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Evaluation of a non-invasive dynamic parameter for optimal fluid management

Diploma thesis

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STATUTORY DECLARATION

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Evaluation of a non-invasive dynamic parameter for optimal fluid management

One of the main goals in managing critically ill patients is the optimization of fluid management. In mechanically ventilated patients, dynamic markers like Pulse Pressure Variation (PPV) have been shown superior for predicting preload responsiveness-i.e. whether or not the patient reacts with significantly increased cardiac output to fluid administration. The goal of this study was the evaluation of a recently developed automatical PPV-algorithm (PPVauto) in comparison to a manually calculated "gold standard" PPV (PPVman). Ten mechanically ventilated patients were studied in the intensive care unit. Blood pressure was continuously measured with an arterial catheter as well as non-invasively with the CNAP-Monitor. Digitally recorded data was retrospectively pre-processed and statistically analyzed. For a total of 100 randomly assigned paired data points, the difference (mean bias ± SD) between PPVman and PPVauto evaluated on the CNAP-signal was 0.98%±1.99%, respectively 0.20%±1.64% for the invasive signal. Agreement between PPVman and PPVauto was shown in this analysis. This suggests that the automated non-invasive PPV-algorithm may be a valuable method for monitoring fluid status with potential for clinical application. Further clinical studies with more patients have to be conducted to prove this non-invasive monitoring system as an accurate predictor of fluid responsiveness.

Fluid management, Pulse Pressure Variation (PPV), CNAP, non-invasive blood pressure, critical care monitoring, algorithm evaluation

Evaluierung eines nicht-invasiven dynamischen Parameters zum optimalen Flüssigkeitsmanagement

Zum zielgerichteten Flüssigkeitsmanagement kritisch kranker Patienten stehen eine Reihe von Parameter zur Verfügung, die jedoch großteils auf invasiven Messmethoden beruhen. In den letzten Jahren wurde gezeigt, dass mithilfe dynamischer Parameter wie der Variation des Pulsdruckes (PPV) aus einer Blutdruckkurve eine verlässliche Vorhersage getroffen werden kann, ob ein Patient von einer Flüssigkeitsgabe profitiert. Dies würde sich in einem Anstieg des Herzschlagvolumens zeigen. Ziel dieser Diplomarbeit war die Evaluation eines neu entwickelten Algorithmus für die automatische Bestimmung der Pulse Pressure Variation (PPV) basierend auf der nicht-invasiven Blutdruckkurve des CNAP-Monitors. Diese automatisch berechneten PPV-Werte (PPVauto) wurden mit manuell berechneten PPV-Werten (PPVman) sowohl auf dem invasiven als auch auf dem nicht-invasiven Blutdrucksignal verglichen. In die klinische Studie wurden 10 mechanisch beatmete Intensivpatienten mit einbezogen. Die Blutdruckwerte wurden mit einem invasiven arteriellen Katheter sowie mit dem CNAP-Monitor kontinuierlich aufgezeichnet. Weiters erfolgte eine retrospektive Signalverarbeitung sowie eine statistische Auswertung der Daten. Für insgesamt 100 randomisierte Datenpunkte wurde eine Differenz (gemittelter Bias ± Standardabweichung) zwischen PPVman und PPVauto auf dem CNAP-Signal von 0.98%±1.99% berechnet, respektive 0.20%±1.64% für das invasive Signal. Eine gute Übereinstimmung zwischen PPVman und PPVauto wurde in der Studie gezeigt. Die Resultate deuten darauf hin, dass diese neue hämodynamische Überwachungsmethode für die klinische Anwendung wertvoll ist. Es sollten jedoch weitere Studien mit mehr Patienten durchgeführt werden um zu zeigen, dass der neue automatische Algorithmus für das Flüssigkeitsmanagement geeignet ist.

Flüssigkeitsmanagement, Variation des Pulsdruckes (PPV), CNAP, nicht invasiver Blutdruck, intensiv-medizinische Überwachung

To my parents, Herbert and Gabriele Schmid for their support
and encouragement throughout my studies.

Contents

Abbreviations

ABP – Arterial Blood Pressure

BP – Blood pressure

BIPAP – Biphasic Positive Airway Pressure

BMI – Body Mass Index

CNAP – Continuous Non-invasive Arterial Pressure

CO – Cardiac Output

ECG – Electro Cardio Graph

IBP – Invasive Blood Pressure

ICU – Intensive Care Unit

PP – Pulse Pressure

PP_{min} / PP_{max} – minimal /maximal detected Pulse Pressure

PPV – Pulse Pressure Variation

SPV – Systolic Pressure Variation

SV – Stroke Volume

SVV – Stroke Volume Variation

P_{aw} – Airway pressure

PEEP – Positive end expiratory pressure

PIP – Positive inspiratory Peak

PVI – Pleth Variability Index

1 Introduction

1.1 Motivation

The optimal management of fluid administration is a challenging task during anaesthesia and in critical care medicine. In both settings the patient's hemodynamic status as well as the fluid status is of great importance to the physician. The main goals of fluid management are to obtain sufficient tissue oxygenation, blood pressure and intravascular fluid volume [1-12]. In the hope of improving patients' outcome (e.g. reducing mortality, complications and length of stay in the hospital), fluid optimization during surgery as well as in the intensive care unit (ICU) has been a major topic in the past decade [2], [13-32]. Currently, several hemodynamic monitoring devices operating with fluid parameters are available on the market to guide volume optimization.

These parameters are often calculated from the patient's invasive arterial blood pressure (BP) signal. Therefore they require an invasive arterial catheter, which is accompanied with the risk of complications during the measurement. Regardless of these drawbacks, these invasive parameters from the BP-signal were evaluated to be beneficial for fluid management and patient's outcome. Consequently it would be conceivable to deliver these parameters also in a non-invasive way. The benefit of non-invasiveness would offer the possibility that these parameters could also be employed for patients in minor surgeries where a placement of an arterial catheter would be inappropriate.

The CNAP-Monitor (Continuous non-invasive arterial blood pressure) offers now the possibility of conceiving the arterial BP-signal non-invasively and continuously and could be utilized for the calculation of further dynamic fluid parameters. In 2006, Solus-Biguenet et al. [33] showed that Pulse Pressure Variation (PPV - chapter 1.3.1) can be reliably derived

manually from a non-invasive blood pressure waveform. Up to now, the variations of arterial pressure due to respiratory variation have not been studied with the CNAP-Monitor. Thus, an additional hemodynamic parameter called PPV is proposed to be added to the software of the CNAP-Monitor.

1.2 CNAP - Monitor technology

The technology evaluated in this study is the CNAP 500 patient monitor, developed by the medical device manufacturer CNSystems Medizintechnik AG, Graz, Austria (Figure 1.1). The monitor system performs **c**ontinuous **n**on-invasive **a**rterial blood **p**ressure (CNAP-technology) measurements and is used for BP-monitoring in the operating theatre as well as in the intensive care unit. A finger cuff encompassing two neighbouring fingers is used for continuous blood pressure monitoring. An upper-arm cuff derives the measurement of oscillometric blood pressure and serves for calibration of the device. Principally, the arterial pressure in the finger-cuff is measured on the basis of the volume clamp method described by Peñáz 1973 [34] and further improved by Fortin et al. 2006 [35].

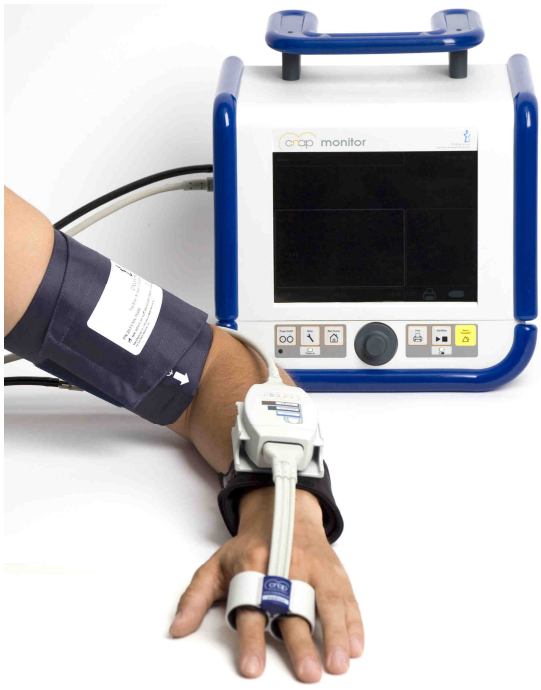


Figure 1.1: CNAP – Monitor: This picture shows the use of the non-invasive BP-monitoring technique. (©CNSystems Medizintechnik AG, Graz)

The goal thereby is to keep the volume of the arteria in the encircling finger-cuff constant, despite the fact that normally the diameter of the arteria changes with different arterial pressures with every heart beat. Briefly, the blood volume in a finger should be kept constant over time. An infrared photoplethysmograph which is placed in the inner part of the finger cuff detects changes in arterial diameter. The resulting volume signal controls the counter pressure in the finger cuff. In the situation where the volume signal is constant, the finger-cuff pressure equals the arterial pressure. This means that the vascular wall is unloaded and the volume of the artery is clamped to constant diameter. This procedure is established by utilizing an external pressure to the finger cuff which is proportional to the intra-arterial pressure of the finger artery. Now, the applied external pressure complies with the continuous arterial BP. In the CNAP-Monitor, non-invasive BP is measured by an improved model of the original vascular unloading principle. Several concentrically interlocking control loops are used to adapt the BP measurement system to fast and long-term adjustments and for this reason improve the stability and accuracy of the non-invasive BP measurement (Fortin et al. 2006 [35]). These control loops eliminate the effect of vascular tone changes on the BP. The blood flow oscillations in the finger, caused by each heart beat, are sensed and then recorded as accurate beat-to-beat arterial BP waveforms. As shown by Jeleazcov et al. 2010, [36] and Biais et al. 2010, [37] the CNAP-Monitor provides beat-to-beat BP values which are comparable to the invasive mean arterial blood pressure.

1.3 Hemodynamic parameters for fluid management

The following hemodynamic parameters have been discussed in the literature in the last years and were implemented by several medical device manufacturers. It has to be taken into account that these parameters incorporate different limitations and possibilities, but they can reduce complications and hence improve the patient's outcome [4], [12], [38].

1.3.1 Pulse Pressure Variation (PPV)

Among all existing hemodynamic indices the parameter PPV is of special interest in this report. This parameter can be calculated based on a short series of consecutive blood pressure readings. Generally, these blood pressure readings can be derived either invasively (e.g. using

an intra-arterial catheter) or non-invasively (e.g. via the CNAP-Monitor, Finapress or others). In Figure 1.2 an arterial pressure signal of an artificially ventilated patient and an airway pressure signal (resulting from the mechanical ventilator) can be observed. In presence of positive pressure ventilation (in mechanically ventilated patients) the respiratory changes in the arterial BP are reflected in the following way: During the inspiratory period the arterial pulse pressure (PP) reaches a maximum (PP_{max}).

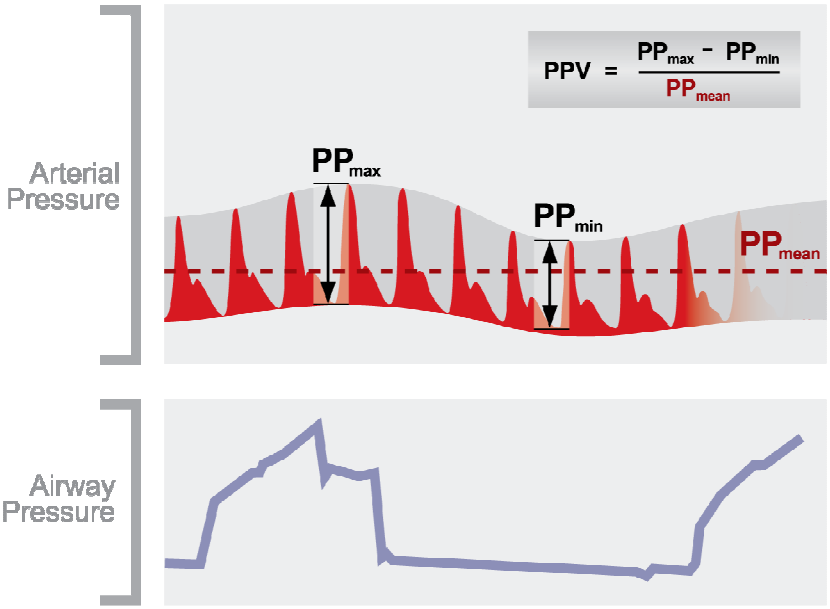


Figure 1.2: Schematic principle for calculating Pulse Pressure Variation. Pulse pressure (PP) is defined as the difference between systole and diastole.

A few heart beats later a minimum during expiration can be observed (PP_{min}). In spontaneous breathing patients without positive pressure ventilation, the phase of the PPV signal shifts by 180° degrees. PPV can be seen as the relative variation of the pulse pressure with respect to the base pulse pressure and is represented as a percentage value during one mechanical breath. Consequently, every minimum (PP_{min}) and maximum (PP_{max}) in pulse pressure can be determined and used for further calculation of the PPV according to equation 1:

$$PPV[\%] = 100 \times \frac{\left(PP_{max} - PP_{min}\right)}{\left[PP_{max} + PP_{min}\right]/2} \quad (1)$$

The upper blood pressure curve in Figure 1.2 reflects the changes due to respiratory variations of the airway pressure curve. One respiratory cycle started with the inspiration and lasted until

the expiration period was completed (flat part of blue curve in Figure 1.2). In 2000, Michard et al. [39] reported a manual calculation of PPV based on the invasive blood pressure waveform, considered as gold standard method for deriving PPV. Michard described the gold standard calculation as an average over 3 consecutive respiratory cycles. These respiratory cycles shouldn't be disturbed by artefacts like spontaneous breathing or external signal perturbations (For the implementation of the PPV gold standard method see chapter 2.4).

In 2004, Aboy et al. [40] presented an algorithm to automatically and continuously estimate PPV from the intra-arterial signal alone, eliminating the need for simultaneously acquiring airway pressure for automatically determining PP_{min} and PP_{max} . Without the use of the airway pressure signal the PP_{min} and PP_{max} search is more challenging, since the use of the airway signal facilitates the definition of the minima and maxima in the PP-signal. Alternatives like envelope estimation or Kernel-smoothing had therefore to be considered. This automated PPV derivation was integrated into the Intellivue monitor MP70 (Philips Medical Systems, Best, The Netherlands) and was based on the invasive BP wave-form [41], [42]. In 2006, Austin et al. [43] presented another PPV algorithm using a non-linear technique for envelope estimation, eliminating the need for automatic beat detection. In 2009, Aboy et al. [44] described an improved automatic algorithm to estimate PPV from the arterial blood pressure signal which allowed for PPV estimation during periods of abrupt hemodynamic changes. So far, no non-invasive method for the automated calculation of PPV has been described and all automatic PPV algorithms have only been relaying on the invasive BP-signal.

1.3.2 Other dynamic parameters

Stroke Volume Variation (SVV)

SVV as another dynamic parameter derived from the arterial BP curve can assist in the process of fluid management. Hereby SVV is computed analogously to PPV, whereas the ratio of the difference between the maximum and minimum Stroke Volume (SV) during one respiratory cycle and the mean SV is calculated. SV is frequently obtained by pulse contour analysis on the invasive arterial BP signal. This parameter has also been shown to predict fluid responsiveness during surgery and other settings [45-47].

However, Marik et al. 2009 [48] outlines in a systematic literature review that the accuracy of PPV (and also the Area under curve of the Receiver Operating Characteristics curve) is better than for SVV. One reason for the relative inaccuracy of SVV could be that the SV calculation is based on partially invalid assumptions. Also Donati et al. [49] reported that SVV is not as reliable as PPV for the appraisement of fluid responsiveness in ICU patients.

Systolic Pressure Variation (SPV)

Likewise to PPV, SPV is the mean difference between the maximal (inspiration) and minimal (expiration) systolic blood pressure. Again these values are calculated over several consecutive mechanical breaths. SPV has been proposed to be affected by ventilation settings (airway pressure [50], tidal volume [51] and inspiratory pressure [52]). SPV has a lower predictive value for fluid responsiveness than PPV.

Other indices for optimized fluid management are mentioned in literature: They include indices of the plethysmographic signal (e.g. Pleth Variability Index) and cardiac output measurements.

1.4 Fluid management & hemodynamic optimization

During the last years, several studies demonstrated that optimized fluid administration can significantly improve the outcome of the patient [17],[21],[29],[53],[19]. Shields et al. [2] suggested that the goal of perioperative fluid administration is to maintain adequate intravascular volume. Optimized fluid management also improves the delivery of oxygen and coagulation factors. Rosenthal et al. reported [10], that the intraoperative and postoperative morbidity and mortality risk is minimized with the application of an optimal fluid administration. Also Vincent et al. emphasizes the need of fluid management: Especially critically ill patients or patients with a lot of fluid loss during surgery will need volume expansion at a certain point [1]. Monnet et al. [3] points out that especially in patients with hemodynamic instability, predicting volume responsiveness (i.e. whether or not the patient

reacts with significantly increased cardiac output to fluid administration) is an important issue since fluid overload is accompanied by the risk of pulmonary oedema formation.

From this point of view fluid management is a balancing act between hypervolaemia and hypovolaemia. The relation between fluid administration and the morbidity risk can be observed in Figure 1.3. The graphic shows clearly that an inadequate use of fluid can have deleterious effects on patient's outcome.

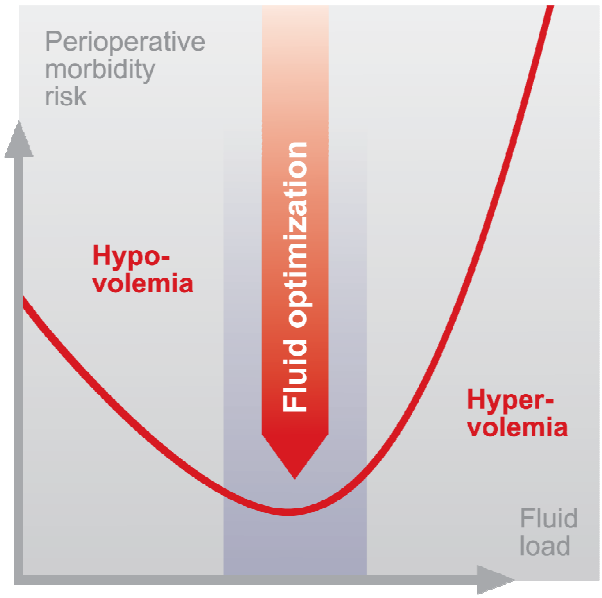


Figure 1.3: The graph indicates the interdependency between fluid administration and the morbidity risk. Importantly, fluid can be given too much but also too little - both resulting in a negative outcome. The global minimum in the red risk curve states the optimum for an adequate fluid management. (Redesigned from [54])

In the attempt of predicting fluid responsiveness several studies have repeatedly demonstrated that static preload markers, like pulmonary artery occlusion pressure or central venous pressure, are not as good as dynamic indicators like PPV or SVV [3],[6]. The use of dynamic hemodynamic parameters on the basis of heart-lung interactions was shown most appropriate for predicting fluid responsiveness [4],[55].

Dynamic parameters based on respiratory variations, particularly PPV, SVV and Systolic Pressure Variation [56], are the most widely studied and validated [3],[48],[57]. Different results were reported for the accuracy of SVV for predicting fluid responsiveness [9]. Highest accuracy for predicting fluid responsiveness was stated for the parameter PPV which is therefore studied in this work.

1.5 Physiological background for PPV

Michard et al. 2005 [58] mentioned that "PPV is not an indicator of volume status, nor a marker of cardiac preload, but it is an indicator of the position on the Frank-Starling curve". The Frank-Starling relationship describes the change in stroke volume (SV) resulting from changes in cardiac preload [58]. Fluid administration with the use of dynamic indicators (PPV, SVV) is based on this relationship (Figure 1.4).

Concisely, a small PPV indicates that the patient's heart is operating on the saturated part of the Frank-Starling slope. In the flat part of the slope the patient has enough preload and fluid in the heart and as a consequence isn't sensitive to the cyclic changes in preload produced by mechanical ventilation. This means that the patient is "non-responsive" to fluid.

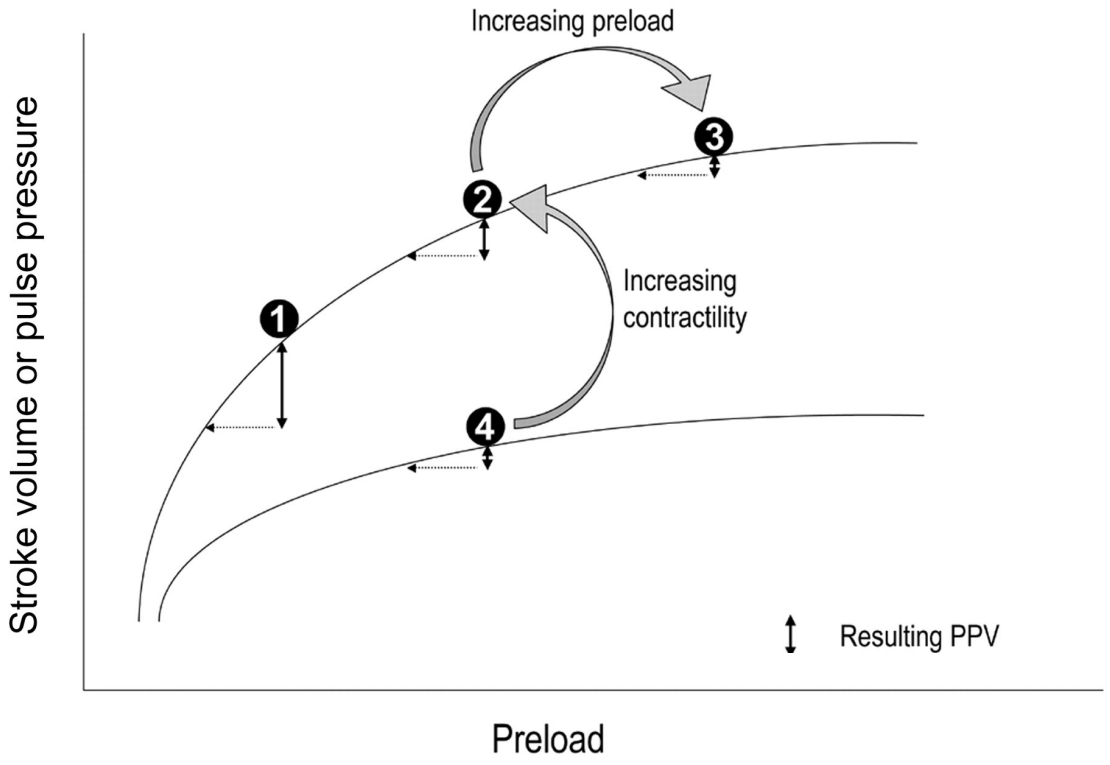


Figure 1.4: PPV and SVV are markers of the position on the Frank–Starling curve. When a patient's preload is increased the PPV is decreased (as seen in the vertical arrow from 2 to 3). When the patient's heart is working on the flat part of the Frank-Starling curve the PPV value is low (3 and 4). The opposite happens, when preload is decreased which results in a high PPV (from 2 to 1), © Michard and colleagues.

Contrary, if the PPV is high the patient's heart is operating on the ascending branch of the Frank-Starling curve. As a consequence a high variation in SV and thus a high variation in pulse pressure are observed, which indicates insufficient preload. The patient's heart is not filled adequately and therefore is sensitive to cyclic changes in preload when mechanically

ventilated. The patient is not enough "filled" and would need fluid. In this case the patient would respond to fluid administration with a significant increase of cardiac output – the patient is called "fluid-responsive".

If the patient is sufficiently provided with fluid and the left ventricle is operating in the saturated region of the frank-starling curve, further fluid loading will affect the patient adversely; e.g. this could cause the development of pulmonary oedema.

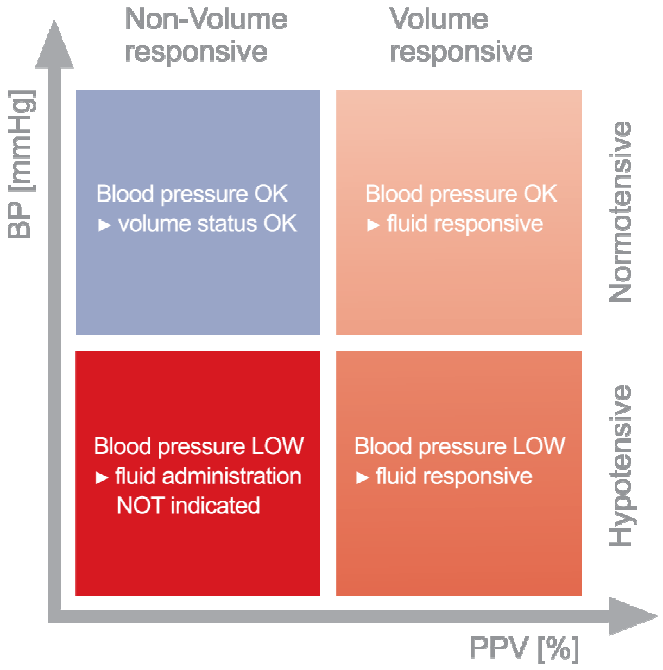


Figure 1.5: Different hemodynamic states of a patient which result in different treatment according to, whether patient has low or high blood pressure or if the patient is responsive to volume or non-responsive.

Hence, for the guidance of fluid management there is a certain threshold of PPV to differentiate between responders and non-responders (Cannesson 2007 reported a threshold between 10-13% [59]). Such a differentiation can now be used for the concept of fluid management. In Figure 1.5 the relationship between blood pressure and PPV is illustrated. A threshold value for BP as well as for PPV is used to distinguish between different hemodynamic states and categorizes patients into four quadrants. Different hemodynamic states of a patient will require different treatments. Judging the patient's hemodynamic state only by a single parameter (BP or PPV) is insufficient. Considering only a patient's BP would not tell the physician anything about the fluid state of the patient. Whether the patient has low or high blood pressure and if the patient is responsive to volume or non-responsive has to be

handled differently. The objective is to keep the mean arterial pressure above approximately 65-70 mmHg and the PPV below the threshold for fluid responsiveness (e.g. 12%). When PPV is higher, fluid should be given (right quadrants). If BP is low but PPV is high, the patient has an unstable BP and is in need of fluid. The use of fluid at a low PPV and low BP is inappropriate as seen in Figure 1.5.

1.6 Pre-conditions for the use of PPV

Maguire et al. [63] summarized the most important limitations for the application of PPV and related dynamic variables. These limitations influence the interpretation of PPV - i.e. they have an impact on the threshold for discriminating between fluid responders and non-responders.

1.6.1 Cardiac arrhythmias

Arrhythmias have a great influence on the modulated arterial signal and hence on the resulting PPV values. Arrhythmias can change the beat-to-beat left ventricular stroke volume and limit the validity of PPV analysis for predicting preload responsiveness [64]. Therefore it is not advisable to use PPV from data sequences containing arrhythmias.

1.6.2 Spontaneous breathing

Another important pre-requisite for the application of PPV is that the patient is mechanically ventilated (positive pressure ventilation). Without controlled mechanical ventilation the variation of the arterial BP induced by ventilation can't be seen and PPV doesn't provide useful data. Several studies have been shown that spontaneous respiration influences the changes in the arterial waveform adversely and PPV is not useful for accurately predicting fluid responsiveness [64],[65].

1.6.3 Mechanical ventilation settings

Tidal volume: The greater the tidal volume, the greater are the cycle-specific changes in venous return, thus augmenting PPV or SVV at the same volume status [66]. Increased tidal volumes lead to progressively greater decreases in left ventricular stroke volume [64]. There is a consensus that PPV is a reliable predictor of fluid responsiveness only if the tidal volume is greater than or equal to 7 ml/kg ideal body weight [67]. Otherwise the modulation of the BP-signal is too small for providing reliable results.

Positive end expiratory pressure (PEEP): PEEP is defined as the lowest pressure at the end of the expiratory cycle during mechanical ventilation. Since the main consequence of PEEP is to widen the lungs and increase intrathoracic pressure, it normally reduces venous return and creates a functional hypovolemic state [66]. Biais et al. [68] reported that SVV and PPV increased significantly with PEEP raised from 0 to 10 cm H_2O.

Respiratory rate: De Backer et al. 2009 [69] showed that SVV and PPV are affected by respiratory rate (study with 14-16 breaths/min baseline, versus 30 and 40 breaths/min): at high respiratory rates, the predictive value of SVV and PPV may be limited.

1.6.4 Closed chest condition

Opening the chest causes a decrease of the airway pressure and therefore increases venous return [70]. These effects cause a relative increase in cardiac preload. While the dynamic parameters PPV and SVV showed good correlation with increases in cardiac output under closed chest conditions, this correlation was lost once the sternum was opened [71],[72]. Thus the use of these parameters as predictors for fluid responsiveness is inappropriate under open chest conditions and their use should not be recommended during cardiac and thoracic surgery.

Additional factors that may influence the use of PPV are not clearly investigated: One-lung ventilation [73], Intra abdominal hypertension (IAH) [74], Patient's cardiac status [61], Acute respiratory distress syndrome (ARDS), ratio between respiratory rate and heart rate, norepinephrine dosage [60] and changes in the patient's cardiac performance [61], [62].

1.7 Objectives of this work

The main goal of this study was the evaluation of a new PPV algorithm in the non-invasive CNAP-monitor for an improved fluid management. The performance of this PPV algorithm was assessed on real life blood pressure recordings from patients in the ICU without the need for recording the airway pressure signal simultaneously. BP was obtained with the CNAP-Monitor and with an invasive arterial catheter, as the gold standard for BP-measurement. The new automatical CNSytems-PPV algorithm was compared to the manual calculation of PPV, which is defined as the gold standard of PPV in literature (Michard et al. 2000 [75]). A new method for calculating the gold standard PPV was proposed in this work.

One aim of the clinical study was to investigate if the non-invasive signal is equivalent to the invasive signal for the calculation of PPV. Secondly, the ability of the new PPV algorithm to perform adequately on the invasive- and non-invasive BP signal had to be evaluated. Another goal was to compare automatically PPV ($CNAP_{\_PPV\_CNSystems}$) and manually calculated PPV ($CNAP_{\_PPV\_Gold}$) from the CNAP-signal.

2 Methods

2.1 Outline

As explained in the introduction, the arterial BP-signal can be used to derive further dynamic parameters like Pulse Pressure Variation. The determination of beat-to-beat blood pressure is considered as input signal for the PPV-algorithm. Therefore the first part of the clinical study was the acquisition of continuous beat-to-beat blood pressure signals. Thereby, continuous blood pressure was measured synchronously with two different measurement devices. BP was recorded invasively with an arterial catheter as well as non-invasively with the CNAP-Monitor. Additional hemodynamic vital parameters were monitored. After all patient data had been obtained, a detailed analysis of the new automatical PPV algorithm followed retrospectively.

The methodic part consists of these subparts:

- Acquisition of BP-signals in the university hospital Graz
- Evaluation of the continuous non-invasive arterial blood pressure measurement (CNAP) and comparison with the invasive arterial BP
- Patient selection for the evaluation of the PPV algorithm
- Design and programming of the gold standard PPV algorithm
- Statistical analysis of the accuracy of the non-invasive PPV-method

2.2 Clinical study design

2.2.1 Conduction of the clinical study

The clinical study was started in October 2009 in cooperation with the internal medicine ICU at the university hospital of Graz and ended in September 2010. All clinical data was retrieved in the context of the study referred to as "Accuracy of continuous non-invasive arterial pressure monitor in critically ill patients". The main purpose of this prospective study was the comparison of the CNAP BP-device with the gold standard, the invasive arterial blood pressure measurement (IBP) in critically ill patients.

This prospective study was performed on 62 critically ill patients in the Medical ICU, given informed consent of patients or legal agents, whereas 13 patients were excluded from the evaluation due to technical limitations. All patients were sedated and mechanically ventilated. Furthermore, all patients were under vasopressor therapy. CNAP was applied on two fingers of the hand contra laterally to the invasive arterial blood pressure catheter in the Arteria radialis. A detailed measuring procedure is described in chapter 2.2.3 (page: 26). Average recording time on each patient was 163 minutes (+/- 37 minutes/patient). A shortened version of the Clinical Study Protocol can be observed in the Appendix. The inclusion and exclusion criteria for the BP study were as follows:

Inclusion criteria:

- Critically ill patients in the ICU which require arterial catheter BP monitoring by clinical standards
- Intact perfusion of both hands evidenced by a positive Allen's test
- Age >18
- Weight > 40 and < 180 kg, Body Mass Index (BMI) < 35

Exclusion criteria:

- Subjects with a BMI > 35, weight < 40 or > 180 kg
- Subjects with excessive movements (e.g. amyostasia)
- Subjects not passing the Allen's test for both hands
- Subjects with pronounced disturbance of peripheral blood circulation

- Subjects with vascular implants at the sites of non-invasive blood pressure measurement (fingers and upper arm of the arm where Arterial-BP is measured)
- Subjects where the BP catheter could not be placed in the Arteria radialis

The results of this blood pressure measurement study were statistically evaluated by Smolle & Schmid 2011 [76] (Abstracts in chapter 7.2).

After study approval by the ethics committee of the university hospital in Graz all the measurements started. Before starting the measurements, the clinical state of the patient was discussed with the responsible doctor. A patient file was set up to enter all necessary clinical and technical parameters. Only when the need of an arterial BP measurement was indicated, being compliant with ethical guidelines of the hospital, the patient was considered as a potential candidate. Since a poor perfusion of the fingers directly could lead to difficulties with the CNAP-monitor, also a perfusion test was performed. In this record for example, the intact perfusion of both hands had to be stated, which has been tested by a positive Allen's test[1] before starting the measurements. Also patient's individual weight, age and sex were documented. For study purposes each patient received an ascending patient ID for the ease of patient management and also for anonymisation of all patient data. Starting time of measurement was noted as well.

2.2.2 Selection of the patient collective for PPV evaluation

For the retrospective evaluation of the new PPV algorithm only patients were selected from the study database (n=62) which met all criteria for a valid PPV measurement as described in the introduction chapter (1.6). Since the clinical blood pressure study was not specifically designed for the PPV-evaluation, this sorting out procedure was essential for further data processing.

[1] Allen's test: Used for testing the blood supply to the hand. In normal anatomical and physiological function the hand is supplied with blood (perfusion) through the ulnar and radial arteria. The idea here is to figure out if the ulnar artery will supply the hand with enough blood, if the radial artery is blocked with an arterial line.

The process of selecting the patients for PPV evaluation due to individual limiting criteria is graphically presented in a flow chart in Figure 2.1 on the following page.

After carrying out the clinical study in the hospital, the next part of this thesis was therefore finding the limiting factors mentioned in the literature for PPV in general and their possible impact on the evaluation. The presence of general anaesthesia and mechanical ventilation was met by all patients. Since PPV relies heavily on various ventilation-parameters potential limitations derived from the mechanical ventilator settings have to be considered. For example, the acquisition of all ventilations signals was not possible for all patients in this study [requirements stated by Maguire et al. 2011, [77]]. This led to a reduction by 16 patients because the ventilation parameters could not be obtained from the ventilator machine. Quite a lot of patients dropped out from the study database due to this selection process. As mentioned before, spontaneous breathing activity during mechanical ventilation was also not allowed and resulted in an exclusion of 7 patients from the study. Furthermore a tidal volume of 7-8 mL/kg of ideal body weight (IBW) was suggested in several publications (Cannesson et al. 2010 [78], Ballmoos et al.2010 [79], Michard et al. 2000 [75]). This requirement led to a reduction by another 7 patients. For the application of PPV also an undisturbed sinus rhythm is necessary. Arrhythmias had been checked in the patient record as well as in the BP-signal and led to a reduction by further 10 patients. A negative influence of a too small or too high positive end expiratory pressure (PEEP) has not been completely confirmed in literature and was therefore not considered.

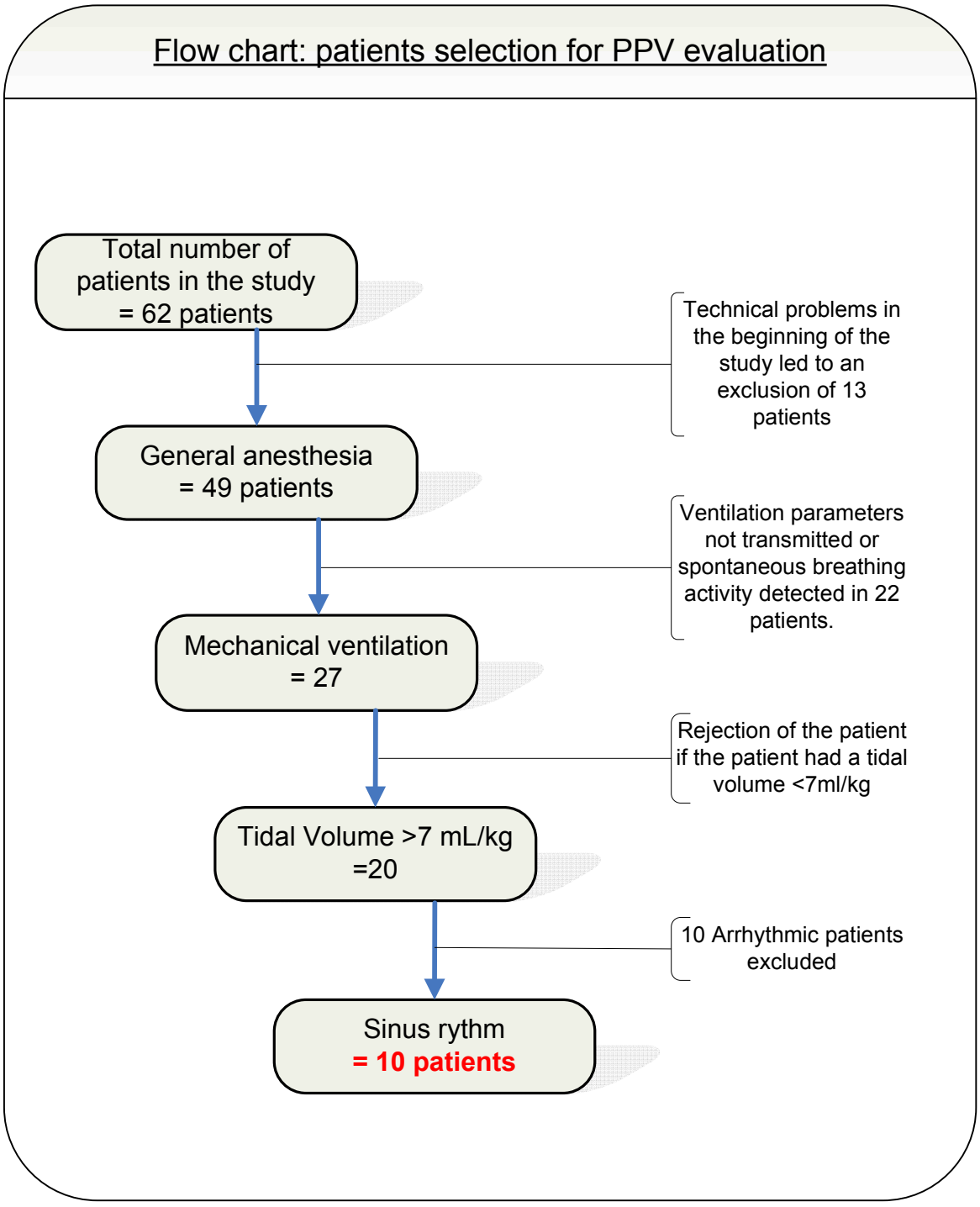


Figure 2.1: Flow chart for the successive exclusion of patient records due to a lack of applicability of PPV analysis [modified from Maguire et al., 2011)]

Finally 10 patients remained for the retrospective PPV evaluation. This final patient collective consisted of most critically ill patients suffering from accompanying diseases like pneumonia, septic shock, intoxication, cerebral infarction or cardiac shock (all selected patients are listed in Table 2.1 below).

Patient ID #	Cause of Intervention	Age (yr)	Tidal volume (ml/kg)	PEEP (cm H_2O)
15	Intoxication	45	7.77	8
16	Septic, ischemic cardio-myopathy	49	7.2	11
35	Meningococcal meningitis	71	11	13
49	Pneumonia, acute myeloid leukaemia	54	7.1	9
50	Pneumonia	41	6.9	10.5
54	Intoxication	22	6.95	10
55	Acute myocardial infarction	71	9.5	10
57	Intoxication	38	7.8	7
61	Pneumonia	34	7.5	13
62	Intoxication	19	8.1	6

Table 2.1: Important characteristics of selected patients for the evaluation of the new PPV algorithm

2.2.3 Monitoring equipment in the ICU

The equipment required for this study consisted mainly of various hemodynamic monitoring devices. All these monitoring devices, which are essential parts in every Intensive Care Unit, had to be connected to the hospital network for data retrieval.

Invasive Blood Pressure Monitoring:

Blood Pressure measurements were taken with an invasive arterial catheter and also with the CNAP-Monitor. The invasive catheter (product picture seen on the right in Figure 2.2), which had been firmly fixed by a medical professional in the Arteria radialis before the BP-measurement procedure, was therefore connected to a Flotrac® BP-pressure transducer (FloTrac®-Sensor, Edwards Lifesciences, Irvine, CA, USA) as seen on the left in Figure 2.2.

The invasive signal from the Vigileo Flotrac® sensor was then connected to the Dräger Infinity® Delta monitor where the measurements were recorded.

Figure 2.2: Left picture: Vigileo Flotrac® IBP pressure transducer: This transducer provided the arterial pressure measured via the arterial catheter. (©Edwards Lifesciences, www.edwards.com)

Right picture: catheter used for BP-measurements (Type: Arteria Cannula, 20G, Becton Dickinson Critical Care Systems Pte Ltd)

To avoid air bubbles or clot formation which would disturb the dynamic response of the resonance system of the fluid filled catheter, the valve of the device was pulled one or 2 times. This so-called “fast-flush test” had to be done in the beginning of every measurement and after repositioning of the patient, as stated for example in [80] and [58]. A BP-change after the flush-test procedure can be viewed on the patient monitor and also retrospectively in the saved BP-signal as seen in Figure 2.3. In the recorded IBP-signal, the returning to a normal cyclic beat-to-beat BP-signal can be seen in Figure 2.3 after a short under-shoot and overshoot of the blood pressure signal. After flushing the catheter, zeroing of the signal on the patient monitor

was done. Therefore the valve of the Flotrac sensor (Figure 2.2) was closed and the connected patient monitor was set to zero, to retrieve correct measurements. Then the valve was opened again.

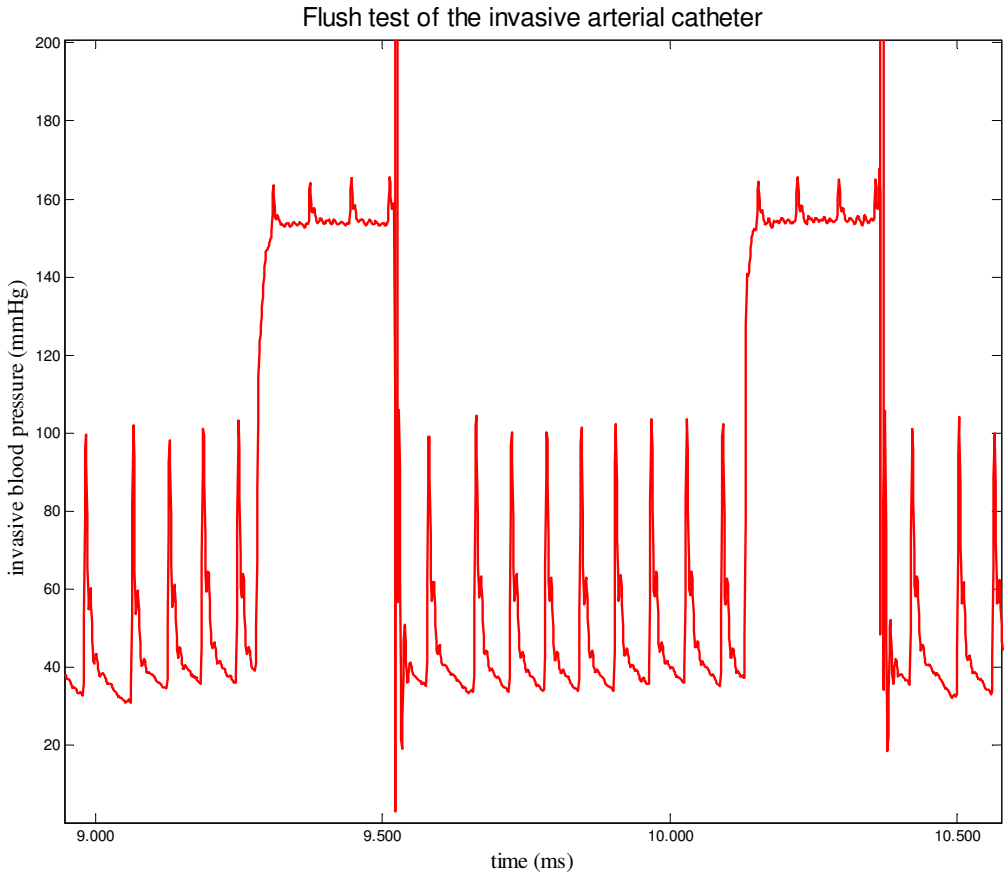


Figure 2.3: Detail of a BP-signal with two consecutive Flush-Tests for retrieving correct arterial BP measurements. Possible disturbances in the BP-signal, formed by clot formation or air bubbles, are minimized by this procedure.

Non-invasive BP Monitoring (CNAP)

In a second step the CNAP-Monitor was connected to the patient. For this study the software version 3.5 of the CNAP-Monitor was used. The CNAP finger cuff was placed contra laterally with respect to the catheterized arm to avoid disturbances in the BP-signal. After selection of the right size of the finger cuff (Small, Medium, Large) the cuff controller was mounted on the patient's forearm and all the corresponding cables were connected to the CNAP-monitor. The upper arm cuff for the calibration of the CNAP-signal was installed on the ipsi-lateral side of the CNAP finger cuff, preferably at heart level.

The CNAP-Monitor has to be zeroed before data recording can be started otherwise the BP-offset would lead to wrong results. A detailed description of a correct measurement procedure can be found in the manual offered by the manufacturer.

Figure 2.4: Dräger Infinity Delta Monitor

This patient monitor was utilized for receiving and viewing all signals in the ICU. Continuous hemodynamic parameters were recorded by software over the Infinity Network. (©Dräger Medical, Lübeck)

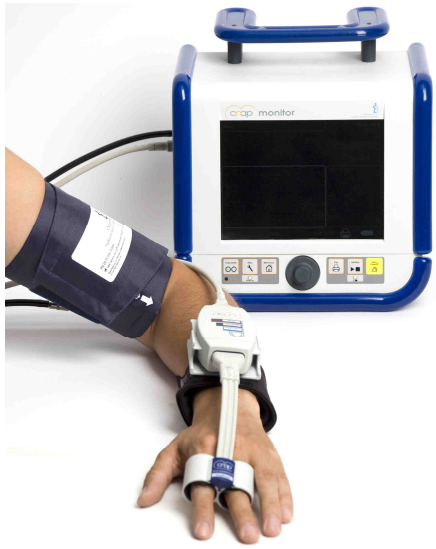


Figure 2.5: CNAP – Monitor: This picture shows the use of the non-invasive BP-monitoring technique, whereas BP was received over the output (BP-out) of the monitor. (©CNSystems Medizintechnik AG, Graz)

The CNAP-signal was retrieved from the BP-wave out of the CNAP-monitor via the connection cable to the Dräger Infinity Monitor (Figure 2.4). To monitor both BP-signals (invasive & non-invasive) synchronously a Y-cable (Y-Adapter, 16 Pins to 10 Pins) was connected to the Dräger Infinity Delta patient monitor. On one input side of the Y-cable the BP-signal from the invasive FloTrac pressure transducer was mounted, on the second one the non-invasive BP-signal from the CNAP Monitor. For a detailed description of the blood pressure monitoring consider the Clinical Study Protocol (Appendix).

Mechanical ventilation parameters:

One of the key elements when determining PPV is the observation of several respiratory parameters. As stated before, respiratory variations modulate the blood pressure signal. Monitoring the respiratory system is therefore of great importance to check if all parameters meet their requirements. The mechanical ventilator Evita XL (Dräger Medical, Lübeck, Germany) was connected to the Infinity Network and transmitted respiratory signals over the supported Medical Information Bus (MIB). All ventilation parameters were transmitted to the Dräger Infinity Network and could be collected by data acquisition software. After

discovering that not all patient beds had been installed properly, this issue had to be addressed in this study. Especially, a careful look on the Dräger Medical Information Bus (MIB) is advised, to guarantee an information-exchange between the network and the ventilation machine. For this reason, the first patients without recordings of the ventilation parameters could not be included in this study.

Additional monitoring:

ECG-monitoring, SpO_2 monitoring over a finger sensor, temperature- and pulse monitoring was realized during measurement. All monitored parameters were displayed continuously or intermittently on the Dräger Infinity Delta Monitor at every bedside. Most hemodynamic parameters are displayed on the screen continuously to help the nursing staff and the doctors for making the right decisions. The relevant parameters were transmitted over the Infinity Network (Figure 2.6) so that a recording of signals from another computer was possible.

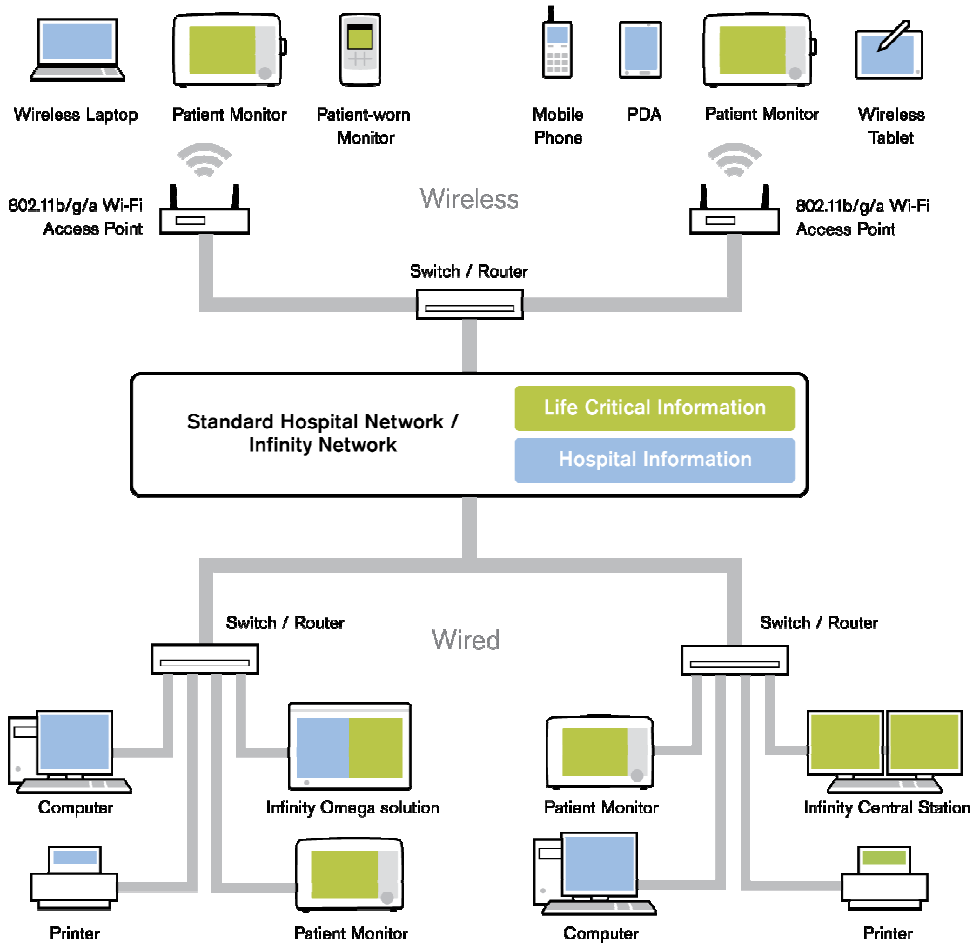


Figure 2.6: Schematic overview of the Infinity Network used for data hemodynamic data recording in the hospital. All hemodynamic data was collected with the Infinity Delta Monitor at the bedside and transmitted to one main computer for recording. (©Dräger Medical, www.draeger.com)

2.3 Data Recording

2.3.1 Bio signals recorded during this clinical study

Taking into account that the PPV-algorithm is showing the small difference between pulse pressures of consecutive beats, a very accurate, time-resolved determination of the blood pressure signals is important. Both blood pressure signals (invasive & non-invasive) were therefore recorded with a sample frequency of 100Hz. Furthermore the respiratory information (airway pressure signal as seen in Figure 2.7) from the mechanical ventilation machine supported to determine the gold standard PPV. The airway pressure signal (P_{aw}) was acquired synchronously from the Dräger Evita XL ventilator and facilitates the determination of the minima or maxima in the pulse pressure curve. Recording of the respiratory signal (P_{aw}) was only possible with a sample frequency of 50Hz and had to be up sampled subsequently.

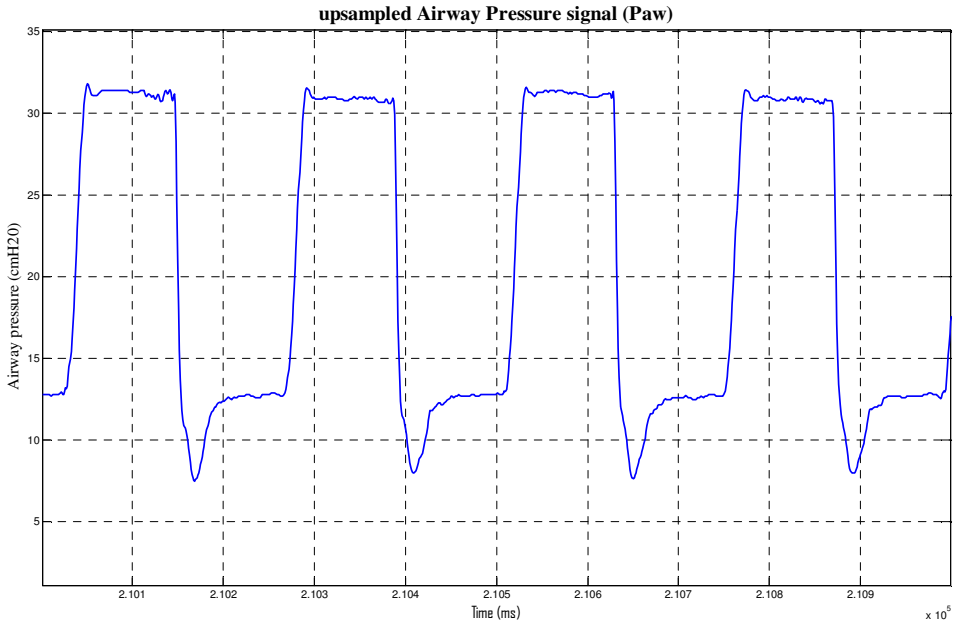


Figure 2.7: Airway pressure signal: Inspiratory and expiratory periods of the signal

The medical data recording software used for this purpose was provided by Dräger Medical and is called Datagrabber. The software accesses to the Dräger Infinity Network and can be used for beat-to-beat data collection. The Datagrabber collects pre-selected signals from a

patient's hemodynamic status over the network. After that the hemodynamic signals were read into Matlab and the CNAP- and IBP-signals were synchronized.

All blood pressure signals were checked visually if the zeroing-process of the IBP and CNAP had been done correctly. If the BP-signal was erroneously zeroed, a manual correction with Matlab was done retrospectively. An uncorrected BP-signal can be seen in Figure 2.8, where a negative BP of about 10mmHg was detected and in a following step corrected. The negative or positive difference to zero during calibration-phase had to be added to the whole BP-signal vector, while taking care of the right data type in Matlab (uint16 or int16).

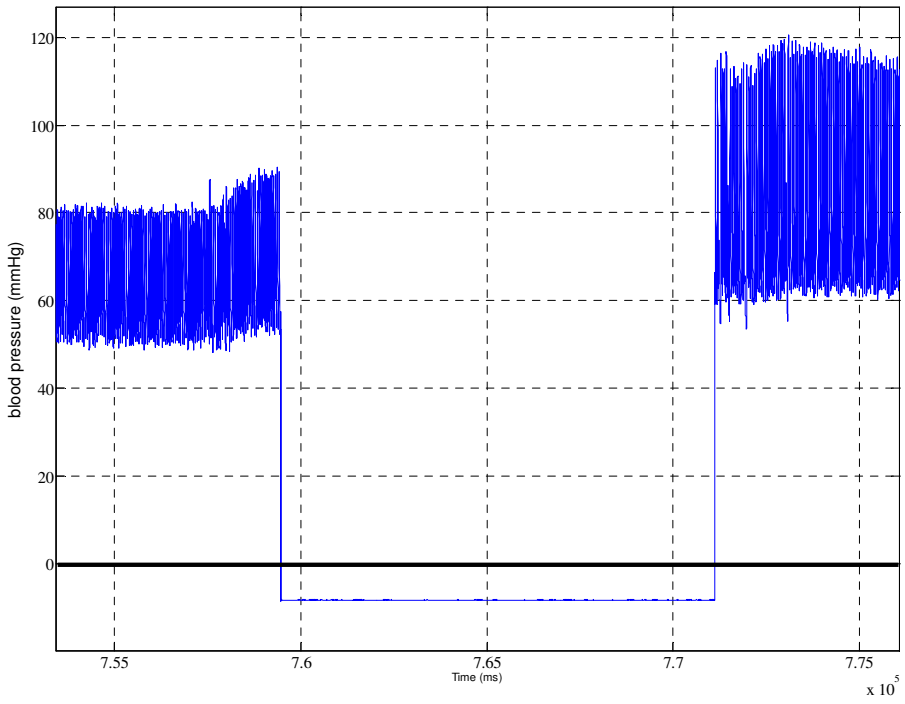


Figure 2.8: Uncorrected- zeroing of a BP-signal. During the calibration period of the CNAP-Monitor the BP-signal normally should rest at zero. In this patient the zeroing of the CNAP-Monitor was not done correctly which results in a negative value of the CNAP-signal during the calibration phase. The negative offset was corrected manually retrospectively.

Considering all the other signals, a lower time resolution is accepted. Further respiratory parameters were only recorded once a second to retrieve information about the respiratory settings of the ventilator (patient's tidal volume, PEEP, respiratory rate, spontaneous breathing activity). The data was also not synchronized to the beat-to-beat BP-signals.

2.3.2 Import of relevant signals into Matlab

After exporting the bio signals into a DAT-format a conversion into one single ASC-File followed. Furthermore, in this pre-processing step the signal of the airway pressure (P_{aw}) was up sampled from 50Hz to a frequency of 100Hz, corresponding to the frequency of the blood pressure signals.

Concluding, synchronized beat-to-beat data from two different BP-measuring methods (IBP & CNAP) and the respiratory signal (P_{aw}) were imported into Matlab (Mathworks) for further data processing.[2] A plot of all three signals can be seen in Figure 2.9.

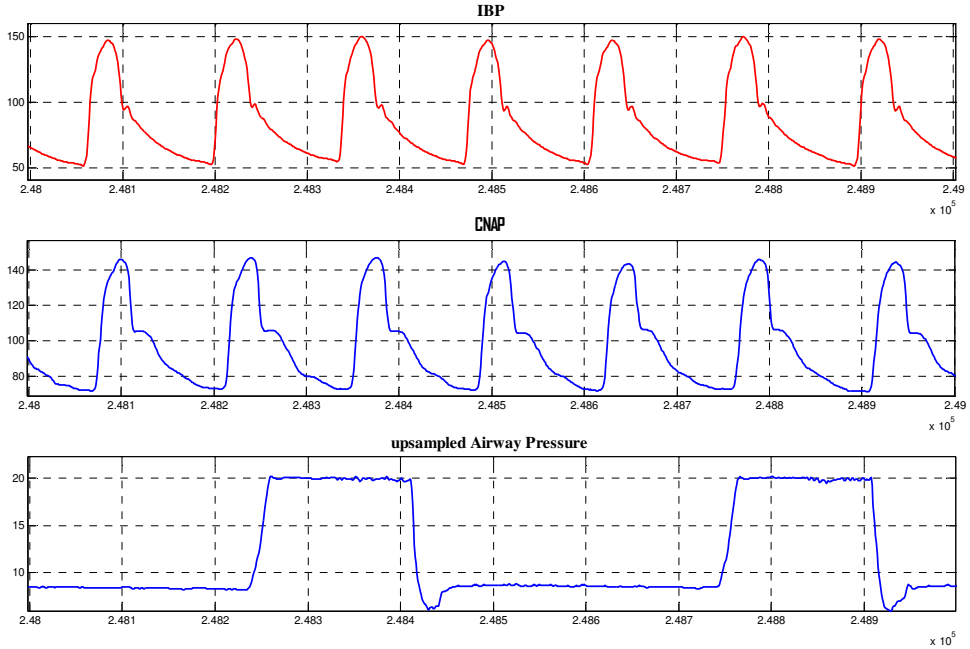


Figure 2.9: Imported signals for further data-processing. Invasive blood pressure and CNAP are displayed above the up-sampled airway pressure signal.

[2] Important Note: After consultation of the software department from Dräger, data-recording with the Datagrabber is limited to the continuous waveforms displayed on the Infinity Delta patient monitor. Signals not displayed on the monitor (beat-to-beat) can't be accessed from the software over the network. This limits the number of recorded signals to the maximum number of monitored channels (depending on the optional software licence) on the Dräger patient monitor at the bedside.

2.4 Algorithm design for gold standard PPV calculation

2.4.1 Definition of the PPV gold standard

In a first step the determination of all diastolic- and systolic-BP values in every beat is performed. Therefore the minima (diastole) and the maxima (systolic pressure) for each pulse-period have to be determined. The pulse pressure (PP) resulted as the difference of the systolic and diastolic BP-value (as indicated in Figure 2.10). In every respiratory cycle a pulse pressure minimum (PP_{min}) and a pulse pressure maximum (PP_{max}) was determined [58] [75]. The synchronously recorded airway pressure signal P_{aw} (bottom in Figure 2.10) shows the inspiratory and expiratory periods during mechanical ventilation.

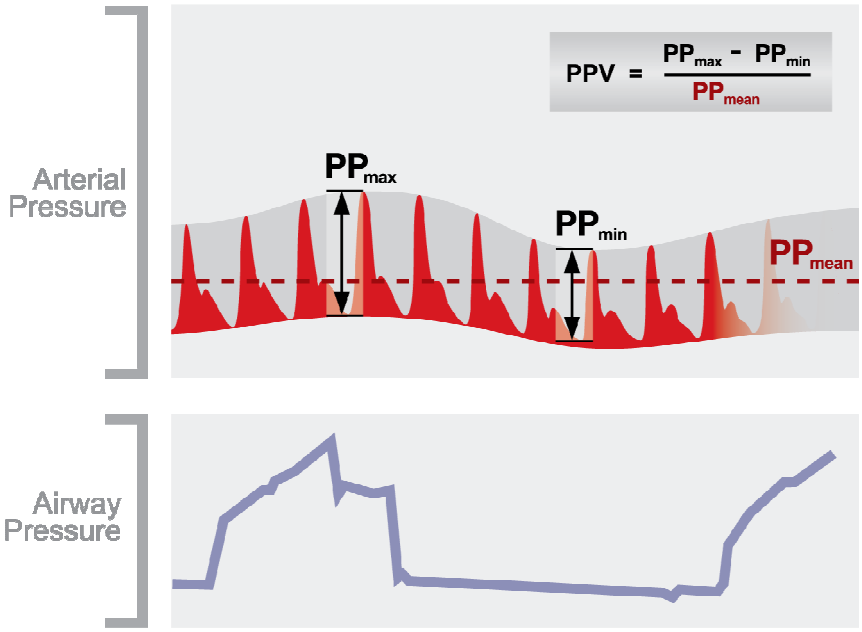


Figure 2.10: Schematic principle for calculating Pulse Pressure Variation. In mechanically ventilated patients the inspiratory maximum enforces a maximum in the pulse pressure (PP_{max}) over one respiratory cycle. After expiration a minimum in pulse pressure (PP_{min}) can be recognized and the final PPV value can be calculated.

With reference to Michard et al. 2000 [39], the PPV values of three respiratory cycles were averaged to reduce the signal variance. In a next step this final PPV-value is compared to the retrospectively obtained value from the CNSystems algorithm.

2.4.2 Different approaches of PPV gold standard calculation

One of the main questions of this work concerned the gold standard calculation of the PPV. Two different ideas for calculating the manual PPV are shortly explained and show the advancement of this work.

Idea 1: PPV calculation per paper, pencil & calculator

In the past, the PPV calculation procedure was limited by technical nature of the monitoring devices. The easiest way for a manual calculation of PPV was done per hand on printed BP-recordings. When printing out the beat-to-beat blood pressure signals, the pulse pressure from each beat can be determined and marked with pencil. The BP-curve can also be scanned and calculated in a software program, as done in the paper of Biais et al. 2011 [37]. Ideally this pulse pressure curve should be plotted over more than 3 respiratory cycles. The final PPV-value can now be calculated with the PPV-formula (equation 1) and averaged over 3 cycles. This monitor guided calculation is a fast forward method when no commercial algorithm, implemented in a monitoring device is available. This time-consuming method was not suitable for this study since a lot of data points were needed for the evaluation of the algorithm.

Idea 2: Auto detection of PP_{min} & PP_{max} for gold standard calculation

A completely automated algorithm for determining the gold standard PPV would have been another plausible possibility and has not been mentioned in literature so far. An automated way for PP_{min} and PP_{max} detection could offer the convenience for evaluating a huge amount of data points and statistically analyse them. Especially with the additional synchronously recorded respiratory signal this approach should have been technically feasible. However, the continuous respiratory signal was not available in the majority of patients and therefore the decision against an automatic method followed.

Nevertheless the verification of these automatically selected PP data points, used for the Gold-Standard PPV, would have to be checked visually again to guarantee a 100% correct evaluation without any artefacts (e.g. with an interactive user interface with correction possibility). Another difficulty would have been the (automatical) artefact detection of all sources.

As there was no validated automatic "gold standard" algorithm available, a semi-automated approach was chosen.

2.4.3 Idea 3: New PPV gold standard calculation method - Semi-automatic approach

The above mentioned methods are two different possible ways for determining the gold-standard PPV. Both come along with advantages and disadvantages. Another new method for determining the gold standard pulse pressure values was developed for this thesis. This method is semi-automated since manual mouse clicks in a Matlab-figure are necessary and the automatical PPV calculation and comparison is done in Matlab. The main advantage of this method is that it allows comparing a great number of PPV values against each other, with far less time effort than with the totally manual approach. Additionally the susceptibility to errors is minimized due to the visual detection of various artefacts.

The following procedure was performed for each patient: After plotting all relevant signals in an adjusted time-scale to see at least 3 respiratory cycles, the minima and maxima of the pulse pressure curve (blue) can easily be seen in Figure 2.11. In the first subplot the non-invasive beat-to-beat BP-curve (black) was overlaid with the varying pulse pressure signal. This PP-signal was printed with a different y-scale (right-scale) to see the effects of the ventilations-induced modulation of the BP-signal more clearly.

For detecting the onset of every arterial BP pulse an open – source algorithm [81] was employed. In this step the starting point of every pulse-wave was determined and the signal was segmented into several pulse-periods. This algorithm used a windowed and weighted slope sum function (SSF) to find the beginning of consecutive BP-beats. In a next step the minimum and maximum was determined in this segmented pulse-period, resulting in a diastolic (BPdia) and systolic (BPsys) value. Pulse Pressure (PP) was defined as the difference between systolic and diastolic pressure, whereas maximal (PP_{max}) and minimal (PP_{min}) values were determined within one respiratory cycle. [75]

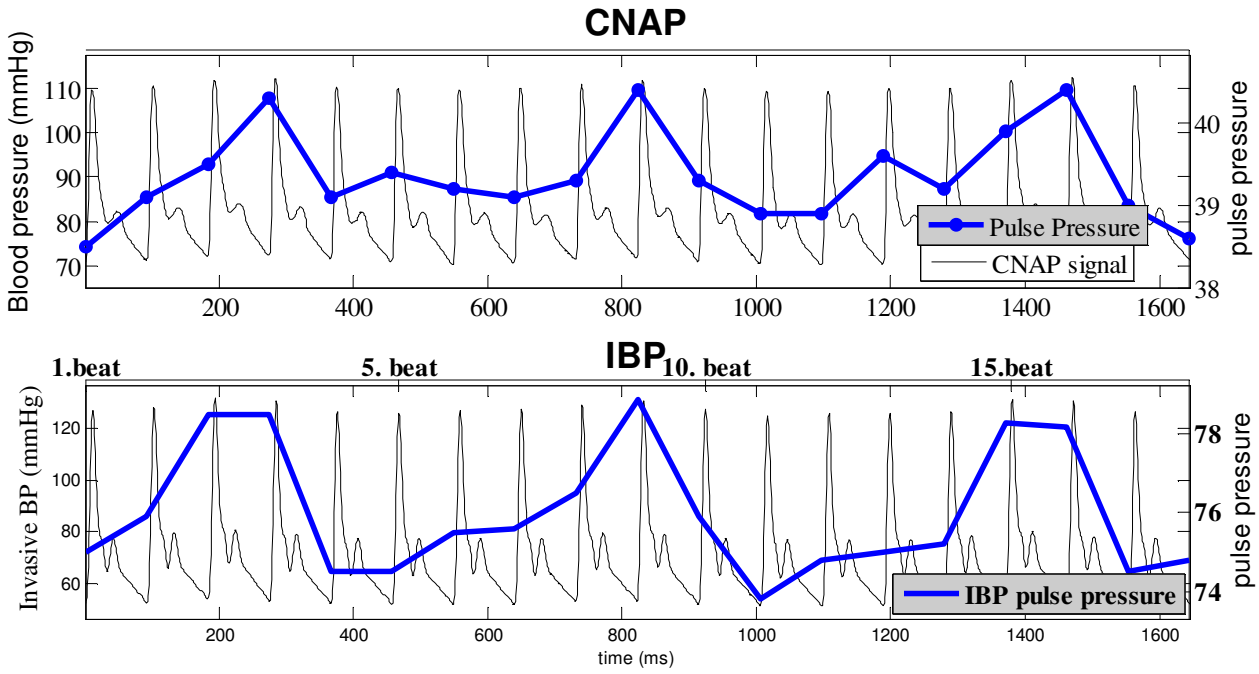


Figure 2.11: The upper graph shows the non-invasive signal from the CNAP monitor. The beat-to-beat BP signal can be seen with the corresponding scale on the left side of the graph. The pulse pressure (thick, blue line) is evaluated for every beat and drawn into the figure. In the lower graph the invasive signal for the same time period is plotted.

After this initial plot, the minima and maxima in the PP-curve showed up for inspection in a next step. The Matlab script was designed to visually mark the minima and maxima with the computer mouse just by clicking the required point on the screen. With the Matlab command *ginput*, a graphical input from the mouse or keyboard can be placed in an intuitive way in the figure. After clicking with the mouse on the appropriate minimal/maximal point in the figure, a PP_{min} or PP_{max} value was selected. When the visual decision was done by the operator, the clicked point was rounded in time-direction to the nearest integer beat number (called: beat ID). This value was assigned to the corresponding pulse pressure signal and resulted in a definitive PP-value in mmHg for each minimum and maximum. In this example the first minimum (PP_{min}) in the CNAP PP-curve was approximately 38,5mmHg (Figure 2.12).

After 6 consecutive values were clicked with the mouse and thereby visually marked with a large coloured circle, the calculation followed for each signal. An approval of all clicked values was done thereon with one additional click in the figure. The same clicking procedure

was done for both signals (non-invasive & invasive). This procedure was reiterated 10 times per each patient (10 program loops/patient).

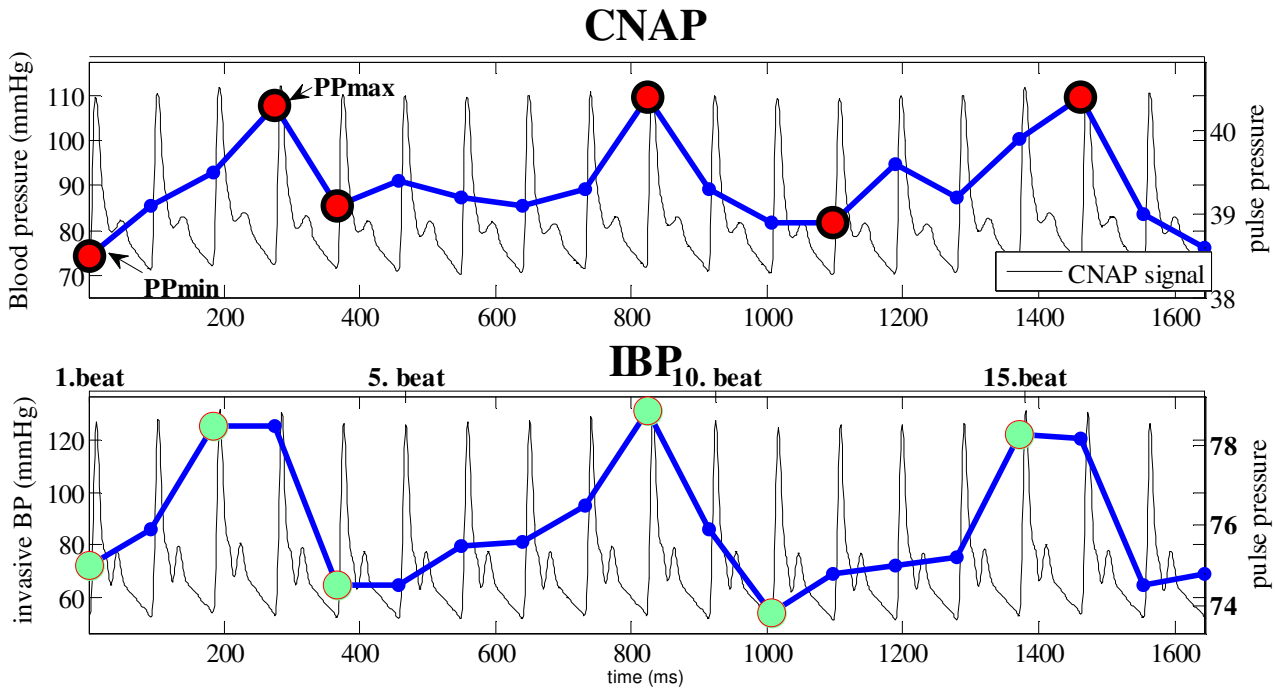


Figure 2.12: Defined minima & maxima in the pulse pressure signal.

Most of the pulse pressure Min/Max-selection was programmed in the Matlab-function *michard_erweitern_doppelt_CNAP.m.* The gold standard PPV was computed from each 2 pulse pressure pairs (PP_{min} / PP_{max}) with the according formula *(1)*. Then a mean over all 3 PPV-values was built, which corresponded to the described three consecutive respiratory cycles (Michard et al. 2005, [58]). This final $\mathbf{PPV_{GOLD}}$ value and the last time stamp of PP_{max} (time in signal vector at the last PP_{max} value of the 3rd respiratory cycle) was forwarded to a Matlab function and saved in a matrix. This data-set was in a later step compared to the automatic CNSystems algorithm PPV value, $\mathbf{PPV_{CNSystems}}$ at the same time. All results from the entire 10 loops per patient were in the end saved in one data matrix together with all times of the last PP_{max} in the signal, for the IBP and CNAP signal respectively.

The minimum in the CNAP and IBP pulse pressure signal (PP_{min}) was always marked first (red marker point in Figure 2.12) to avoid a negative PPV value within the program. If a maximum was clicked as first evaluation point, the program automatically started searching for a new time period and discarded the values within this loop for evaluation. A RETURN-key stroke terminates the loop as well and searches for a new time period out of the BP-signal

vector. After this selection process no arrhythmias or artefacts (e.g. flushing) should be visible any more in the BP-signals used for evaluation. In Figure 2.13 the small oscillations of the systolic BP-values can also be noted vaguely (also called “Swing”).

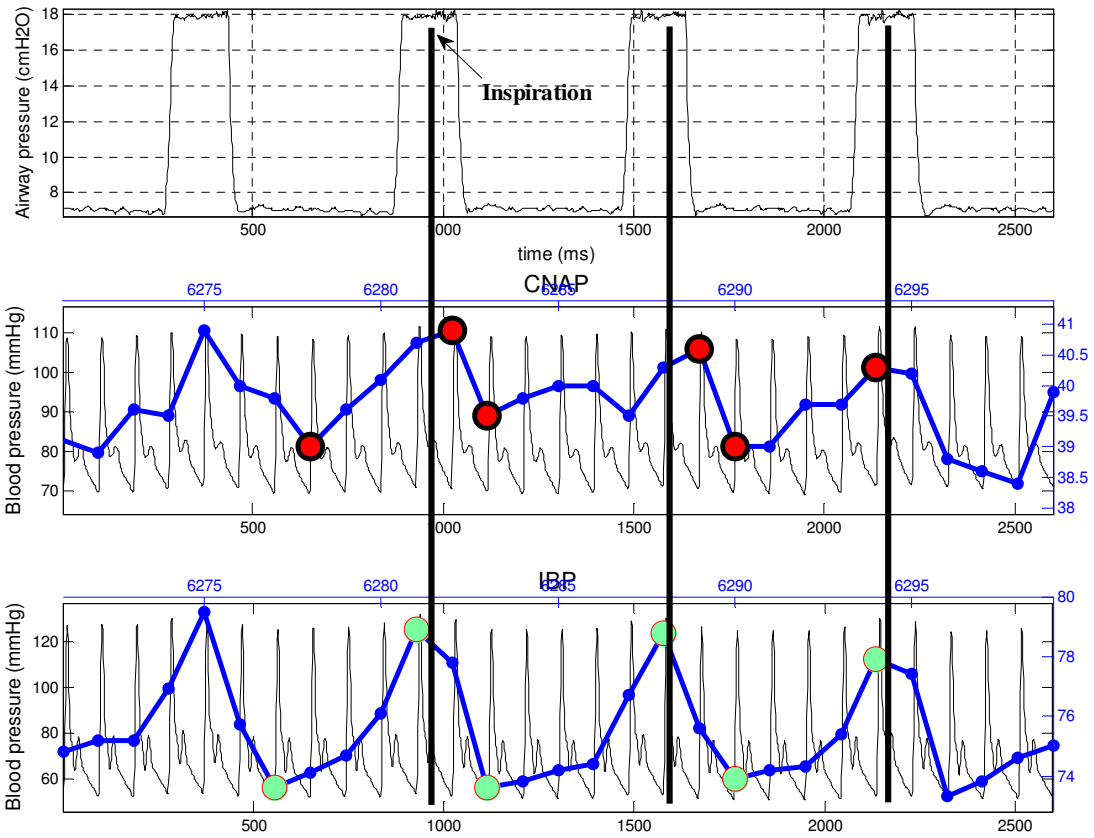


Figure 2.13: The uppermost graph shows the airway pressure signal from the ventilation machine. In the middle the minima and maxima of the pulse pressure curve (blue) are marked with a cycle. The red marked points indicate the minima and maxima of the PP-curve of the invasive arterial signal. Green markers, in the lowest graph correspond to the PP_{min}/PP_{max} of the CNAP-signal.

Upon the condition that the airway pressure signal (P_{aw}) was available in a patient record, this signal was also plotted as additional subplot as seen in Figure 2.13. Here the uppermost plot in the Matlab-figure shows the simultaneously acquired airway pressure (P_{aw}). The inspiratory and expiratory periods of the ventilated patient can be recognized in the signal. Although the airway pressure signal was only recorded in the last 8 patient files, these files were initially important for discovering the disturbing effects of spontaneous breathing. This respiratory signal initially supported the correct finding of PP_{min} / PP_{max}.

Choosing random time points for PPV evaluation:

The need for more than one time point for evaluating agreement between a continuous algorithm ($CNAP_{\_PPV\_CNSystems}$) and the gold standard ($CNAP_{\_PPV\_Gold}$) is important when evaluating an algorithm. Cannesson et al. 2008 [82] used 8 different time steps for each patient. For this work 10 randomly time points per patient were chosen.

Randomly chosen beats, which were automatically selected with the Matlab-command *randi* from the pulse pressure vector, were used. Initialisation of the default random number stream for the command *randi* was done in every program loop. From this automatically selected beat out of the whole signal, a vector with a length of 38 heart beats was displayed. This vector length proved to show more than 3 respiratory cycles for every patient, also allowing for higher and smaller respiratory rates of different patients.

In the course of the evaluation of all PPV values, the program was then looped for 10 different times per patient to get 10 comparable results per each individual patient. The output of the program printed all chosen beat numbers (equals all chosen time points) which were then compared with the calculated PPV from the CNSystems algorithm ($CNAP_{\_PPV\_CNSystems}$) at the corresponding time point. Time points were only chosen once to evaluate 10 different periods per patient.

2.4.4 Artefact recognition

Spontaneous breathing activity:

Spontaneous breathing activity can be detected in an airway pressure curve (P_{aw}). When comparing a normal breathing signal (Figure 2.14) with a spontaneous breathing signal (Figure 2.15), the difference in the wave-form is detectable. Since the patients were allowed to breathe spontaneously in BIPAP-respiratory mode, the respiratory waveform had to be considered. Therefore the observation of the P_{aw}-signal in the patient's data record was essential.

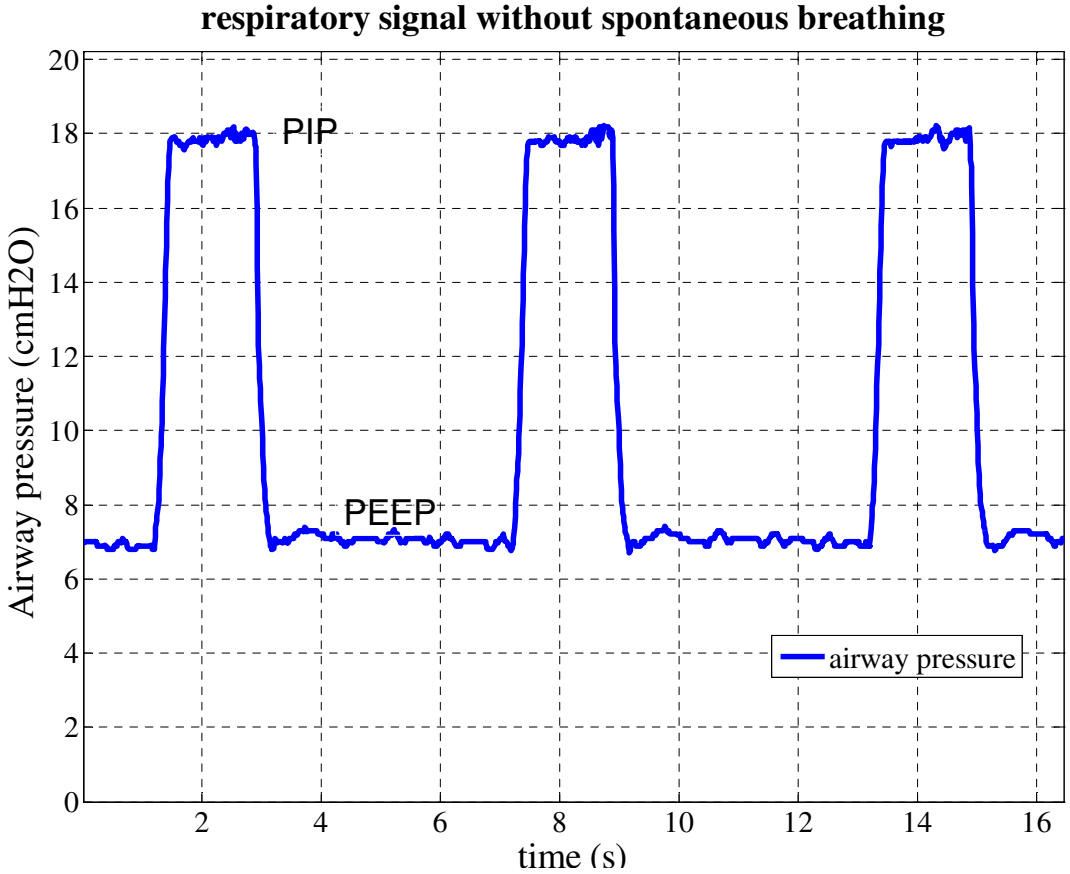


Figure 2.14: Respiratory signal obtained from the ventilator with a constant respiratory rate. The lowest airway pressure (about 7 cmH_2O) value indicates the positive end-expiratory pressure (PEEP) which was set by the medical staff. The maximum of 18 cmH_2O in the ventilation signal is also referred to as Peak Inspiratory Pressure (PIP). No spontaneous breathing activity can be seen in this signal.

This fundamentally different signal waveform helped initially to discover the importance of breathing parameters in the PPV-evaluation and led to a rejection of the spontaneously breathing patients. One example with a spontaneous breathing period can be seen in Figure 2.15. Spontaneous breathing was in this patient noted by visual inspection of the ventilation signal (P_{aw}) and the patient was excluded from analysis. Although this is not a state of the art artefact detection method for abnormal bio signals, this method offers advantages: Since all bio signals, including BP and respiratory activity, are varying by a great degree a very sophisticated algorithm would be needed. When comparing different signals from all patients of this study, this visual artefact recognition is a valid method to observe the abnormality of the breathing signal. High detection accuracy is also accompanied by this strategy.

A second approach for guaranteeing the absence of spontaneous breathing was done. All recorded ventilations parameters in the CSV-files from the Infinity Network offer the possibility to display these parameters as well (e.g. spontaneous tidal volume, respiratory rate, minute volume). These files were in fact very helpful for finding out if the patient had spontaneous breathing activity or not. The variables in the CSV-file for the spontaneous Respiratory Rate (mib RRs) and the spontaneous Minute Volume (mib MVe spon.) were checked for adverse (=positive) values, indicating spontaneous breathing activity.

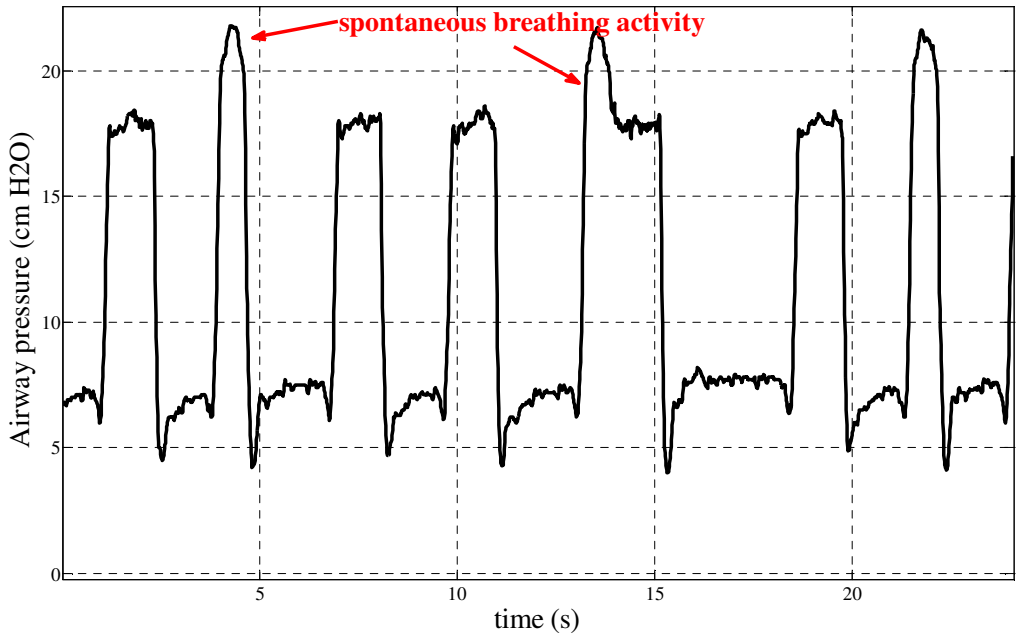


Figure 2.15: Respiratory signal containing periods of spontaneous breathing activity. This patient was ventilated in BIBAP-mode and was retrospectively rejected from the study.

To sum up, these two alternative ways of finding non-compliant patients for PPV evaluation seem sufficient. The feasibility of sorting out the data based on two different sources was considered as a reliable method.

Arrhythmias in the blood pressure signals:

A second aspect when working with signals for PPV calculation is the importance of a sinus rhythm. Arrhythmias disturb the regularity of the modulated BP-signal and therefore can not be used for valid PPV calculations. Arrhythmic signals have therefore been rejected from the patient base. Although the type of disorder was not of great importance for the study these abnormalities were protocolled by medical staff. The specific type of cardiac disorder was defined by inspecting and analyzing the electro cardio graphs (ECG) [83]. Depending on the type of cardiac disorder (e.g. normotop or ectopic & ventricular- and supraventricular arrhythmias) different identification strategies would have to be considered for an automatic detection in the ECG signals. Hundreds of automatic detection algorithms for arrhythmias exist in the literature and are used in ECG-software for instance. State of the art examples for detection and classification algorithms are based on Support vector machines, neural networks, Principal Component Analysis, Wavelet Transform and combinations there from (e.g. [84]). Also recent publications in this field show that there is still a high research interest for finding the best detection and classification strategies.

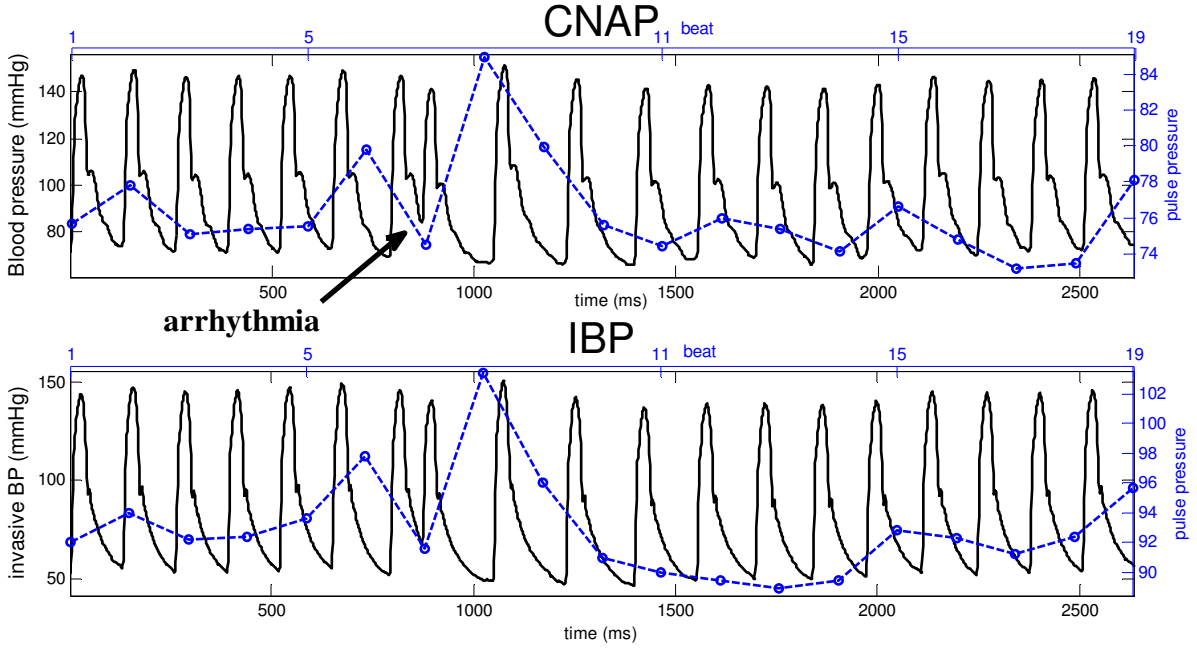


Figure 2.16: Overlaid blood pressure signal containing a period of an arrhythmic signal. An abnormally fast increase of the pulse pressure can be observed in the following beat

Although widely accepted, these arrhythmia detection algorithms still show a certain percentage of misclassification and the implementation of a sophisticated arrhythmia detection

algorithm would have been out of the scope of this thesis. Therefore another strategy of arrhythmia detection was chosen. Arrhythmias are not only reflected in the recorded ECG but also as blood pressure perturbations in the BP-signal. The blood pressure curve as for example plotted in Figure 2.16 was used for arrhythmia detection purposes. The visual recognition of the BP-signal was a reliable indicator for recognition of arrhythmias. A very clear example of an intermittently occurring arrhythmia can be observed in the following figure (Figure 2.16). Furthermore, the presence of cardiac arrhythmias was also identified by professional medical staff with the additional help from the monitored ECG. This approach served as a second source for guaranteeing the absence of disturbing cardiac disorders. When a persistent arrhythmia was recognized in the patient record the whole data-set was rejected. Intermittent arrhythmias were allowed for evaluation.

2.4.5 Decision guided workflow for data selection

The process of selecting and sorting out patients from the patient data base worked as shown in the flow chart in Figure 2.17. After collecting all patient files in the hospital the CSV-File (where all parameters from the Infinity network were collected) was checked for abnormal spontaneous breathing activity. If very small periods of spontaneous breathing occurred, this was tolerated or the relevant part was cut out of the file. If the patient was more or less able to constantly breathe spontaneously (which is allowed in BIPAP-Mode of the ventilator), the whole patient file was rejected. If the continuous breathing signal (P_{aw}) was available, the signal was overviewed for invalid signal characteristics (as seen in Figure 2.15, page 41) in the plot. Another relevant process step was the detection of disturbing arrhythmias in the patient's file. Therefore the patient record was checked for arrhythmias and if the patient had any cardiac diseases. Thereon an observation of the BP-signal followed: Arrhythmias were noticeable in the invasive as well as in the non-invasive signal, and led to an exclusion of the patient. Another important step included the handling of artefacts in the BP-signal (for example flushing of the catheter, repositioning of the patient). When an adverse event occurred in the signal period relevant for observation this period was skipped. This procedure automatically searched for a random new time period for evaluation. If all signal parameters were properly checked for correctness, the selection of the needed minima and maxima of the pulse pressure points followed.

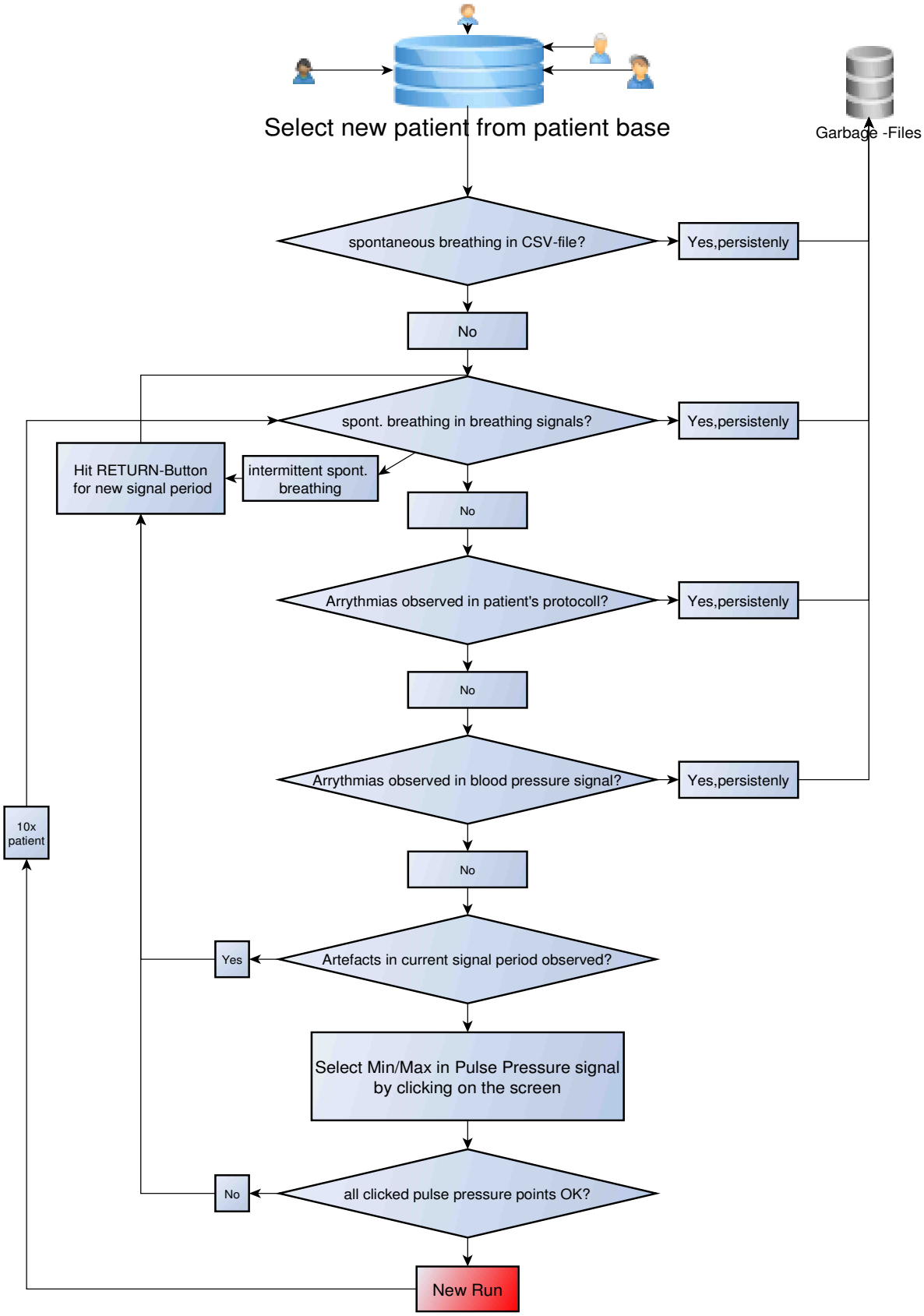
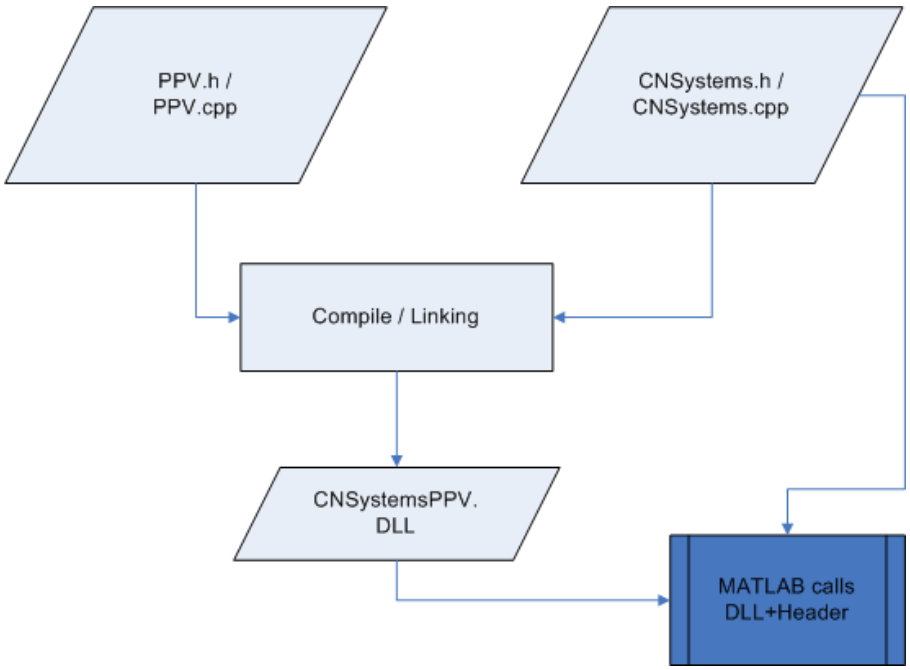


Figure 2.17 Decision path for the Pulse Pressure Min / Max selection. All steps were done accordingly to this flow chart when evaluating the individual patients.

2.4.6 Integrating CNSystems' PPV algorithm into Matlab

Since the PPV algorithm from CNSystems was intended to be implemented into the current version of the CNAP monitor, is was important that the software code of this future product is tested in its original code version. The possibility of implementing bugs during transfer of Matlab code into the CNAP-Monitor's software has to be considered. Therefore, the CNSystemsPPV DLL-file from the CNAP-Monitor was used for validation against the manually calculated gold standard PPV. Since the calculation of the PPV is an encapsulated C++ Software module (class) in the firmware of the CNAP-Monitor, it can be used independently of the remaining firmware. Basically it can be uncoupled from all the other source code of the monitor and still can be used. For this reason also a dynamic library (CNSystemsPPV.dll, date: 20.8.2010) can be produced, which can be used in Matlab.



Because Matlab can't create an instance of the PPV- class, a C-Wrapper (CNSystemsPPV.h & CNSystems.cpp) was necessary. This equals to a mapping of C-functions on the class-methods. These C-functions now can call the methods of the global PPV class instance (class: CPPV). As seen in the workflow diagram, the interface for Matlab is called CNSystemsPPV.h and CNSystemsPPV.dll. These two files can be used for calculation within a Matlab function and it is guaranteed that it is a 1:1 copy of the original firmware. Also the integration of the Dll in other languages (Python) is possible. The Matlab function *loadlibrary* was used to call the CNSystemsPPV-Library and then was used for further calculation of the automatic PPV

algorithm. A comparison of the manually calculated PPV value (gold standard) to the CNSystems PPV value was carried out at the same time point as the last PP_{max} of the 3rd respiratory cycle. The decision for evaluating the last PPV value from the last respiratory was made, because this is the most recent automatical value which is available in the CNAP-Monitor. The benefit of this method is that the possibility for implementing bugs in the course of transferring the source code from Matlab to C++, are minimized.

2.5 Statistical data analysis

All statistics were carried out using SPSS 16 (SPSS, Chicago, IL). Using a P-value of 0.05 as most commonly done in literature was considered statistically significant. Data are presented as mean ± standard deviations. All comparison analyses are based on 10 randomly chosen PPV values for each patient, resulting in a total of 100 paired data points. Agreement between PPV values is assessed by the calculation of bias, standard deviation of the bias, regression plot and Bland-Altman analysis. To measure the agreement between two different measurement methods the Bland-Altman plot is a scientifically accepted method. For the Bland-Altman analysis always the difference between two data pairs is used for the plot, (Bland-Altman, Lancet 1986,[85]). For non normally distributed data Bland & Altman [86] suggest the use of log transformation of the data. For understanding the basis of the underlying data of the PPV values, a descriptive statistic was done. Skewness values above 0 indicate that the distributions are skewed to the right, a high kurtosis mean a sharper peak and longer tails, whereas a low kurtosis has short tails and an arched peak. Furthermore testing the data for normal distribution was done graphically with a histogram and QQ-plots, and also mathematically with a Kolmogorov-Smirnov-test. The Shapiro-Wilkins test is more often used in sample sizes smaller than 50 for testing for normal distribution. To show the relationship between the four different PPV variables a Spearman correlation analysis was performed. Additionally a regression analysis of the different PPV values was done to compare between manual and automatical PPV calculation. To test for a difference between the manual and automatical PPV calculation a nonparametric Wilcoxon rank sum test was assessed. This test was used because parametric methods (t-tests) assume that the data follows a normal distribution.

3 Results

Results named **CNAP**$_{\text{PPV\_Gold}}$ represent all PPV values which were determined manually on the basis of the CNAP-signal of totally 100 data points. Automatically computed PPV values from the implemented CNSystems algorithm on the CNAP-signal were labelled with **CNAP**$_{\text{PPV\_CNSystems}}$. The same naming convention was used for the invasive blood pressure signal (IBP) and the resulting PPV values. **IBP**$_{\text{PPV\_Gold}}$ states the manually calculated gold-standard PPV on the invasive signal and **IBP**$_{\text{PPV\_CNSystems}}$ the automatically calculated PPV from the CNSystems algorithm again on the invasive BP-signal.

3.1 Descriptive statistics

The values in Table 3.1 indicate that the mean PPV from the CNAP systems is lower than the values coming from the invasive signal (IBP). A higher standard deviation in IBP PPV values is observed. Skewness values above 0 indicate that the distributions are skewed to the right, which can also be seen in the histograms in Figure 3.2.

	Mean (%)	Standard deviation	Skew ness	Kurtosis
CNAP_PPV_Gold	5,675916	3,3366519	1,650	3,286
CNAP_PPV_CNSystems	4,693315	2,2235247	1,277	1,526
IBP_PPV_Gold	6,899400	4,0189686	2,122	7,270
IBP_PPV_CNSystems	6,712370	3,6057027	1,636	4,827

Table 3.1: Descriptive statistics for all PPV values

The presented box plots (Figure 3.1) show the different values of PPV for the 4 different methods. The blue box indicates where 50 percent of the data is situated in. The whisker length is equivalent to the smallest or largest value within the 1.5*Inter-quartile-range. Outliers are values between 1.5 IQR's and 3 IQR's from the end of a box marked with a cycle,

extreme outliers are values more than 3 IQR's from the end of a box and were indicated with a star.

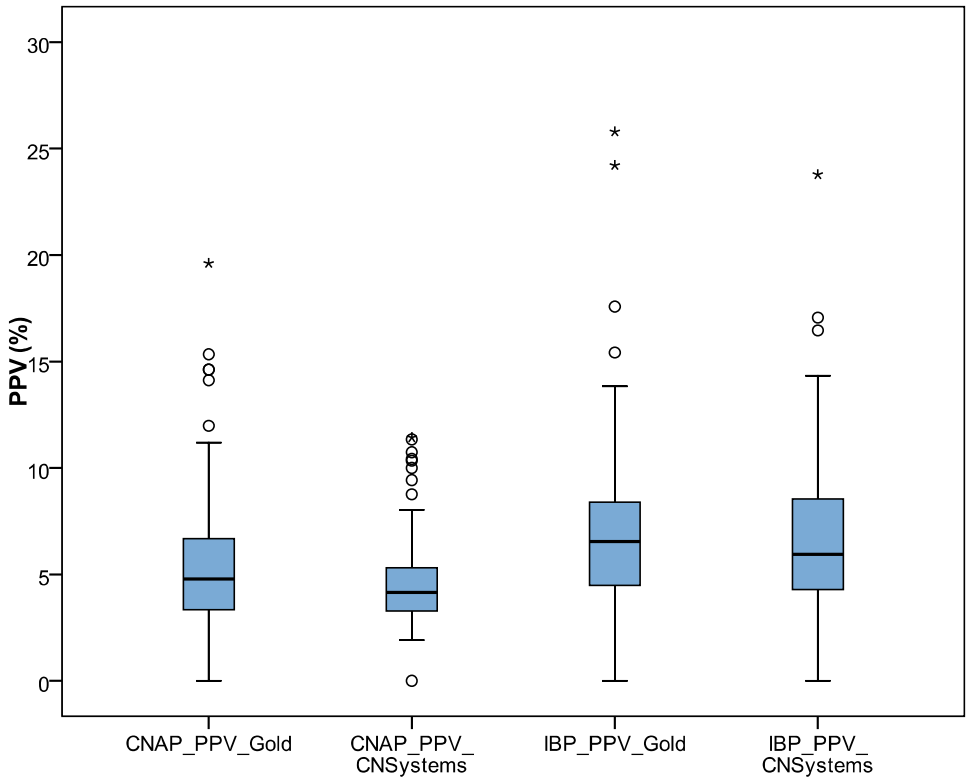


Figure 3.1 Box plots of all PPV values

Bias values for all possible combinations were calculated between manual and automatically obtained PPV values. As seen in Table 3.2, the difference between **CNAP**$_{\text{PPV\_Gold}}$ and **CNAP**$_{\text{PPV\_CNSystems}}$ was 0.98%±1.99%. For a total of 100 randomly assigned paired data points, the difference (mean bias ± STD) between **IBP**$_{\text{PPV\_Gold}}$ and **CNAP**$_{\text{PPV\_CNSystems}}$ was 2.26%±3.53%, revealing an offset between the CNAP signal and the IBP signal.

Bias (=Difference of horizontal minus vertical table listing)	**CNAP**$_{\text{PPV\_Gold}}$	**CNAP**$_{\text{PPV\_CNSystems}}$	**IBP**$_{\text{PPV\_Gold}}$	**IBP**$_{\text{PPV\_CNSystems}}$
CNAP$_{\text{PPV\_Gold}}$	0	**0.98 (1.99)**	1.27 (3.88)	1.06 (4.3)
CNAP$_{\text{PPV\_CNSystems}}$		0	**2.26 (3.53)**	2.04 (3.61)
IBP$_{\text{PPV\_Gold}}$			0	0.20 (1.64)
IBP$_{\text{PPV\_CNSystems}}$				0

Table 3.2: Bias analysis matrix: Differences between manual and automatically calculated PPV's (%) in 10 critically ill patients. Results presented as means ± standard deviation. Analysis was done for invasive BP (IBP) as well as non-invasive BP (CNAP).

3.2 Test for normal distribution

For further information on the underlying data histograms in Figure 3.2 were plotted. The histograms for the PPV values don't show normally distributed shape. PPV values in % are shown on the abscissa, whereas the frequency of occurring data is plotted on the ordinate. A skew in the range of 1.65 – 2.12 and a kurtosis of 1.5 - 7.3 reveal the non-symmetry of the distributions.

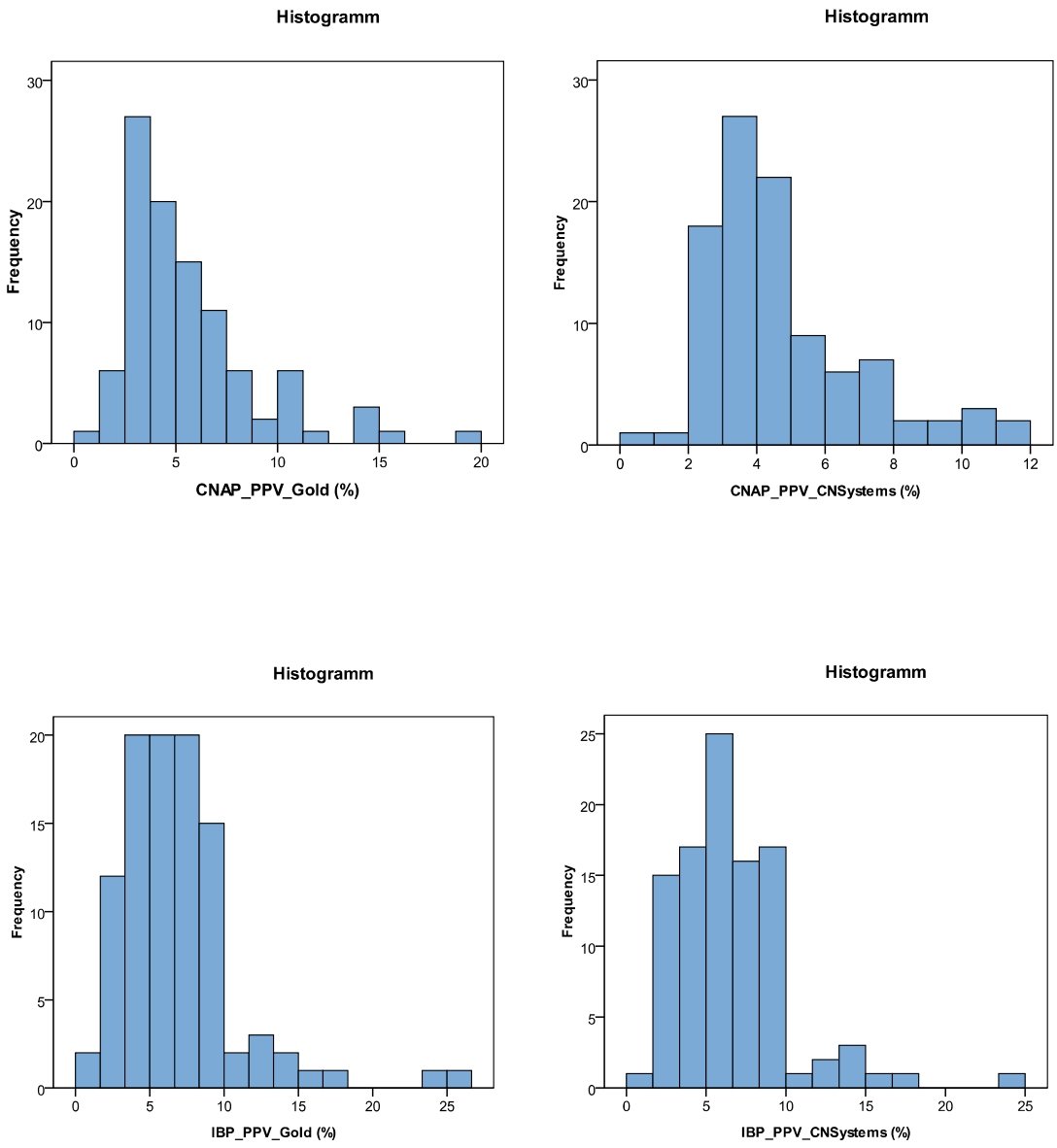


Figure 3.2: Histograms of all PPV values

Another method for checking graphically for normal distribution is the Q-Q-Plot. Here, the expected values of a normal distribution are plotted against the observed data values. As comparison the quartiles of the theoretical distribution are used. If the observed values are resulting from the compared normal distribution then the empirical and theoretical quartiles match. The values therefore should be placed on the diagonal line in the QQ-plot. Exemplarily the plotted data of **CNAP**$_{\text{PPV\_CNSystems}}$ is shown in Figure 3.3 and shows a clear deviation from a normal distribution. All other QQ-plots show a very similar shape and no normal distribution can be assumed for the further analysis.

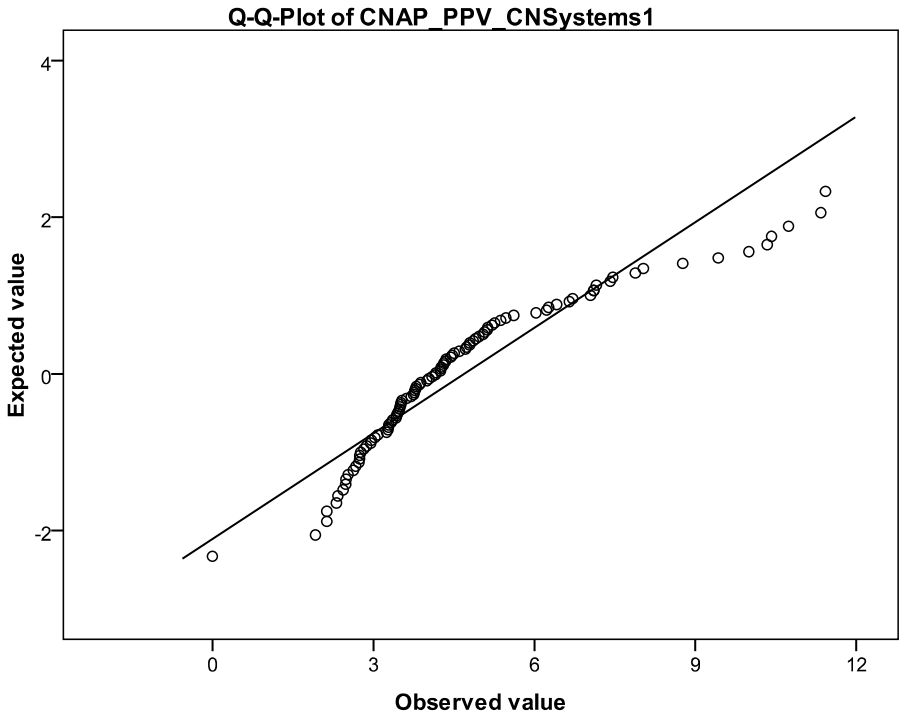


Figure 3.3: QQ-Plot of calculated PPV values with the CNAP_PPV_CNSystems algorithm

Since graphical analyses are limited by testing for normal distribution a Kolmogorov-Smirnov test was done as well. This test works with the cumulative empirical distribution and the cumulative expected reference distribution, in our case with the normal distribution. The maximal difference between both distributions is used for calculation of the Kolmogorov-Smirnov Z. The critical value for the maximal difference at a certain significance level (0.05) and a certain sample size can be looked up in a normal distribution table. If the maximal difference from the table (for n=100 samples, max allowed Distance=0.136) is exceeded, then the data actually represents no normal distribution with a 95% probability. As seen in Table 3.3 the Kolmogorov-Smirnov test results for CNAP_PPV_Gold the most extreme difference value of 0.151 is higher than 0.136 and therefore the hypothesis of a normal distribution was rejected.

Kolmogorov-Smirnov Test

		CNAP$_{PPV_Gold}$	**CNAP$_{PPV_CNSystems}$**	**IBP$_{PPV_Gold}$**	**IBP$_{PPV_CNSystems}$**
N		100	100	100	100
Normal Parameters	Mean	5,675916	4,693315	6,899400	6,712370
	Std. Deviation	3,3366519	2,2235247	4,0189686	3,6057027
Most Extreme Differences	Absolute	**,151**	**,152**	**,140**	**,134**
	Positive	,151	,152	,140	,134
	Negative	-,127	-,105	-,107	-,089
Kolmogorov-Smirnov Z		1,507	1,523	1,400	1,343
Asymp. Sig. (2-tailed)		**,021**	**,019**	**,040**	**,054**

Table 3.3: Kolmogorov-Smirnov Test for testing on normal distribution of the data

Also the asymptotic significance with a value of 0.02 indicates a much smaller value than our claimed significance level of 0.05. In all cases, except for the **IBP$_{PPV_CNSystems}$** values, the assumption of a normal distribution has to be rejected. It can be said that there exists a

significant variation for 3 cases from the normal distribution for all PPV values. Therefore we have to deal with the non-parametric approach in the following statistical investigations.

3.3 Spearman correlation analysis

Since the data is not normally distributed, the correlation analysis was done with the Spearman correlation method. This method works on the correlation analysis with the ranks of the samples. The correlation coefficient between manually and automatically calculated PPV of the CNAP-Signal is for example $r_{spearman}$= **0.763**, whereas the correlation of the IBP-Signal results in a higher value of $r_{spearman}$= **0.862**. When comparing IBP and CNAP directly, the correlation coefficient is lower as seen in Table 3.4.

Spearman's-Rho $r^2_{spearman}$	**CNAP**$_{PPV\_Gold}$	**CNAP**$_{PPV\_CNSystems}$	**IBP**$_{PPV\_Gold}$	**IBP**$_{PPV\_CNSystems}$
CNAP$_{PPV\_Gold}$	1	**0,763**	0,579	0,300
CNAP$_{PPV\_CNSystems}$		1	0,435	0,227
IBP$_{PPV\_Gold}$			1	**0,862**
IBP$_{PPV\_CNSystems}$				1

Table 3.4: Correlation analysis performed on the individual PPV calculation methods

3.4 Bland – Altman analysis

The PPV measurements were compared using Bland and Altman statistics (Bland&Altman 1986,[85]) to describe agreement between to measurement methods, including the lower and upper limits of agreement. To measure the agreement between two different measurement methods the Bland-Altman plot has evolved as a scientifically accepted method. For the analysis the difference of the two paired PPV measurements is plotted versus the mean of the two measurements. Agreement (mean bias ± SD) between **CNAP**$_{PPV\_Gold}$ and **CNAP**$_{PPV\_CNSystems}$ was 0.98%±1.99%. Lines of lower and upper limit of agreement are plotted in the figures (bias±1.96*standard deviations). Bland&Altman suggest transforming

data logarithmically if the scatter plots show increased differences with higher values and no normally distributed data. This was the case with our plots (example seen in Figure 3.5) and therefore a logarithmic transformation was applied. The mean difference of $CNAP_{\_PPV\_CNSystems}$ and $CNAP_{\_PPV\_Gold}$ is 0.144 on the log scale and the limits of agreement are -0,458 and 0,746 in the log scale.

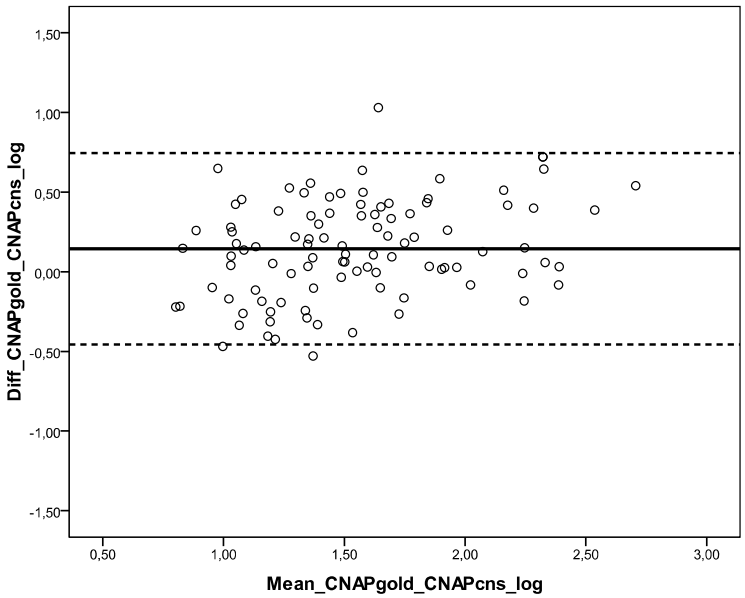


Figure 3.4: Bland-Altman plot: PPV values of log-transformed $CNAP_{\_PPV\_CNSystems}$ and $CNAP_{\_PPV\_Gold}$ are shown above

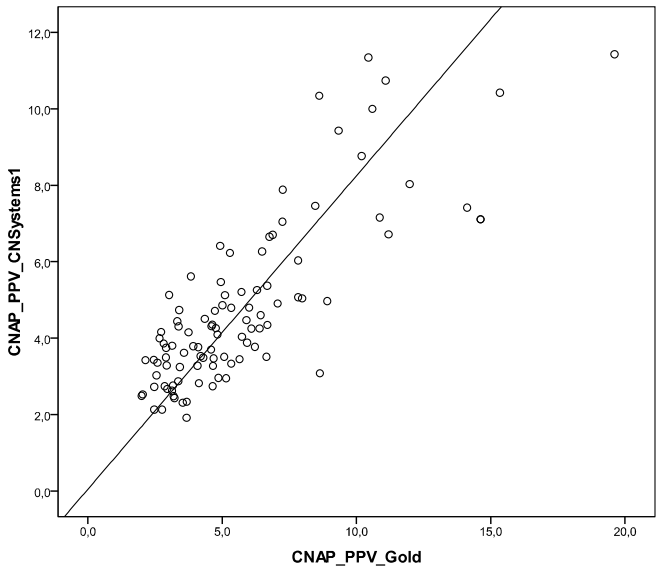


Figure 3.5: Scatter plot: PPV values of $CNAP_{\_PPV\_CNSystems}$ and $CNAP_{\_PPV\_Gold}$ are plotted against each other

Plots for **CNAP$_{PPV_Gold}$ and IBP$_{PPV_Gold}$** are shown below:

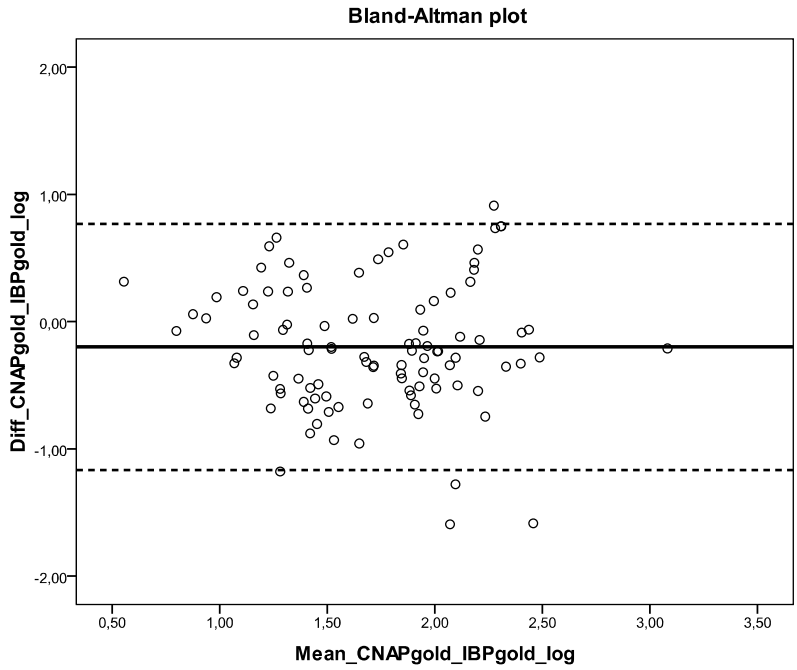


Figure 3.6: Bland-Altman plot: PPV values of log-transformed CNAP$_{PPV_Gold}$ and IBP$_{PPV_Gold}$ are shown above

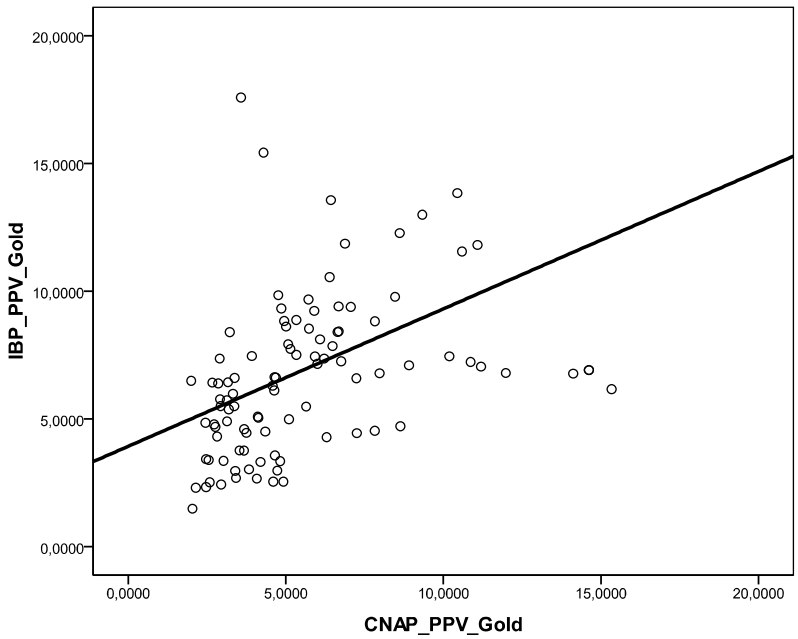
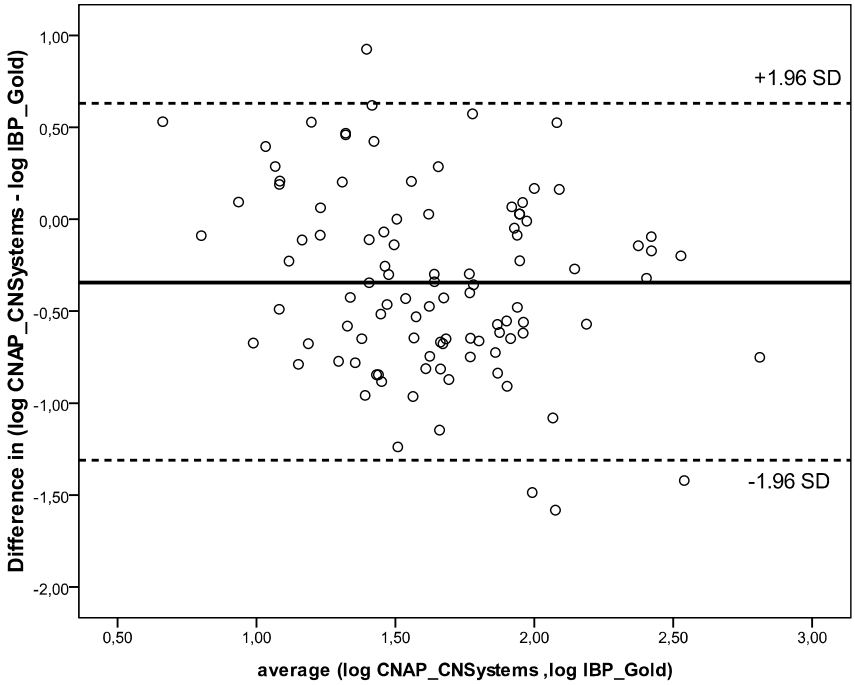


Figure 3.7: Scatter plot: PPV values of CNAP$_{PPV_Gold}$ and IBP$_{PPV_Gold}$ are plotted against each other

Plots for **CNAP$_{_PPV_CNSystems}$ and IBP$_{_PPV_Gold}$** are shown below:



Bland-Altman plot: PPV values of log-transformed CNAP$_{_PPV_CNSystems}$ and IBP$_{_PPV_Gold}$ are shown above

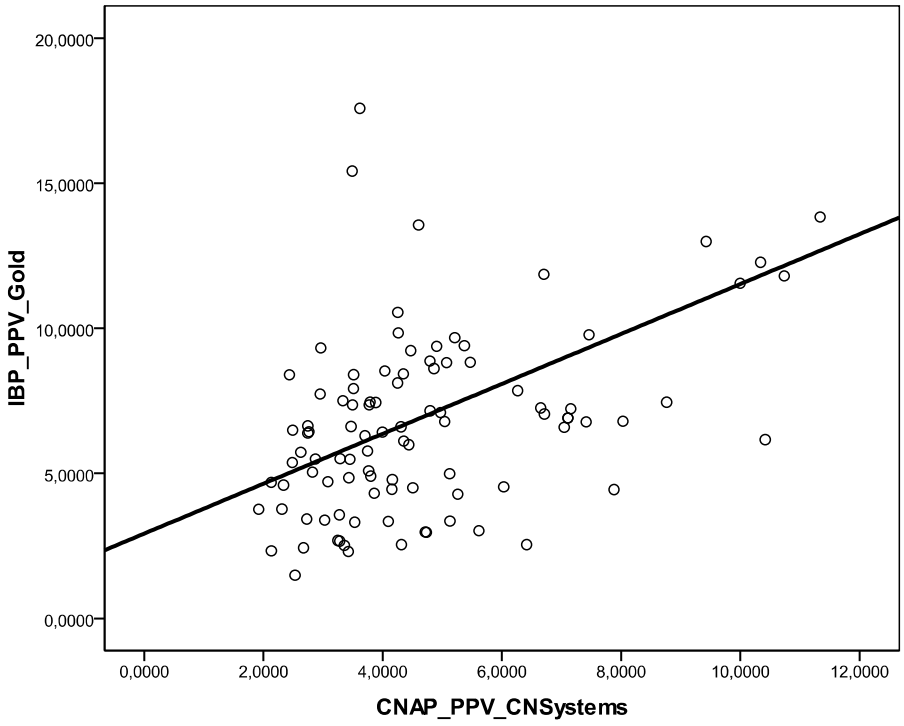


Figure 3.8: Scatter plot: PPV values of CNAP$_{_PPV_CNSystems}$ and IBP$_{_PPV_Gold}$ are plotted against each other

3.5 Non-parametric test

The advantage of the non-parametric Wilcoxon-rank sum test is that it does not need any assumption about the kind of distribution (e.g. normal or Poisson). This test is used to examine if the difference between two series of measurements is statistically significant (e.g. if two independent distributions belong to the same basic population). Instead of using the t-test (which relays on normally distributed data), the Wilcoxon-rank-sum compares the ranked values of the data.

Wilcoxon-test results:

	CNAP_PPV_CNSystems - CNAP_PPV_Gold	IBP_PPV_CNSystems - IBP_PPV_Gold	IBP_PPV_Gold - CNAP_PPV_Gold	IBP_PPV_CNSystems - CNAP_PPV_CNSystems
Asymptotic significance	,000	,906	,000	,000

Table 3.5: Results for the Wilcoxon-rank-sum test

No statistical significant difference was found for the data pair IBP_PPV_CNSystems - IBP_PPV_Gold (with a p-value of 0,906). The test yielded a statistical significant difference for the combinations of CNAP_PPV_CNSystems / CNAP_PPV_Gold (p-value: 0,000), IBP_PPV_Gold / CNAP_PPV_Gold (p=0,000) and IBP_PPV_CNSystems / CNAP_PPV_CNSystems (p-value: 0,000). Therefore the latter can be regarded as not equivalent. A bias of the PPV results could contribute to these findings.

4 Discussion

4.1 Study findings

The main goal of this thesis was the evaluation of a new PPV algorithm within in the CNAP-Monitor for an improved fluid management in critically ill patients. One aim of the clinical study was to investigate if the non-invasive signal is equivalent to the invasive signal for the calculation of PPV. Secondly, the ability of the new PPV algorithm to perform adequately on the invasive- and non-invasive BP signal had to be evaluated. Another goal was to compare automatically PPV ($CNAP_{\_PPV\_CNSystems}$) and manually calculated PPV ($CNAP_{\_PPV\_Gold}$) from the CNAP-signal.

For the invasive BP-signal the manually calculated gold standard PPV values ($\mathbf{IBP_{\_PPV\_Gold}}$) and the automatically obtained PPV values ($\mathbf{IBP_{\_PPV\_CNSystems}}$) differed by a bias of 0.20% ±1.64% (as seen in Table 3.2, page: 49). Therefore the algorithm seems to work adequately on the IBP signal with an insignificant offset (0.20% ±1.64). In contradiction to all other comparisons, also the Wilcoxon-test between $\mathbf{IBP_{\_PPV\_CNSystems}}$ and $\mathbf{IBP_{\_PPV\_Gold}}$ yielded no significant difference.

For the comparison of the automatically obtained PPV values ($\mathbf{CNAP_{\_PPV\_CNSystems}}$) with the manually obtained PPV values ($\mathbf{CNAP_{\_PPV\_Gold}}$) from the CNAP-signal, a larger bias was observed (0.98% ± 1.99%). One reason could be that the CNAP-Monitor delivers not as distinctive BP-waves and pulse pressures waveforms as the IBP-signal does, and therefore the minima and maxima in the PP-signal are more difficult to detect for the automatic CNSystems-PPV algorithm. Thus, the non-invasive signal is not totally equivalent to the invasive signal for the calculation of PPV. Adjusting the algorithm to the CNAP-signal or changing the number of averaging periods in the algorithm could lead to a performance improvement. Comparing these results to the PPV evaluation done by Cannesson et al [82] nonetheless the new CNSystems algorithm shows similar performance (bias on IBP: 0.74%±3.4% versus bias on CNAP: 0.98% ± 1.99%). This bias comparison in this study is relevant since the evaluation was performed also by the same gold standard PPV method and

on an already commercially available automatical PPV algorithm (Philips Intellivue MP70 monitor).

The comparison between the manually calculated PPV values of **CNAP$_{_PPV_Gold}$** and **IBP$_{_PPV_Gold}$** showed a higher bias (1.27%±3.88). The Wilcoxon rank sum test confirmed that there was a statistically significant difference between PPV values of **CNAP$_{_PPV_Gold}$** and **IBP$_{_PPV_Gold}$.** Also the scatter plot of **CNAP$_{_PPV_Gold}$** and **IBP$_{_PPV_Gold}$** as seen in Figure 3.7 shows this offset. The different signal characteristics of IBP and CNAP have to be taken into account which could contribute to this large offset. It has to be stated that different blood pressure waves and also different resulting systolic and diastolic BP values can be observed in the Arteria brachialis, the Arteria radialis and the Arteria digitalis. The BP measurements for IBP (and consequently **IBP$_{_PPV_Gold}$**) are received from the Arteria radialis, the BP upper-arm calibration for the CNAP-Monitor from the Arteria brachialis and the measurements of CNAP on the finger in the Arteria digitalis. As can be noted in the BP-signal of the CNAP Monitor (for example in Figure 2.12, page: 37) these BP-signals incorporate different systolic and diastolic values, in comparison to the gold standard for BP-measurement, the invasive catheter. As a consequence of the CNAP-monitor's measurement principle, these intrinsic measurement characteristics are one source for an offset of the **CNAP$_{_PPV_Gold}$** against the **IBP$_{_PPV_Gold}$**. For the guidance of fluid management this leads to another threshold-level for PPV in % to differentiate between responders and non-responders. Since most patients included in this study were hemodynamic stable, fluid responsiveness could therefore not be studied. In future clinical studies fluid responsiveness should be tested, while in the same turn proposing a new PPV threshold to decide between responders and non-responders. This should confirm the proper working of the algorithm also in hemodynamic unstable patients, e.g. patients under shock. In a recent study of Biais et al. 2011 [37] a PPV-threshold between 10-11% for the CNAP-monitor was suggested to discriminate between responders and non-responders. In this study the bias between invasive arterial PPV and PPV obtained by CNAP was 0.9%±0.4.

Discussion of the new gold standard PPV algorithm method:

One drawback of the semi-automatic gold standard PPV-method is the manual clicking procedure done by mouse. This evaluation method is still time consuming, especially for an evaluation with more patients (e.g. 100). The difficulty of finding a trade-off between automatic and manual recognition has been faced in this study. One improvement would be to use an automated pattern recognition algorithm for the detection of the PP_{min}/PP_{max} values. These automated suggested PP_{min}/PP_{max} points can for example be presented with a coloured circle in the plot. A confirmation of the automatically found PP_{min}/PP_{max} values still would have to be guaranteed, for example with an interactive graphical user interface in combination with a correction possibility for PP_{min}/PP_{max} values. For this automatical recognition method the corresponding respiratory signal (P_{aw}) would be of importance for all patients, which was not the case in this study. Without the additional knowledge of the respiratory cycles and the manual confirmation by the user, the comparison would be senseless because the calculated PPV would be an evaluation of an automatic against an automatic algorithm.

This proposed semi-automatic method is still advantageous when comparing the PPV gold-standard method with the evaluation completely done by hand and printed out on paper, as for example recently done by Biais et al. 2011 [87]. The visual PP_{min}/PP_{max} detection and the artefact detection are also superior and more precise than an automated method. Future research steps should also include performing the analysis on more patients, together with more data points per patient to get statistically more convincing results.

Clinical study

The first goal of this study was to record and evaluate the non-invasive BP-signal in comparison to the invasive BP-signal in the internal medicine ICU in Graz. The CNAP-monitor offers the benefit of delivering a continuous non-invasive BP-signal without the risk of shortcomings and complications induced by the invasive catheter. The findings of the BP-study revealed agreement in the mean arterial BP of the CNAP-signal to the invasive signal [see abstract in section 7.2].

For the retrospective evaluation of the new PPV algorithm versus the manual gold standard the patients had to be selected from this study base. Since the study was not specifically designed for the evaluation of PPV, a lot of patients dropped out in the selection-process as shown in the flow chart (Figure 2.1, page 24). For future PPV studies attention has to be paid especially to the limiting factors for using PPV. In fact, an evaluation of this algorithm with more patients, as cited for example in the meta analysis of Michard & Teboul, 2002 [56] with patient numbers ranging from 18-40 patients per study, should be considered. It has to be mentioned that drawing a conclusion from only 10 patients doesn't support the findings with a high significance. The most important limiting factors for the evaluation of a PPV study are stated in chapter 1.6 (page 17). Especially patients in the ICU suffer from cardiac problems with a relatively high percentage, which influence the rhythmic modulation of the BP-signal and therefore the PPV value should be interpreted with care. A future PPV study on another ward of the hospital with less critical patients should be performed. Also the market opportunity for the CNAP monitor to guide fluid management in the ICU seems to be limited in such critically ill patients with various limiting factors.

The value for the positive end-expiratory pressure (PEEP) has been argued to be less than 5 cmH_2O (Michard et al. 2000 [75]). In ICU patients with pneumonic diseases the PEEP value is in general a bit higher to meet the demand for a higher intrapleural pressure, and prevent an inflation of the lung. Studies with different levels of PEEP and the calculation of PPV have not been published so far. Also the ventilation signal difference "PEEP minus Peak Inspiratory Pressure" has not been proposed in literature so far, but could be another influencing factor for the assessment of PPV or SVV. Since these variables are depending on tidal volume and the compliance of the patient's respiratory system, this difference could influence the respiratory modulation of the BP and therefore the threshold between responders and non-responders. Several questions referring to the respiratory ventilation settings are not resolved completely and should be answered in future studies: What is the impact of the difference between positive inspiratory pressure (PIP) and PEEP on PPV? Could the type of mechanical ventilation (Synchronized Intermittent Mandatory Ventilation (SIMV), Biphasic Positive Airway Pressure (BIPAP), Pressure Controlled Ventilation (PCV) and Volume Controlled Ventilation (VCV)) have an influence on the PPV-threshold or does it leave the PPV unaltered?

Possible algorithm improvements:

Diverse approaches of PPV-algorithms have been used in other hemodynamic monitoring devices. For example Aboy et al. 2009 published an algorithm which relies on the use of automatic beat detection, envelope detection by kernel smoothers and a Kalman filter for PPV estimation [44]. Although a previous version of this algorithm was validated (Cannesson et al. 2008, [82]) and showed similar performance to CNSystems' algorithm, the disadvantage of a higher computational power has to be considered. Especially the calculation of the kernel smoothing function (directly) on the minima and maxima of detected BP requires a lot of memory and computational power, which wasn't available in the current version of the digital signal processor and memory in the CNAP500 Monitor. The decision against this specific algorithm or amendments there from was part-way made on the basis of required hardware, since the current CNAP-Monitor had limited hardware resources. An adoption of this Aboy-PPV algorithm to work "online" on the CNAP-signal would be a possible future research step, in the same turn when improving the CNAP Monitor's hardware. Aboy proposes to firstly smooth the detected min/max beats and in a following step search for the required PP_{min}/PP_{max}. In contradiction to the Aboy-algorithm the CNSystems algorithm firstly performs the minima & maxima "search" on the raw PP-signal and then the PPV values are averaged over the last updated 6 values. Since the CNAP signal is not as robust against artefacts as the invasive one the averaging period could be altered. Changing the number of averaging periods from 6 to 5or7 could therefore be a possible improvement. This would smooth the resulting PPV more or less. The question "How can a modified algorithm be evaluated and the performance compared to the old version?" can be met by this idea:

1. For all available patients the manually clicked gold standard PPV values (invasive & non-invasive) should be determined in a first "clicking-round". The PPV results for randomly chosen time points get evaluated and saved with the according timestamp (beat ID) in a matrix as previously done in this study.

2. In a next step an improved version of the automatic CNSystems PPV algorithm is integrated in the CNSystemsPPV.DLL (compare chapter 2.4.6) and further into Matlab. (Altering the averaging period for the PPV calculation, performing a pre-filtering on the BP- or PP-signal, using a kernel smoother for PP- envelope estimation)

3. The improved algorithm now can be evaluated on the same time points (beat ID's previously saved in the matrix). The results indicate if the new version of the CNSystems PPV algorithm performs better or worse than the last version.

The following evaluation would show if the results for a new CNAP-PPV algorithm have been improved or worsened. The manually calculated invasive or non-invasive PPV values (**IBP**$_{\_PPV\_Gold}$ or **CNAP**$_{\_PPV\_Gold}$) would serve as gold standard. The better these gold standard PPV values are approximated the better the algorithm results represent real life variations in pulse pressure. This would be a good way for improving the algorithm step by step. Enough patients for the evaluation should be available, otherwise the performance improvements only base on the intra-individual differences between the patients and could therefore even lead to a degradation of the current algorithm.

4.2 Conclusion

Summing up, the goal of this work, to evaluate a new non-invasive PPV algorithm for the assessment of fluid responsiveness was achieved. In the first part of the work the clinically measured blood pressure signals were analyzed and led to the finding that the non-invasive BP-signals showed good agreement to the invasive signals [abstract in chapter 7.2]. In the second part of this thesis, the evaluation of the PPV algorithm was done with a new way determining the gold standard PPV semi-automatically. This semi-automatic strategy offered a fast-forward approach for a correct identification of the manual calculated gold standard PPV values. Critical limiting factors for PPV calculation were discussed. Technical as well as medical questions were addressed in this work and should help for the design and conduction of future fluid management studies and the development of enhanced new algorithms. Comparing the results from this study to the PPV evaluation done by Cannesson et al. 2008 [82], this new algorithm shows similar performance (bias of 0.74%±3.4% on the invasive signal versus bias of 0.98% ± 1.99% for CNAP-signal in this study). These results also match the results from Biais et al. satisfactorily well [87]. In order to be able to compare the results to other studies the number of patients should be increased. Additionally, a threshold value for fluid responsiveness should be defined for the CNAP-Monitor's PPV algorithm. Further clinical studies have to be conducted to prove this totally non-invasive monitoring system as an accurate predictor of fluid responsiveness. As the number of recent publications shows, PPV and fluid management is still an interesting future research topic and a lot of variables play into the assessment of this hemodynamic parameter.

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6 Table of figures

7 Appendix

7.1 Short description of CNSystems' PPV algorithm

A short description of the important program blocks of the new PPV algorithm developed by CNSystems follows. The individual process steps were broken down into a single flow chart diagram to understand the basic principles better. The program blocks nestled in the dotted line represent the actual PPV-algorithm as can be seen Figure 7.1. This part was integrated as CNSystemsPPV.dll in the Matlab evaluation, as described before (2.4.6 Integrating CNSystems' PPV algorithm into Matlab). For further information, the source code and the flow chart of the PPV-algorithm offers in detail steps how the algorithm works.

The non-invasive CNAP BP-signal serves as the input parameter of the proposed algorithm. In a first step (step1) the algorithm automatically detects all beats of the calibrated BP-signal. For detecting the onset of every arterial BP pulse an open – source algorithm [Zong et al 2004,[81]] was employed. In this step the starting point of every pulse-wave was defined and the signal was segmented into individual pulse-periods. Thereon the minimum and maximum were determined in this segmented pulse-period, resulting in a diastolic (BPdia) and systolic (BPsys) value. Pulse pressure (PP) was defined as the difference between systolic and diastolic BP.

In the following step a beat rejection (step2) was implemented to ensure only valid beats for evaluation. Arrhythmic beats were detected by a high variance of PP or heart rate (HR) in relation to the current history. If too many discarded beats (25% of total beats) appeared, no values were displayed and the PPV algorithm was reset.

Step3: Searching the minima & maxima in the Pulse Pressure vector is done in the next step. Here, the minimum-maximum episodes and maximum-minimum episodes are representing

the respiratory variation as “swing” on the BP-signal. Detected minima (PP_{min}) and maxima (PP_{max}) were cross-checked for plausibility. If the algorithm does not detect any PP-values in the last 15 seconds, a reset of the algorithm is performed and no values are displayed. This also helps for finding a new starting point during calibration of the CNAP-Monitor during finger change.

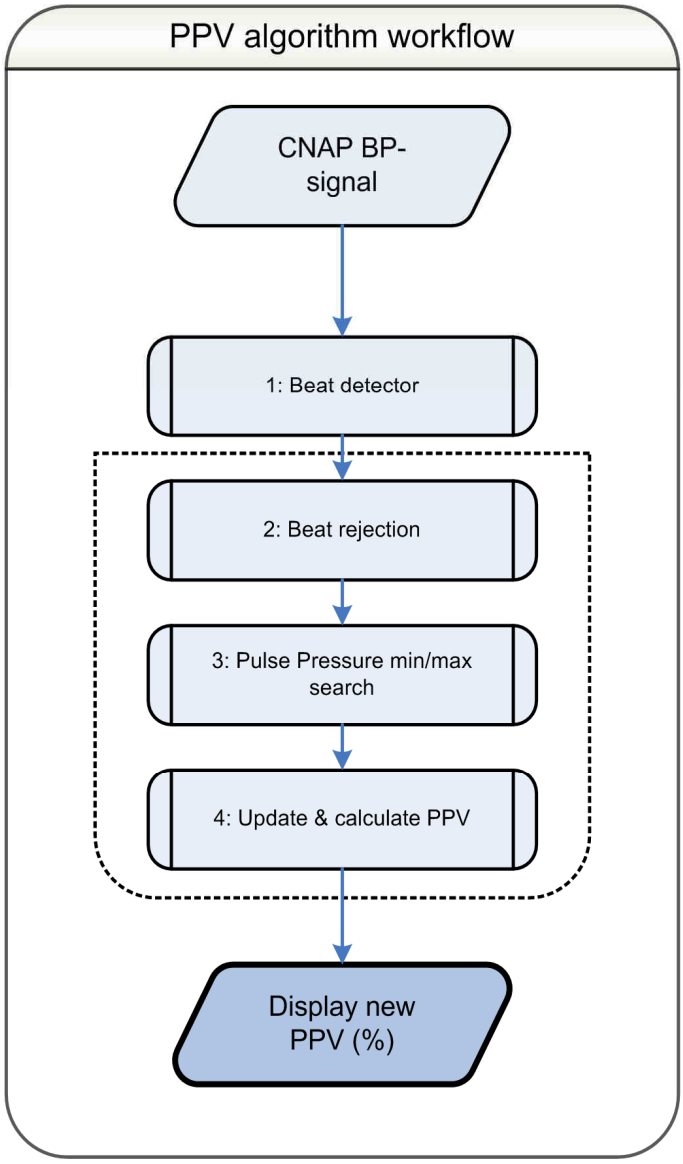


Figure 7.1 Flow chart of the automatical PPV algorithm developed by CNSystems.

PPV calculation and averaging: In the last step (step4) an averaging over the last detected 6 slopes values is computed. Additionally, an update filter with an adaptive coefficient to correct for abnormal strong physiological changes in PPV is applied. The final PPV value is displayed on the monitor, whereas only physiological possible values (PPV between 0.2 - 40%) are accepted. During calibration or technical alarms no PPV is displayed as well.

7.2 References associated with this thesis

Abstract A:

Title: Evaluation of a novel non–invasive Pulse Pressure Variation algorithm

@American Society of Anaesthesiologists (ASA 2011 Congress in CHICAGO, IL on October 15-19 2011), K.H. Smolle, M. Schmid; accepted for presentation

INTRODUCTION: One of the major goals in managing critically ill patients is the optimization of fluid management. In mechanically ventilated patients, dynamic markers like Pulse Pressure Variation (PPV) perform superior over static parameters in predicting preload responsiveness. Additionally, minimal & non-invasive methods are gaining greater importance due to a lower risk of complications. The goal of this study was to evaluate a recently developed non-invasive PPV-method in comparison to the manually calculated gold standard PPV (PPVman), as proposed by Michard (2).

METHODS: We studied 20 critically ill patients in the ICU, upon receipt of informed consent. All patients were mechanically ventilated with tidal volume >8ml/kg ideal body weight and received vasopressor therapy. A subgroup (n=10), include patients with cardiac arrhythmias was defined, to evaluate the problems with PPV-measurements. Blood pressure was continuously measured with an arterial catheter (IBP) as well as non-invasively with the CNAP-Monitor (CNSystems, Graz, Austria). Continuous non-invasive arterial blood pressure (CNAP) was applied on two fingers of the hand contra lateral to the invasive arterial blood pressure catheter in the A. radialis. Digitally recorded data was retrospectively pre-processed (artefact removal) and statistically analyzed. We compared manually determined PPV (PPVman) to automatically calculated PPV (PPVauto), obtained from the new CNAP-Monitor PPV-algorithm. For every patient 10 randomly chosen PPV-values were evaluated, resulting in 200 paired data points for this study.

RESULTS: Patients (n=10) without cardiac arrhythmias were analysed for the evaluation of PPVauto. For a total of 100 randomly assigned paired data points, difference (mean bias ± STD) between PPVman, CNAP and PPVauto,CNAP was 0.98%±1.99%. As seen in Table1 the difference between PPVman,IBP and PPVauto,CNAP was 2.26%±3.53%, stating an offset of the CNAP signal to the IBP signal. Values for additional 10 patients with arrhythmias are given in the right column of Table1.The difference between PPVman and PPVauto in this group was significantly higher.

CONCLUSION: Our study shows good agreement between PPVman and PPVauto and therefore, the non-invasive PPV-method is a valuable method for hemodynamic monitoring. Comparing the results to the PPV evaluation done by Cannesson(3):0.74%±3.4%, this new algorithm shows similar performance. The importance of the presence of a sinus rhythm has been confirmed. Further clinical studies have to be conducted to prove this non-invasive monitoring system as an accurate predictor of fluid responsiveness. Moreover, a threshold PPV-value to differentiate between responders and non-responders has to be declared for this device.

REFERENCES: (1) British Journal of Anesthesia 2010; 105 (3):264-72 (2) Anesthesiology 2005; 103: 419-28 (3) Anesthesia & Analgesia 2008; 106(4):1195

Table1: Differences between PPVman and PPVauto for calculated Pulse Pressure Variation (%) in 20 critically ill patients. Results presented as means ± standard deviation.

	without arrhythmias	with arrhythmias
	$PPV_{auto,CNAP}$	$PPV_{auto,CNAP}$
$PPV_{man,CNAP}$	0.98% ± 1.99%	2.34% ± 3.72%
$PPV_{man,IBP}$	2.26% ± 3.53%	1.13% ± 5.61%

American Society of Anesthesiologists

Abstract B:

Title: Evaluation of a continuous non–invasive arterial blood pressure monitoring device in comparison with an arterial blood pressure measurement in the ICU

@31st International Symposium on Intensive Care and Emergency Medicine (ISICEM Congress 21.3–25.3.2011 in Brussels), K.H. Smolle, M. Schmid; Poster presentation
http://ccforum.com/content/15/S1/P72

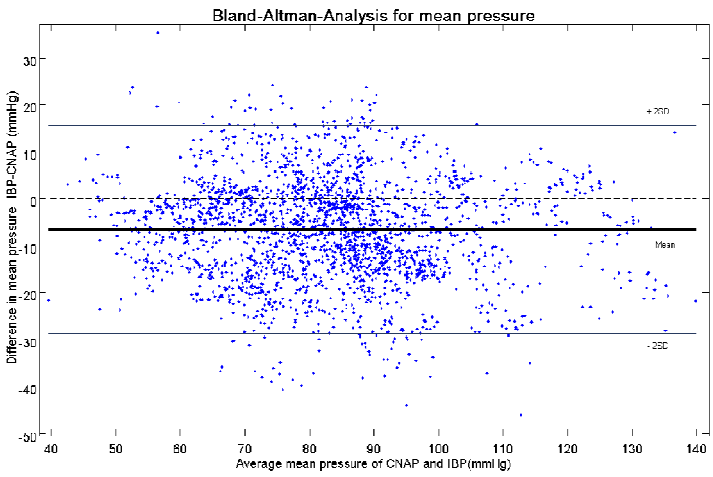
Introduction: Due to a lower risk of complications, non-invasive monitoring methods gain importance. Measuring arterial blood pressure belongs to the standard hemodynamic monitoring. A newly developed continuous non-invasive arterial blood pressure (CNAP) measurement method is available and has been validated perioperatively [1]. We compared the CNAP monitoring device with invasive arterial blood pressure measurement (IBP) as the gold standard in critically ill patients.

Methods: We performed a prospective study on 49 critically ill patients at a medical ICU. All patients were sedated and mechanically ventilated (BIPAP, tidal volume 7 to 8 ml/kg ideal body weight). Furthermore, all patients were under vasopressor therapy. CNAP was applied on two fingers of the hand contra lateral to the invasive arterial blood pressure catheter in the A. radialis. All measurements were digitally recorded with a sample frequency of 100 Hz, every pulse beat was automatically identified by an algorithm [2] and subsequently artefacts were removed from the datasets. The average recording time in each patient was 163 minutes (±37 minutes/patient).

Results: In total we analysed 500,000 beats. Overall we observed a bias in mean pressure of -7.49 mmHg with a standard deviation of 10.90 mmHg. The Bland-Altman plot (Figure (Figure1)1) showed a uniform distribution of the variances over all measured blood pressure values and a good agreement of the mean blood pressure between CNAP and IBP. When analysing the data of each individual patient, larger differences were found. The bias ranged from 0.28 to 23.9 mmHg (median = -6.6 mmHg), with a standard deviation between 2.0 and 14.9 mmHg (median = 5.8 mmHg).

Conclusions: In our study we detected a good overall agreement between CNAP and IBP. The future perspective of this study is to investigate whether the continuous non-invasive blood pressure waveform is suitable for deriving further hemodynamic parameters of fluid responsiveness.

References: Jeleazcov, Br J Anaesth. 2010. pp. 264–272. ; Zong, Comput Cardiol. 2003. pp. 259–262.



Abstract C:

Titel: Evaluierung eines kontinuierlichen nicht-invasiven arterialen Blutdruckmonitorings (CNAP) im Vergleich zur invasiven arteriellen Messung bei kritisch kranken internistischen Patienten

@ Kongreß der Deutschen Interdisziplinären Vereinigung für Intensivmedizin und Notfallmedizin(DIVI), HAMBURG, 01.–04.Dez. 2010), – K.H. Smolle, M. Schmid, H. Prettenthaler, H. Scharfetter ;Poster Präsentation

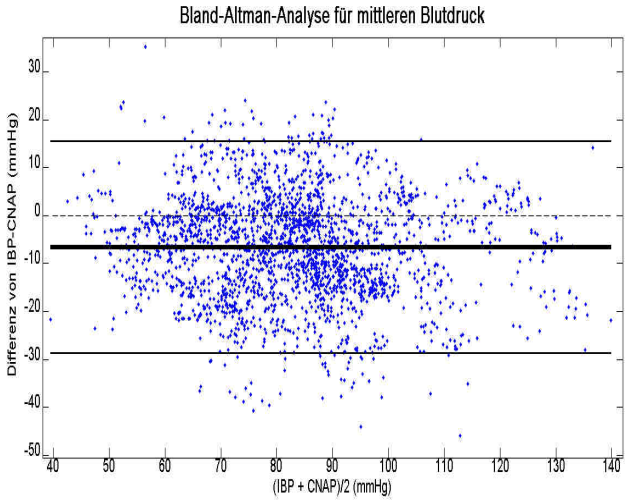
Einleitung: Nicht invasive oder semiinvasive Meßmethoden gewinnen in der Intensivmedizin auf Grund geringerer Komplikationsraten zunehmend an Bedeutung. Der arterielle Blutdruck (RRart) intermittierend oder kontinuierlich gemessen nimmt dabei eine ganz zentrale Stellung in der hämodynamischen Überwachung von Intensivpatienten ein. Eine neuentwickelte kontinuierliche nicht-invasive RRart Messung (CNAP, CNS Systems, Graz, Austria) steht nun zur Verfügung. Ziel unserer Untersuchung war es diese Methode (CNAP) mit dem Goldstandard der invasiven arteriellen RR-Messung (IBP) zu vergleichen.

Methode: 38 kritisch kranke Patienten (26 Männer, 12 Frauen) wurden in einer prospektiven Studie untersucht. Alle Patienten waren analgosediert, mechanisch beatmet (BIPAP, AZV 7-8 ml/kg/KG) und standen unter einer Vasopressorentherapie. CNAP wurden an den Fingern der kontralateralen Hand gegenüber der invasiven arteriellen Messung über die Art. radialis, gemessen. Alle Werte wurden im 1-Sekunden Intervall aufgezeichnet bei einer durchschnittlichen Messdauer von 159 Minuten (±30 Minuten)/Patient.

Resultate: Insgesamt wurden 256000 beats in die Auswertung einbezogen. Über allen beats wurde im Mitteldruck ein Bias von -7,4 mmHg mit einer Standardabweichung von 10,6 mmHg beobachtet. Der Bland Altman Plot zeigt eine Gleichverteilung der Abweichungen über alle gemessenen Blutdruckwerte und eine gute Übereinstimmung der mittleren Blutdruckwerte zwischen CNAP und IBP. Die Auswertung der einzelnen Patienten zeigte Unterschiede zwischen den Patienten. Der Betrag Bias lag in einem Range von 0,07 mmHg bis 23,1 mmHg (Median = 7,6 mmHg), die Standardabweichung zwischen 2,9 mmHg und 13,7 mmHg (Median = 5,9 mmHg).

Konklusion: Die Analyse der bisher eingeschlossenen Patienten zeigte im Mittel eine sehr gute Übereinstimmung zwischen CNAP und IBP. Bei der Auswertung der Einzelergebnisse von Patienten waren Abweichungen bis zu 23 mmHg feststellbar. Weitere Analysen sollten die Ursachen dieser Abweichungen aufzeigen.

Referenzen: Jeleazcov et al. Precision and accuracy of a new device (CNAP) for continuous non-invasive arterial blood pressure monitoring: assessment during general anesthesia. British Journal of Anesthesia 2010 vol. 105 (3) pp. 264-72; An Zong et al, Open-source Algorithm to Detect Onset of Arterial Blood Pressure Pulses



7.3 Clinical study protocol: shortened version

CLINICAL STUDY PROTOCOL
Version 1

Accuracy of continuous non-invasive arterial pressure monitor (CNAP™ Monitor) in critically ill patients

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Background

The accurate assessment and monitoring of arterial pressure is a key issue in the intensive care unit (ICU). The arterial pressure signal conveys valuable information concerning diagnosis, pathophysiology, prognosis and treatment of shock states. Restoring adequate mean arterial pressure is one of the main therapeutic goals in shock states. Blood pressure monitoring is done either intermittently using an oscillometric pressure device (NBP) or continuously by an arterial line (ABP). A number of clinical studies show that both methods come along with a number of shortcomings. Since the NBP provides discontinuous pressure readings - the Association for the Advancement of Medical Instrumentation (AAMI) standard is once every 3–5 min - haemodynamic events may be missed or noticed with delay. Furthermore, it is shown that a prolonged use of an NBP device may cause nerve and skin damage. On the other hand, the placement of an arterial catheter requires time and skill and is an invasive procedure that can include rare but serious complications. A number of studies report arterial related infections. The most common complications of invasive cannulation are artery occlusion (13% of cases), hematoma (12%), abnormal pulse (15%) and rarely blood loss due to unintended disconnection, infections, sensory disturbance, necrosis and fistulas. Particularly in ICU patients, where a long-term measurement of continuous blood pressure is often required, the arterial cannulation comes up with a high rate of complications. For a catheterization lasting ≥ 4 days in ICU patients, 57% of the patients developed thrombosis without vessel occlusion and 19% showed vessel obstructed by the thrombus. Bedford reported a 29% incidence of occlusion in cannulation lasting 4 to 10 days in ICU patients and the rate of radial artery thrombosis was 76%.

The maintenance of normotension is crucial in the ICU setting. A significant decrease in mean arterial pressure in the critically ill patient often signifies inadequate blood flow to vital tissue. Autoregulatory mechanisms in the vasculature of the brain and the kidney may fail because of this impaired oxygen delivery and the perfusion of these organs is then a direct function of the blood pressure. The surviving sepsis campaign recommends the mean arterial pressure to be constantly maintained at ≥ 65 mmHg. A number of studies stress the importance of reliable blood pressure monitoring in critically ill patients. Shoemaker et al. showed that critically ill patients who survive have a significantly higher mean arterial pressure than nonsurvivors during hospital stay. Diastolic arterial blood pressure has been shown to be a reliable early predictor of survival in human septic shock. Finally, providing the appropriate therapy within the hour of onset of hypotension is associated with clinical improvement and higher survival in shock states. A newly developed method for continuous non-invasive blood pressure (CNAP™; CNSystems Medizintechnik AG, Graz, Austria) provides beat-to-beat pressure readings and is risk-free. Especially in patients where hemodynamic instability has to be anticipated or the maintenance of norm tension is crucial, this device may be of great value. The primary aim of this study is to evaluate the accuracy of CNAP™ in the intensive care unit.

Study objectives

The aim of the study is to evaluate the accuracy of CNAP™ compared to simultaneous ABP measurement in critically ill patients. The beat-to-beat readings of CNAP™ and ABP will be automatically recorded electronically. Safety will be assessed by clinical observations as well as adverse events (AE) recording.

Study design: Prospective, open, single-center study with 1 group

Study materials

The technology evaluated in this study is the CNAP™ Pod for Dräger patient monitor, developed by CNSystems AG, Graz, Austria, and CE-certified as of 24/04/2008. The system performs non-invasive continuous blood pressure measurement and is used both in clinical and in ambulant settings. A finger cuff encompassing two neighbouring fingers is used for continuous blood pressure monitoring; an upper-arm cuff derives the measurement of oscillometric blood pressure. Thus, blood pressure is measured in two ways: on the one hand as absolute blood pressure values (oscillometric measurement) and on the other hand as continuous blood pressure changes (CNAP™ technology). The trend of the latter is automatically corrected towards the absolute values of the oscillometric device derived at the beginning of the measurement. Through novel electronic components, blood pressure is thus continuously monitored, typically without the need for interruptions.

Data acquisition

Blood pressure is monitored using one half of the CNAP™ finger cuff at any one time, changing to the other half every 30 minutes. Each change of finger is accompanied by an oscillometric measurement for calibration purposes.

The CNAP™ Pod and the ABP transducer are connected to a Dräger patient monitor where the data collecting software records all data synchronously and, after completion of data acquisition, allows the export of all measurements in a resolution of 1 value/second into a text file for further analysis. These data include the ABP as well as text markers specified by the physician and/or care giver (e.g. movement of patient, ABP flushing) to be considered during data analysis.

Risk assessment

All materials used in this study are CE-marked, are in accordance with medical products' law and are only used according to the specifications of the corresponding producer. The purpose of the CNAP™ device is the monitoring of continuous non-invasive blood pressure. Due to its completely non-invasive nature, there exists no risk of a serious adverse event or life-threatening complication caused by the device. No invasive measures are performed for reasons of this study; all invasive interventions are part of the standard therapy protocol and are performed on the patient regardless of whether he participates in the study or not. The study itself includes no therapeutic interventions. Therefore, the study can be regarded as a minimum-risk study.

Detailed study methodology

Screening and entry: Subjects who are potential candidates for the study and who meet the inclusion and exclusion criteria must sign and date a written informed consent form after a full explanation of the study has been given. To provide sufficient time for informed consent, patients will receive the study information form at least one day prior to data collection in the intensive care unit. After the subject has signed the informed consent, he/she will be assigned an available subject number for the study and will then be considered enrolled in the study. For those patients who are not conscious prior to data collection the consent will be requested after recovery. The investigator will assure that all subjects give both written and oral informed consent and that subjects' consent is documented in accordance with local laws.

Furthermore, the investigator should indicate in the medical records the subject's participation in the trial as well as provide the subject with a copy of his signed and dated informed consent.

Case report form

After a subject is identified that he matches the inclusion criteria, a case report form is filled out recording the following: Date and time of data recording, Patient ID, age, height and weight, Cardiovascular, rheumatic, vascular, peripheral diseases, History of arrhythmias

Data recording procedure

The following parts of the case report form are filled out in the course of data recording: Arm used for CNAP™ monitoring (left/right) and its peripheral perfusion (result of Allen's test);Arm used for ABP monitoring (left/right) and its peripheral perfusion (result of Allen's test);Recording of initial and subsequent oscillometric measurements: time and systolic/diastolic (mean) values. Times and durations of movement (e.g. changing the patient's position, moving the arm where blood pressure is monitored), of blood sampling, of ABP flushing and of other disturbances to be excluded from evaluation in the course of artefact rejection

Time and duration of time-markers is not included directly into electronic data-collection System (e.g. beginning and end of data recording). Since no difference between CNAP™ and ABP caused by ipsilateral versus contralateral measurement is assumed, the placement of both devices will be determined by clinical requirements or will be assigned randomly. 50 Patients will have CNAP™ and ABP placed ipsilaterally and 50 patients contra laterally. The arm to be used for blood pressure monitoring (left/right) is determined by the physician placing the radial arterial catheter. After completion of ABP placement, the CNAP™ finger cuff is mounted on fingers of the same or opposite hand and the CNAP™ upper-arm cuff on the ipsilateral to the finger cuff. CNAP™ and ABP will be measured synchronously for duration of at least 1 hour and at most 4 hours per patient, depending on the patient's availability and therapeutic requirements.

Statistics

All statistical analyses will be carried out using SPSS 16.0. Continuous variables will be presented as mean, standard deviation, median, range, while categorical variables will be presented as number and percentage. For all statistical tests a p-value of $p<0.05$ will be considered significant. The sample size of 100 patients is chosen based on the recognised standards from the Food and Drug Administration and the American National Standards Institute for evaluation of non-invasive blood pressure monitors. According to the AAMI SP10, a minimum of 15 subjects and 10 readings per subject should be reported for the proof of accuracy for non-invasive blood pressure devices.

Agreement between CNAP™ and ABP

The agreement between CNAP™ and ABP is calculated on the basis of systolic, diastolic and mean pressure readings. Descriptive statistics and Bland-Altman and correlation analysis will be performed.