood pressure during anesthesia. Unfortunately, there are only few reliable NIBP measuring systems on the market (Skleding & Valverde, 2021). One explaination for inaccuracy of NIBP data in general is the way the blood pressure is calculated: While an IBP device measures the SAP, MAP and DAP inside the artery directly, NIBP devices like petMAP measure a variable related to blood pressure and calculate BP with an equipment-specific algorithm (Henneman & Henneman, 1989). Reliabilitiy depends on the positioning and size of the cuff, the size of the patient, the species, the hair coat, the amount of the fat covering the artery, the algorithm, and can be patient-specific. In human medicine different algorithms and specific devices are used for different subset of patients (e.g. devices developed specifically for diabetic, obease, hypertensive patients). In this study on pigs we have used a species–unspecific mode of the petMAP graphic II as recommended by the manufacturer which may have added to the variability since this device is primarily designed for dogs and cats. In addition to the obvious phenotypical variation within a species other factors like systemic vascular resistance and potential arrhythmias are aspects that can influence NIBP measurements.

In this study each individual was anaesthetized twice seven weeks apart and multiple times in the course of anesthesia. Variation in BP was due to the biological as well as the technical variation. The variance/covariance analysis allowed differentiation between technical and biological variation. V_n, the technical variation of non-invasively obtained measurements was high for all three measurements, SAP, MAP and DAP compared to IBP. The variability of SAP was high compared to MAP and DAP. This is concordance with other studies which also described higher variavility in SAP measurements (e.g. Piel, 2018, Cerejo et al., 2017).

Interestingly, technical variability for SAP_n was very similar to SAP_i: 220,03 and 226,68 respectively. However, the technical variability of the MAP_n and DAP_n was much higer then MAP_i and DAP_i: 118,45 and 94,28 compared to 182,09 and 205,08, respectively.
The technical variability in SAP_i and SAP_n can be explained by lung-heart interaction and limitations of both systems to recognize beat to beat changes. However, high technical variability of the SAPi is also partly due to comparing only one reading of the SAP_i every 5 minutes which was noted immediately after the start of the NIBP measuring cycle. Some other studies have considered the mean of three SAP_i measurements during one NIBP (e.g. Seliskar et al., 2013; Almeida et al., 2014; Cerejo et al., 2017). However, also in these studies SAP_n showed higher variability compared to DAP and MAP. Technical variability of the SAP_n could partly be due to lung-heart interaction, just like SAP_i, however SAP_n is a calculated value by the petMAP software algorithm while SAP_i is a measured value. Drynan and Raisis (2013) showed the influence of the gradual air relaese from the cuff on the accuracy of SAP_n. PetMAP devices do not release the air linearly, but at a different product-specific speed, which could also be a reason for high SAP_n variability. Furthermore, Piel (2018) describes pulsewave amplification as another possible explanation for the inaccuracy of SAP_n. The blood pressure changes at different sites of the vessel in regard to wall stiffness, vasomotor tone or calcifications. (Avolio et al., 2009). In peripheral arteries, this could have an impact on invasively and non-invasively measured blood pressure and therefore lead to slightly different results in SAP_n. Animals are generally not as affected by atherosclerosis as humans, mainly due to nutrition, but this could still play a role in variability of the measured values (Wang et al., 2020). Of course, in the study presented here high variability of the SAP_n could be also due to long extension lines from the PetMAP to the cuff.

The technical variability of the NIBP described in this study is probably mainly correlated to cuffsize or cuff location. The cuff size in this study was chosen according to the manufacturer's instructions for dogs and cats and was about 40% of the limb's circumference. Geddes et al. (1977) found that in horses the cuff should only be 25% of the tail's circumference. Thus, for every species and device, another setting may be optimal. Geddes et al., (1980) stated that too small cuffs cause overestimation, while too big cuffs usually cause underestimation. In this study three sizes of the cuff were used, to best to the requirement of

40% of the limb’s circumference. Possibly for older (and generally larger) pigs no adequate cuff size is provided by the manufacturer of petMAP since this device is designed for small animals. Of course, not in all animal's cuff width was exactly 40% of the limb’s circumference and therefore some cuffs may have fitted better than others. This variation is almost impossible to avoid in clinical settings. Further, because all the cuffs were always placed at the very uniform metatarsus a technical variability caused by different location can be excluded. Other factors increasing variability may be tightness of the cuff i or the placement of the artery mark on the cuff.

The manual of PetMAP graphic II recommends the base of the tail or front leg as cuff sites, while other studies found that the hind leg showed better results for oscillometric blood pressure evaluation in dogs with other oscillometric blood pressure measuring devices.

(e.g. Sawyer et al., 2004). In pigs, Chow et al., 1999, achieved good results with neonatal cuffs around the base of the tail. In this study, only left and right tarsi were used as cuffsites. As our pigs were only five weeks old in the first session, the tail would have been too thin. Also, because of the positioning of the patient in the MRI and limited access due to the sternal recumbency and because the pigs have very short legs, which widen shortely after carpus it was not possible to place the cuff at the front limbs. Thus, the tarsus was chosen as a cuffsite for both session, also because on the contralateral site at almost the same level an arterial line could be placed.

Another important factor for the validation of new devices is the IBP measuring site. Pressure waves change towards the periphery. Systolic arterial pressure shows an increase while diastolic pressure tends to decrease away from the heart. This is due to pressure wave reflections from smaller arteries and arterioles, which have a thicker lamina muscularis and therefore provide a higher resistance. Due to this pressure variation, the femoral and dorsal pedal artery, for example, experience a higher SAP than the carotid artery (Skelding & Valverde, 2020). Hence, it is of importance that indirect and direct measurements use similar bodyparts to minimise deviations. In our study we can exclude this because both IBP and NIBP measurements were taken at the same height (medial tarsal artery for IBP vs. metatarsus for the NIBP cuff). Therefore this factor should cause no bias or variation. Gladczak et al. (2013) for example, measured the non-invasive blood pressure of pigs on the metatarsus and IBP values in the auricular veins and still came to the conclusion that an oscillometric cuff (not PetMAP but a childsize Criticon-Dura cuff) is able to deliver reliable results. Therefore, the deviation due to the positions must have been quite small in their case. Other studies used very variable positions for BP measurement, e.g., the auricular vein vs. metacarpus/metatarsus (Almeida et al., 2014), dorsal pedal artery vs. metatarsus/tail (Seliskar et al., 2013), dorsal pedal artery vs. metacarpus/tail (Cerejo et al., 2017; Vachon et al., 2014). All those studies were performed with either dogs or cats. In the present study, the size and position of the pigs made it possible to use the same position for invasive and non-invasive measurements (metatarsi) - this certainly didn't have a negative effect on the concordance of both methods.

Anatomical features of the species as well as differences among individuals like sex, height etc. can in part explain the differences between IBP and NIBP measurements (Piel, 2018). Many other parameters like autonomic response, vasovagal reactions, or perfusion differences of different tissues can influence systemic vascular resistance, pain, stress, age, sex and species/breed also contribute to intersubject variability and have an impact on BP measurements and should be kept in mind when interpreting the results (Piel, 2018; Bodey & Michell, 1996).

We used linear models and more specifically two factorial model to exclude variability among individuals and between time points. This allows to focus on the variability due to the device. Indeed, SAP_n, DAP_n and MAP_n displayed lower variability after the removal of the variation among individuals and between time points. This means that a large part of variability was probably due to the intrasubject variability or systemic during the course of anesthesia.

The MAP showed lower variability compared to SAP and DAP as in Piel (2018) and Shih et al. (2010). The SAP and DAP values are calculated by the device, while MAP is measured. As already shown in recent studies, MAP values therefore often were the most reliable parameter, while SAP and DAP values showed more deviation from the gold standard (e.g. Piel, 2018; Cerejo et al., 2017).

The high technical variability of SAP_i was observed in the variance/covariance analysis: while it was nearly negligible for MAP_i and DAP_i. This means that IBP data reflected the

actual blood pressure for these parameters quite acurately. For SAP_i on the other hand, variability was almost as high as for SAP_n, the technical variation of non-invasively obtained data. This can be partly explained by variable cardiac preload during different ventilation phases known as lung-heart interaction. Michard et al. (2005) reported “that mechanical ventilation induces cyclic changes […] [in the blood flow of the vena cava, the pulmonary artery and the aorta.] During the inspiratory period, the vena cava blood flow decreases first, followed by a decrease in pulmonary artery flow and then in aortic blood flow. […] According to the Frank-Starling mechanism, […] the inspiratory decrease in right ventricular preload results in a decrease in right ventricular output and pulmonary artery blood flow that finally leads to a decrease in left ventricular filling and output” (Michard, 2005, pp. 419-428). Thus, depending on the phase of ventilation, cardiac output and systolic blood pressure show higher variability (Kyhl et al., 2013). Thus, variable cardiac preload during ventilation is probably responsible for the high SAP_i variation also shown in this study.
Skleding & Valverde (2020) compared results of many studies evaluating oscillometric BP devices. Indeed, in most cases, SAP_n values showed the most bias compared to MAP_n and DAP_n. Those studies compared the non-invasively measured BP values to the IBP values but did not calculate technical or biological variation. This means, that for SAP, findings only described whether NIBP compared to IBP delivered similar results but not whether those results reflect the actual blood pressure. The correlation between SAP_i and SAP_n in this study was moderate (0.57) but below the required >0.9 by ACVIM guideliens. This was to be expected, considering the high technical variations of both methods.

Bland-Altmann plots supported the findings of the variance/covariance calculations. The ranges of x- and y-axis advised by AAMI were too low for our data. Therefore, plots with adjusted ranges were displayed as well. Hodgkin et al. (1982) found SAPi between 73 and 230mmHg and DAP_i between 52 and 165mmHg in pigs. Non-invasive BP via the Doppler method tended to be lower. In this study SAP_i ranged between 56 and 125mmHg. In this study we observed relatively wide range of blood pressures, generally in the lower to normal range. This could be partly explained by the anaesthetic protocol using azaperone and sevoflurane, both known to induce vasodilatation. However, although the minimal alveolar concentration (MAC) of sevoflurane during anesthesia in juvenile pigs is reported to be 3.5 ±

0.1% (Moeser et al., 2008), in this study, exspiratory sevoflurane (ET_{Sevo}) was consistently lower than the MAC. Periods of hypertension were not induced as this was not allowed by the main study. Generally, in these rather low blood pressure ranges, the concordance between IBP and NIBP was similar to that in higher BP ranges.

To present trendibility, four-quadrant plots were produced. These showed an acceptable correlation between subsequent measures for all three values: SAP, MAP and DAP. However, most datapoints were inside the ±5mmHg exclusion zone and therefore could not be interpreted. This could be due to the intervals being too short to show a trend compared to the variability. The majority of the remaining data were in the upper right and lower left quadrants confirming trendibility, while others were in the other two quadrants, opposing trendibility. With the same method Cerejo et al. (2017) reported a concordance rate of over 93% comparing petMap graphic and petMAP classic results with IBP measurments in cats. Generally, the four-quadrant plots have been used by few studies as it is a new method that was initially invented for evaluating the tracking ability of cardiac output measurement devices.

Furthermore we looked if the results of this study are in concordance with ACVIM guidelines which is needed to confirm validity of the modified petMAP measurements. Our resuls showed that the modified petMAP method used, met the criteria stated by ACVIM (bias, SD, <10mmHg and <20mmHg ranges) except for the correlations for SAP, MAP and DAP. Similar results many studies which were published over the years on this topic including validation of petMAP graphic II. These studies were able to show that some but not all of the criteria by ACVIM for dogs and cats were reached (Skelding & Valverde, 2020). Moreover, we compared our measurements with the more stringent human AAMI standards and found that neither SAP nor MAP nor DAP met the criteria. We are not aware of a published study where an NIBP device reached all of the standards set by the AAMI in conscious dogs, cats or other animals (Brown et al., 2007, Skelding 2020). Studies of anesthetized animals fulfilled some of the requirements, similar to this study (Deflandre & Hellebrekers, 2008; Bosiack et al., 2010; Cerejo et al., 2018). Factors such as size, fur, anatomical differences and compliance in awake animals make it significantly more difficult to develop a device that provides reliable measurements in veterinary medicine. Recent studies are therefore including AAMI criteria together with ACVIM requirements (e.g. Cerejo et al., 2017; Almeida et al., 2014).

Validation of the new devices in human medicine includes comparison of the new device with another validated device which measures BP on the same principle (i.e. oscillometric). Moreover, the comparison of indirect and direct measurements is not recommended in human medicine (Skleding & Valverde, 2020). This is due to the BP variaton between consecutive beats which is measured by direct devices but not via oscillometric evaluation. This discrepance can lead to differences of up to 24mmHg for SAP and 16mmHg for DAP between indirect and direct BP (O'Brien et al., 1993). Despite this variance, the consensus statement for veterinary medicine recommends the comparison of NIBP with the gold standard in order to validate NIBP's accuracy.

Limitations of this study

This study has the following limits: the AAMI guideline (Stergiou et al., 2018) requires a minimum of 85 participants for validation of a BP device; in the present study only 24 individuals were tested. Even if both ages (five and twelve weeks) are counted separately, as the pigs differed in size and proportion, this would still only result in 48 individuals. The ACVIM guidelines (Brown et al., 2007), which are specifically for the veterinary field, recommend a study group of at least 8 subjects; this has been met in this thesis. The number of NIBP measurements per pig and age in the present study exceeded the requirements by far. With one exception, where a pig was measured only four times, each pig was measured between 14 and 24.

Additionally, the AAMI guidelines require a protocol where three IBP measurements are compared to one NIBP measurement. In this study, one NIBP value was compared to one IBP value. In the author's opinion, the extremely high number of measurements in this study still provided enough data for calculations. Therefore, a clear statement about the accuracy of NIBP measurements could be made and was not compromised by this discrepance to the guidelines.

The data for the present study were acquired during MRI scanning for the main study; no periods of induced hypo- or hypertension were allowed by the protocol. We note that 248 of 616 IBP measurements showed a MAP below 60mmHg (per definition hypotensive). The pigs were treated with an adaption of anaesthetic depth and fluid therapy. Concordance between IBP and NIBP was not significantly different from that during normotensive or hypertensive states. Still, an interesting observation was made: For MAP and DAP, the lower blood pressure ranges tended to show deviations towards -30mmHg, while the higher blood pressure ranges showed deviations towards +30mmHg. This means hypotension was overestimated by petMAP which is in concordance with other studies (e.g. Shih et al., 2010; Bosiack et al., 2010; Sawyer et al., 1991).
Several studies have tested oscillometric devics in other species, e.g. cats, dogs and sheep (Almeida et al., 2014; Acierno et al., 2013; Cerejo et al., 2017) including hypo- and hypertensive periods. The family of PetMAPs, petMAP, petMAP graphic II, delivered mixed results and showed poorest reliability in hypotensive states compared to other oscillometric devices in dogs and cats (e.g. Acierno et al., 2013; Vachon et al., 2014, Skelding & Valverde, 2020). As hypertension was not induced in this study a further studies could investigate this.

Another limitation of this study was the use of only females. The AAMI recommendation requires mixed gender study groups with at least 30% females and 30% males. In the ACVIM guidelines there is no recommendation on the gender. Note that Almeida et al. (2014) could show that sex does not influence the blood pressure or BP evaluation.

The studies evaluating othe NIBP measurements devices in pigs with neonatal or child-size cuffs, delivered quite promising results (Gladczak et al., 2013; Chow et al., 1999). This may have to do with the fact, that pigs have many physiological similarities to humans and are quite different from dogs and cats. In some aspects, the skin anatomy of pigs is closer to that of humans than to dogs. The skin of pigs is firmly attached to the subcutaneous tissue, just like in humans, while it is only loosely attached in dogs and cats (Summerfield et al., 2015). The lack of a covering fur in pigs and humans is another factor. Thus PetMAP, which is designed for cats and dogs, might not be the best option for pigs.

To the author's knowledge use or validation of petMAP graphic II with extension lines has not been reported in any species. It is unclear whether petMAP would deliver better results in pigs without 7m extension lines. This needs further evaluation. Nevertheless our study design is relevant as MRI is becoming more frequently available, not only for research but also for use in small animal veterinary clinics. Thus, the use of the modified device in MRI outside of the Faraday cage, could be a starting point for evaluating a similar set up often used for cats and dogs.

In conclusion, moitoring BP with a modified petMAP graphic II with 7 m extension lines delivered acceptable measurements of BP during general anesthesia in pigs undergoing MRI. Compared to invasive blood pressure measurements the modified petMAP met the criteria by ACVIM for SAP, DAP and MAP except with respect to the correlation. In contrast, only bias and SD criteria of the AAMI guidelines were fulfilled. While an absolute quantification of blood pressure by PetMAP might be misleading, relative temporal quantification was shown to be more accurate.

5. ABSTRACT

Introduction: Measuring the blood pressure during magnetic resonance imaging (MRI) in animal patients under general anesthesia is difficult due to lack of access and monitoring equipment. Invasive blood pressure (IBP) measurement is the current gold standard. This technically demanding and expensive technique via an arterial catheter, has negligible technical variation. However, measuring the blood pressure with non-invasive oscillometric techniques (NIBP) is cost-effective and less invasive and would thus be preferable, if the technical variation could be controlled.

Objective: The main goal of this study was to examine the feasibility of the modified oscillometric NIBP system PETMAP II graphic with 7 m extension lines in anaesthesized pigs undergoing MRI.

Results: Blood pressure values were recorded invasively and non-invasively every five minutes during one hour of general anesthesia in 12 Landrace pigs (35 ± 3,5 kg BW) at week 5 and 12. In total 618 repeated measurements for SAP and 617 for MAP and DAP were collected and analysed by a comparison of variances and covariance of the methods, Bland-Altman plots, 4-Quadrant plots. The IBP measurements of DAP and MAP, reflect the biological variation with little variation such that linear models can be used. For the IBP SAP measurement the variance of IBP was more than 60% higher than the covariance. The NIBP showed an excess of the variance over the covariance of about 60% in all three cases. The bias of the NIBP measurements were 2.75mmHg, 1.75mmHg and 3.47mmHg with the standard deviation of 14.3mmHg, 8.73mmHg and 10.0mmHg and correlation coefficient of 0.57, 0.78, and 0.73 for SAP, DAP and MAP, respectively. The 4-Quadrant plot analysis showed adequate trendibility.

Conclusion: Modified petMAP graphic II with 7 m extension line delivered acceptable measurements reflecting serial changes of BP during general anesthesia in pigs undergoing MRI. Compared to invasive blood pressure measurements modified petMAP met the criteria by ACVIM for SAP, DAP and MAP in all criteria except the correlation. In contrast, only bias and SD criteria of AAMI guidelines were fulfilled. While an absolute quantification of blood pressure by PetMAP might be misleading, relative temporal quantification was shown to be acceptable.

6. ZUSAMMENFASSUNG

Einleitung: Die Blutdruckmessung während der Magnetresonanztomographie (MRT) stellt bei narkotisierten Tierpatienten eine Heruasforderung dar, die auf den Mangel an kompatiblem Eqipment und den erschwerte Zugang zum Patienten zurückzuführen ist. Invasive Blutdruckmessung (IBP) ist der derzeitge Goldstandard. Die technische Variation dieser vergleichsweise aufwändigen und teuren Methode ist vernachlässigbar gering. Die Blutdruckmessung mittels einer nicht-invasiven, oszillometrischen Methode ist kosten-effizient und einfacher und daher vorzuziehen, falls die technische Variation kontrollierbar wäre.

Zielsetzung: Das Hauptziel dieser Studie war es, die praktische Durchführbarkeit und Genauigkeit des oszillometrischen Gerätes PetMAP graphic II modifiziert mit 7m Verlängerungsschläuchen an anästhesierten Schweinen während des MRTs zu testen.

Ergebnisse: Blutdruckwerte wurden sowohl innvasiv als auch nicht-invasiv alle 5 Minuten in einem Zeitraum von etwa einer Stunde Vollnarkose von 12 Landrasse Schweinen (35 ± 3,5 kg) gemessen – einmal im Alter von 5 Wochen und einmal im Alter von 12 Wochen. Insgesamt konnten 618 wiederholte Messungen von systolischen Werten (SAP) und 617 von mittleren und diastolischen Werten (MAP and DAP) ausgewertet warden. Der Vergleich der Varianzen und Covarianzen, Bland-Altmann-Graphen, 4-Quadranten-Diagramme wurden zur statistischen Auswertung herangezogen. Die IBP Messungen von DAP und MAP reflektieren die biologische Varianz mit so geringer Abweichung, dass lineare Modelle genutzt warden konnten. Für die invasiven SAP Werte war die biologische Varianz mehr als 60% größer als die Covarianz. Die nicht-invasive Blutdruckmessung zeigte einen Überschuss der Varianz gegenüber der Covarianz von 60% in allen drei Fällen (SAP, MAP, DAP). Der Bias der nicht-invasiven Blutdruckmessung war 2.75mmHg, 1.75mmHg und 3.37mmHg mit einer Standardabweichung von 14.3mmHg, 8.73mmHg und 10.0mmHg. Der Korrelationskoeffizient war 0.57, 0.78 und 0.73 für SAP, DAP und MAP. Die 4-Quadranten-Auswertung zeigte eine annehmbare Trendfähigkeit.

Conclusio: Das modifizierte PetMap graphic II mit 7m Verlängerungen lieferte akzeptable Messungen und verfolgte Blutdruckänderungen während der Vollnarkose bei Schweinen. Im Vergleich zur invasiven Blutdruckmessung konnte die oszillometrische Methode die Kriterien

von ACVIM für SAP, MAP und DAP in allen Punkten, außer die Korellation erfüllen. Im Gegensatz dazu konnten nur Bias und Standardabweichung von AAMI Empfehlungen erfüllt werden. Während eine absolute Quantifikation von Blutdruck durch PetMAP eher irreführend sein kann, so erwies sich die relative zeitliche Quantification als akzeptabel.

7. ABBREVIATIONS

AAMI	Association for the Advancement of Medical Istrumentation
ACVIM	American College of Veterinary Internal Medicine
BA	Bland-Altmann
BP	Blood pressure
CO	Cardiac output
$DAP_{(I)}$	Diastolic arterial pressure (of the invasive method)
$DAP_{(n)}$	Diastolic arterial pressure (of the non-invasive method)
GA	General anesthesia
IBP	Invasive blood pressure
LOA	Limits of agreement
$MAP_{(I)}$	Mean arterial pressure (of the invasive method)
$MAP_{(n)}$	Mean arterial pressure (of the non-invasive method)
MRI	Magnetic Resonance Imaging
NIBP	Noninvasive blood pressure
$SAP_{(I)}$	Systolic arterial pressure (of the invasive method)
$SAP_{(n)}$	Systolic arterial pressure (of the non-invasive method)
SD	Standard deviation
V_B	Biological variation
V_I	Technical variation of the invasive method
V_N	Technical variation of the non-invasive method

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9. LIST OF TABLES AND FIGURES

Meiner geliebten
kleinen & großen Familie