Masterthesis

Investigating interactions between heart and lungs - correlation between heartrate variability and respiratory mechanics

submitted to

Vienna University of Technology

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by

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Vienna, January 2019

Declaration of Academic Honesty

I certify that the master thesis at hand is to the best of my knowledge and belief the result of my own investigations and is composed by myself unless stated otherwise in the text. All content derived from the work of others has been specifically acknowledged. Furthermore, I confirm that I have not submitted this master thesis either nationally or internationally in any form.
I point out that the present master thesis, as well as another master thesis of mine, which will be transmitted to the Medical University of Vienna, is part of a larger scientific research project. This project was submitted to the ethics committee of Viennas Medical University with the title "*Heart rate variability during conventional and variable pressure support mechanical ventilation: a cross-over study*". While the master thesis for the Technical University of Vienna concentrates on the development of a suitable algorithm to determine the frequency domains of heart rate variability under strongly varying respiratory frequency, the master thesis submitted to the Medical University of Vienna will focus on the clinical relevance of variable pressure support ventilation and the influence on patients outcome.

Maximilian Schnetzinger, BSc

Abstract

Recent research demonstrates that about a third of all postoperative complications are due to cardiovascular reasons, and in addition, more than every second postoperative death is attributed to major cardiovascular events. Increasing evidence indicates that the compromised autonomic nervous system (ANS) shows a strong correlation with adverse cardiovascular events. With the intention to reduce perioperative risk for patients, assessment of ANS activity might be used as a risk indicator. It has been proposed that - additionally to other factors - mechanical positive pressure ventilation may cause stress to the ANS. A possible method to observe the ANS activity is heart rate variability (HRV) analysis. In this study, we investigate the influence of two ventilation modes on HRV. To be more specific, we apply classical pressure support ventilation with positive endexpiratory pressure levels and the novel variable pressure supported ventilation (VPS), which varies the pressure support with each breath in a pre-set range. The 15 included patients were ventilated for 1 hour both ways and the resulting parameters of HRV and clinical parameters, such as blood oxygen saturation, blood pH level and other physiological parameters, were assessed and compared.

Results show no significant differences of HRV parameters between both groups. Also the variability of applied tidal volumes is not influenced significantly by the VPS. Concluding it can be said, that with this study we were not able to detect any relevant advantage of VPS regarding heart rate variability and further research will be necessary to show any significances. This may be started with another clinical trial, which only investigates the impact of variable pressure support on applied tidal volumes, which could be performed in study design, which is easier to perform.

Kurzfassung

Aktuelle Studien belegen, dass etwa ein Drittel aller postoperativen Komplikationen auf Störungen des Herzkreislauf-Systems und mehr als jeder Zweite postoperative Todesfall auf schwerwiegende Herzkreislauf-Ereignisse zurückzuführen ist. Evidenzbasierte Untersuchungen deuten darauf hin, dass ein komprimiertes autonomes Nervensystem (ANS) eine starke Korellation mit unerwünschten kardiovaskulären Ereignissen hat. Eine Messung der ANS-Aktivität könnte als Risikoindikator angesehen werden, um das perioperative Patientenrisiko zu senken. Es wurde in Betracht gezogen, mechanische Überdruck-Beatmung zusätzlich zu anderen Faktoren als Stressor für das ANS anzuerkennen. Eine Möglichkeit das ANS zu messen, ist die Bestimmung der Herzratenvariabilität (HRV). In dieser Studie untersuchen wir die Auswirkung zweier Beatmungsmethoden auf die HRV. Genauer gesagt, wenden wir klassische druckkontrollierte Beatmung mit positivem endexpiratorischem Atemwegsdruck und die neue Beatmungsmethode Variable druckunterstützende Beatmung (VPS), bei welcher die applizierte Druckunterstützung mit jedem Atemzug in einem vorher eingestelten Bereich variiert, an. Die 15 in die Studie eingeschlossenen Patienten wurden jeweils 1 Stunde mit beiden Beatmungsmethoden beatmet und die resultierenden Parameter der HRV und klinische Parameter wie arterielle Sauerstoffsättigung, der pH Wert des Blutes, so wie andere physiologische Parameter wurden gemessen und verglichen.

Die Ergebnisse zeigen keine signifikanten Unterschiede der HRV Parameter zwischen den beiden Gruppen. Auch die Variabilität des Tidalvolumens wird durch die variable Druckunterstützung nicht signifikant beeinflusst. Zusammenfassend kann gesagt werden, dass wir mit dieser Studie nicht in der Lage waren einen relevanten Vorteil der VPS betreffend Herzratenvariabilität zu zeigen und dass weitere Forschungsarbeit notwendig sein wird um signifikante Unterschiede zu zeigen. Dies könnte durch eine einfacher aufgebaute Folgestudie begonnen werden, die ausschließlich die Auswirkung der variablen Druckunterstützung auf die applizierten Tidalvolumina.

Contents

List of Abbrieviations

AKH	Vienna General Hospital
ASB	Assisted Spontaneous Breathing
ATI	Alveolar Type I
ATII	Alveolar Type II
ANS	Autonomous Nervous System
AKH	General Hospital of Vienna
ASB	Assisted Spontaneous Breathing
BGA	Blood Gas Analysis
CNS	Central Nervous System
CO_2	Carbon Dioxide
ECG	Electro Cardiogram
HF	High Frequency Components of Heart Rate Variability
HiP-HiV	High Airway Pressure - High Tidal Volume
HiP-LoV	High Airway Pressure - Low Tidal Volume
HMV	Heart Minute Volume
HR	Heart Rate
HRV	Heart Rate Variability
ICU	Intensive Care Unit
LF	Low Frequency Components of Heart Rate Variability
LoP-HiV	Low Airway Pressure - High Tidal Volume
MAP	Mean Arterial Pressure
$MAwP$	Mean Airway Pressure
NN	Normal-to-Normal
O_2	Oxygen
pCO_2	Carbon Dioxide Partial Pressure
P_{aw}	Airway Pressure
PEEP	Positive Endexpiratory Pressure
P_{L}	Transpulmonary-Pressure
P_{max}	Maximum Airway Pressure

PNS	Parasympathetic Nervous System
P_{supp}	Upper Pressure-Level
Press.var.	Pressure Variability
PIP	Maximum Inspiratory Pressure
PSD	Power Spectral Density
$RMSSD$	Root of Mean Squared Differences of Successive Normal-to-Normal Intervals
RF	Respiratory Frequency
RR	Beat-to-Beat
$SDNN$	Standard Derivation from Normal-to-Normal
SNS	Sympathetic Nervous System
sO_2	Arterial Bloods Oxygen Saturation
SPN-CPAP/PS	Spontaneous-Continous Positive Airway Pressure/Pressure Support
SpO_2	Arterial Oxygen Saturation
TP	Total Power
ULF	Ultra Low Frequency Components of Heart Rate Variability
VALI	Ventilator Associated Lung Injury
VILI	Ventilator Induced Lung Injury
VAP	Ventilator Associated Pneumonia
Variable PS	Variable Pressure Support Ventilation
VIP	Ventilator Induced Pneumonia
VLF	Very Low Frequency Components of Heart Rate Variability
VPS	Variable Pressure Support Ventilation
VREACT	Vital-signs REal-time Analysis for Clinical Translation
v_{T}	Tidal Volume

1. Introduction

Recent research demonstrates that 33% of postoperative complications due to cardiovascular reasons, and further, over 50% of postoperative deaths are attributed to major cardiovascular events [1]. Critical patients are often ventilated postoperatively and will stay at Intensive Care Units (ICUs) for a longer time period. However, the independent role of mechanical ventilation on those cardiovascular effects largely remains unknown.

Importantly, classical mechanical ventilation differs significantly from physiological breathing. In contrast to negative pressure ventilation during normal breathing, the positive pressure mechanical ventilation mechanics may lead to volu-, baro- and atelectotrauma, which cause shear stress and strain in the lung tissue [2]. Furthermore, lung inflammation results in lung biotrauma and processes further regional lung and remote organ injury [3]. These mechanisms, including mechanical and non-mechanical harm to the lungs, have been identified to cause ventilator-induced lung injury (VILI) [4].

There are known cardiorespiratory interactions during physiological breathing, which are significantly impaired during mechanical ventilation [5, 6]. While breathing, changes of intrathoracic pressure and lung volume induce changes in ventricular pre- and afterload. To maintain cardiac output and tissue perfusion, there is a regulatory reaction of the autonomic nervous system (ANS), which leads to alteration of the ventricular afterload, heart contractility, and heart rate (HR) [7]. Furthermore, HR can be described as a regulatory mechanism, which responds to external stimuli due to the human hearts efferent innervation by vagal and sympathetic nerve fibers. Therefore, resulting fluctuations of HR, better known as heart rate variability (HRV) [8, 9] are seen as an indicator of a healthy heart and ANS with regulatory ability. Positive pressure mechanical ventilation induces a significantly different modulation of the described physiologic parameters as compared to physiologic breathing [5, 6, 7, 9]. Thus, mechanical ventilation is assumed to be stressful for the cardiovascular system as compared to physiological breathing. Therefore, it is crucial to monitor and analyze the cardiovascular homeostasis and clinical outcome during

specific types of mechanical ventilation.
It has already been proved that ANS dysfunction may complicate the perioperative handling of patients undergoing anesthesia, increase perioperative morbidity and mortality, and in general may worsen clinical outcome of critically ill patients [10]. HRV has also been shown to be an important predictor of mortality in coronary care units [11]. Thayer and Lane recently found that low HRV is associated with an increasing mortality and proposed to use low HRV as a marker for critical illness [12, 13, 14, 15, 16]. Therefore, the investigation of HRV parameters in clinical settings have become more important over the last years.
Recently, a new ventilation mode called Variable Pressure Supported Ventilation (Variable PS), also known as noisy pressure supported ventilation, has been introduced to the market [17]. This novel ventilation mode is largely similar to conventional spontaneous continuous positive airway pressure support ventilation (SPN-CPAP/PS), however, it differs in application of pressure support. The underlying rationale is to support the patients with mechanical ventilation mimicking the physiologic situation, with typically varying tidal volume, v_{T}, by variable pressure support and thus improved cardiorespiratory state.
Studies show that there is an improvement of oxygenation through redistribution of pulmonary blood flow from dependent to independent zones without lung recruitment and a reduction of venous admixture through Variable PS [18]. Furthermore, slightly reduced hyperaerated areas at both end of expiration and end of inspiration compared with conventional pressure support ventilation (SPN-CPAP/PS) can be shown [19]. A significantly higher comfort of breathing, assessed by the Aachen Breathing Comfort score, lower levels of carbon dioxide partial pressure, pCO_2, total lung and gas volumes respiratory drive, and pressure time product have been demonstrated for Variable PS [18]. It has been shown that those parameters all lead to a better clinical outcome of the critically ill ICU patient.
Although potentially of major clinical importance, the impact of Variable PS on the vitally important HRV – as mentioned before a major cardiac and autonomic measure – during mechanical ventilation has not been investigated yet. We hypothesize that a variability of pressure assistance will lead to a variability of v_{T}, which in turn leads to a higher variability of intrathoraxic pressure. This would lead to a higher HRV (schematic illustration see Figure 1.0.1). Therefore, in this study, we will, for the first time, analyse the beneficial effect of Variable PS compared to the standard SPN-CPAP/PS during mechanical ventilation in ICU patients with the aim to better control postoperative adverse cardiac events (e.g. acute myocardial

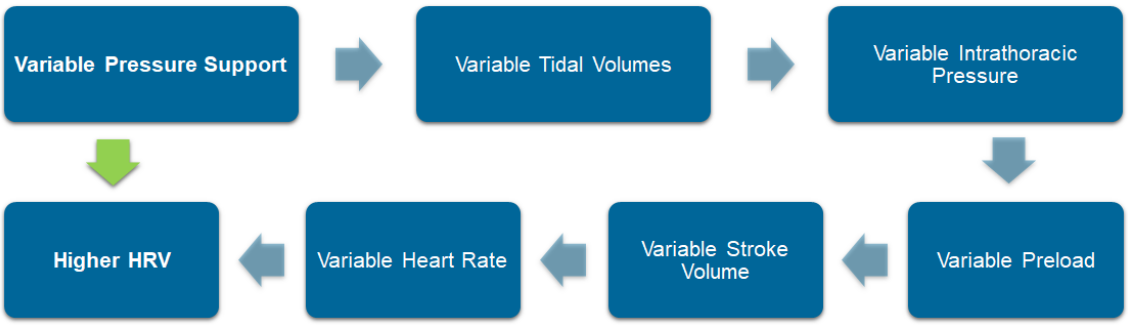


Fig. 1.0.1.: The drawing should give a schematic overview of the hypothesis of this study: by variation of pressure support, v_T should also vary more widely. As this leads to a higher fluctuation of intrathoracic pressure levels and therefore a variable preload, it might furthermore lead to higher variation of heart rate and therefore artificially gain HRV.

infarction or coronary syndrome and intermittent atrial fibrillation) in the future.

Aim of this Work

Since mechanical ventilation and ventilator induced lung injury is not only a very intensively discussed topic in today's intensive care medicine and anaesthesiology but also a relevant topic of daily routine in these disciplines, we wanted to create a cross-link to the HRV of ventilated patients. Since the new ventilation mode Variable Pressure Support Ventilation (VPS) should imitate a more physiologic breathing of the patient, we think that this difference must be measurable in terms of HRV. Furthermore, we hypothesize a higher variability of heart rate due to the promised higher variability of tidal volumes applied to the patient by the manufacturers.
ECG-, respirator- and blood gas analysis-data was therefore recorded in a group of intensive care unit patients. These patients had different reasons for staying at an intensive care (from lung-transplant- to polytrauma patient) but were all breathing spontaneously with pressure support and were free of any heart diseases (see section 3.2).

2. Theoretical Background

2.1. Intensive Care Unit Patients

The following section should give an idea of an intensive care unit patient to non physicians. Since these patients are critically ill and often have lots of comorbidities, they need technically extensive treatment and care. Some of the necessary treatments put the patients at risk to suffer from new injuries and diseases.
Risks and complications of mechanically ventilated patients occur mostly due to two facts:

- There is a tremendous difference between physiological (underpressure) breathing and mechanical (overpressure) ventilation for the lung tissue (further details see subsection 2.2.2).
- Especially in case of ventilation through a endotracheal tubus, the natural defense mechanism (provided by the mucociliar clearance) for most pathogens is circumvent.

These technically simple modifications are enough to cause different types of injuries, which are described on the following pages.

Ventilator associated/induced lung injury

Since mechanical ventilation differs essentially from physiological breathing, there are lots of complications, which may happen to mechanical ventilated patients. These complications are summarized with the expressions ventilator associated/induced lung injury (VALI/VILI). In both cases, non-physiological transpulmonary-pressure, P_{L}, leads to damage of the tissue. The biggest difference between physiological breathing and mechanical ventilation is the inversed transpulmonal pressure. This pressure inversion ends in an imbalance between stress and strain of the lung parenchym. The increase of tissue stress and strain may lead to baro-, volu- and atelecttrauma, which may each result in biotrauma.

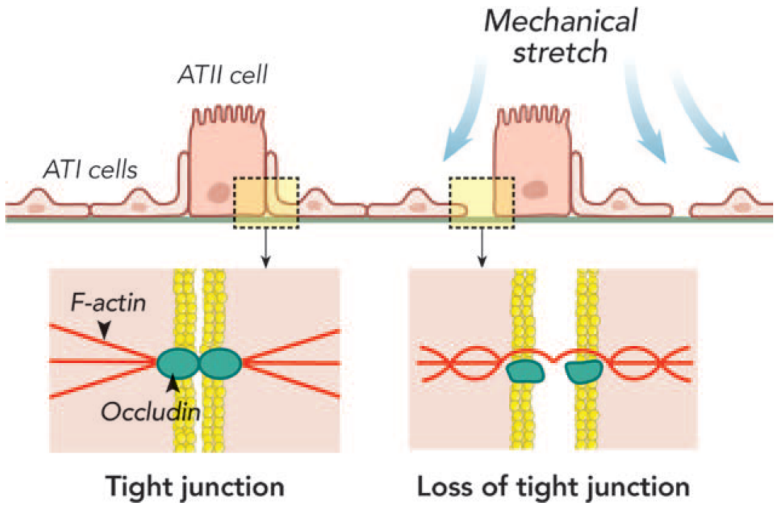
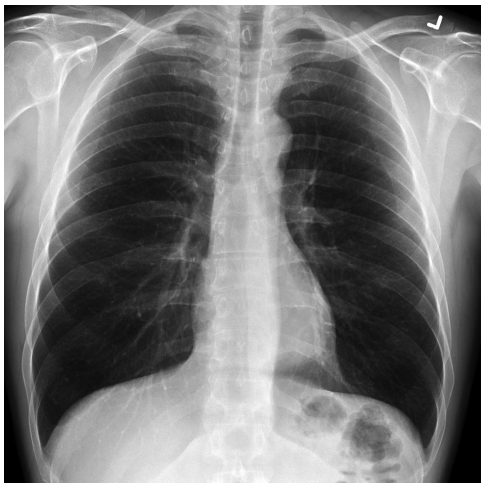


Fig. 2.1.1.: Alveolar type I (ATI) and alveolar type II (ATII) epithelial cells are connected through so called *tight junctions*. Mechanical stretch leads to the loss of epithelial integrity these cells. In this way substances at both sides of this biological barrier are enabled to cross that barricade and to cause damage to the lung tissue. Image taken from [22].

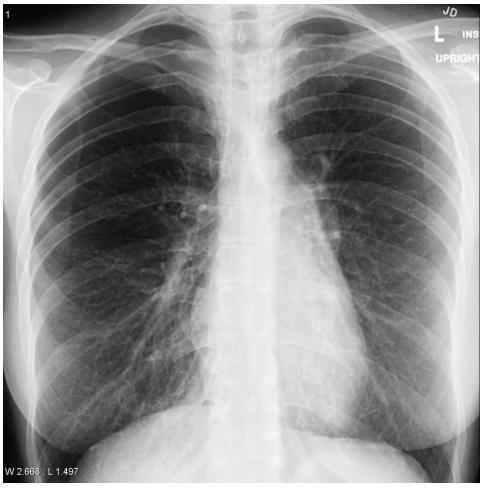
Baro- and volutrauma

Even though barotrauma was recognized as a first possible complication of mechanical ventilation recognized more than 250 years ago [20], it is currently believed that injuries corresponding to high v_T are of higher importance than those induced by the airway pressure factor [21].

Dreyfuss et al. [25] performed an experiment, which proves that not a high airway-pressure, P_{aw}, itself leads to trauma of the lung tissue but the transpulmonary-pressure does. In his experiment, he subjected three groups of healthy rats to different methods of mechanical ventilation. One group to high P_{aw} and high v_T (HiP-HiV), one to high P_{aw} and low v_T (HiP-LoV) by immobilization of chest and abdominal cave and one group to low P_{aw} and high v_T (LoP-HiV). As a result of this study, the groups of rats, which were subjected to higher v_T, had significant lungs edema, whereas the HiP-LoV-group did not differ from the control group. This indicates, that the amount of lung parenchym trauma depends on the difference of P_{aw} and the pleural pressure and therefore on the v_T but not only on P_{aw} itself. Barotrauma itself can be understood as a loss of tight junctions mediated attachment between cells, which is further associated with a decreased quality of the peripheral transmembrane protein occludin band and F-actin perturbations [26] as illustrated in Figure 2.1.1. Due to loss of the epithelial integrity, certain blood, tissue, and



(a) Image taken from [23]



(b) Image taken from [24]

Fig. 2.1.2.: The radiographs compare a anterior-posterior view of physiological lung tissue (a) with an image of a patients lung, who suffers from barotrauma (b). The lungs structures are lightened, since they absorb x-ray to a higher degree due to inflammatory and emphysematous processes.

air constituents can cross this essential environmental barricade, which leads to inflammatory response processes and shift of fluids to interstitial space.

Biotrauma

Ventilator induced lung injury is not only the result of the mechanism of mechanical damage of lung tissue but also of the release of mediators, which induce inflammatory processes. This process is termed biotrauma [26]. Even without disconnecting pneumocytes or loss of connection via tight junctions, a release of proinflammtory cytokines, local recruitment of leucocytes, and initiation of inflammation processes can be observed. In addition to this, attention has been focused on so called *mechanotransduction theories* [27]. The term refers to intracellular messenger pathways, which respond to applied external forces. By exerting critical stretch to the cell, these messenger systems are influenced and inflammation processes start.

Atelecttrauma

If patients are intubated, their lungs would collapse if no positive endexpiratory pressure (PEEP) was set at the ventilator. This is a result of the missing function of closing the airway at the end of expiration. To prevent the repeated derecruitment of alveoli PEEP is applied. PEEP should not be too high in order to avoid the inflation of the tissue. If lung tissue collapses and is reopened by another breath, this leads to

traverse shear forces, which may be strong enough to damage the airway epithelium. These forces furthermore lead to critical stress of the pulmonary capillaries, cause surfactant dysfunction, and would lead to beginning inflammatory processes at the end.

Ventilator associated pneumonia

A natural barrier for nosocomial infections is formed by the airways anatomy. Inhaled air is filtered by ciliated epithelium of the mucous membrane - this specialized tissue is called *respiratory epithelium*. This surface tissue furthermore contains goblet cells and glands, which produce mucus, which helps to bind and carry the pathogens away. The respiratory epithelium has sections, which are rich in blood vessels. They heat the inhaled air and are the position, where immunologic cells can leave the blood vessel and invade the epithelium. [28] The circumvention of this barrier is a major reason for ventilator associated pneumonia (VAP). Other factors that increase the risk of infection are obviously due to worse immunologic constitution of critically ill patients or any other circumstance that has negative impact on this self-cleaning-property of the lungs tissue (underlying diseases such as cystic fibrosis or others).

2.2. Mechanical Pressure Support Ventilation

With the intention to understand the effects of mechanical pressure support ventilation, a brief overview of the respiratory tract architecture as well as the physiological breathing process will be given in this section. This part will be followed by an introduction of the basics of mechanical ventilation and a brief introduction to its effects on the patient.

2.2.1. Physiological respiration

Since hypoxia leads to irreversible brain damage after about 3 minutes [29], it becomes obvious that oxygen, O_2, delivery and therefore breathing is the most important task of a human's body next to circulation of blood. Nevertheless, it also has to be mentioned that the delivery and elimination of carbon dioxide, CO_2, via the lungs is not less important than the uptake of O_2 since any accumulation of this waste product would lead to a disturbance of the necessary homoeostasis.
To understand the main goals of mechanical ventilation, it is necessary to brielfy summarize the physiological breathing, gas exchange, and gas delivery process.

The respiratory anatomy

This chapter should give a brief overview of the respiratory section in terms of anatomy and histology. The interested reader will find further information in [30, 31].
The respiratory system is be roughly subdivided into the following components:

- **Structures necessary for the respiratory movement**
  A breathing cycle consists of an inspiration- and an expiration-period. While expiration is a passive process (forced expiration is the only active kind of expiration), muscles are necessary for inspiration. The diaphragm and chest muscles contract, which leads to an increase of the thoracic volume. The lung is connected to the thoracic wall, which is formed by the rips, via the pleural space. This space is a very thin fluid filled chamber between the visceral and the thoracic pleura, which provides an almost frictionless gliding of the lung in the thorax during movement and, due to the missing of air in this space, the lung will stick on thorax and follow its movement, which results in a strain of the lung in case of inspiration.

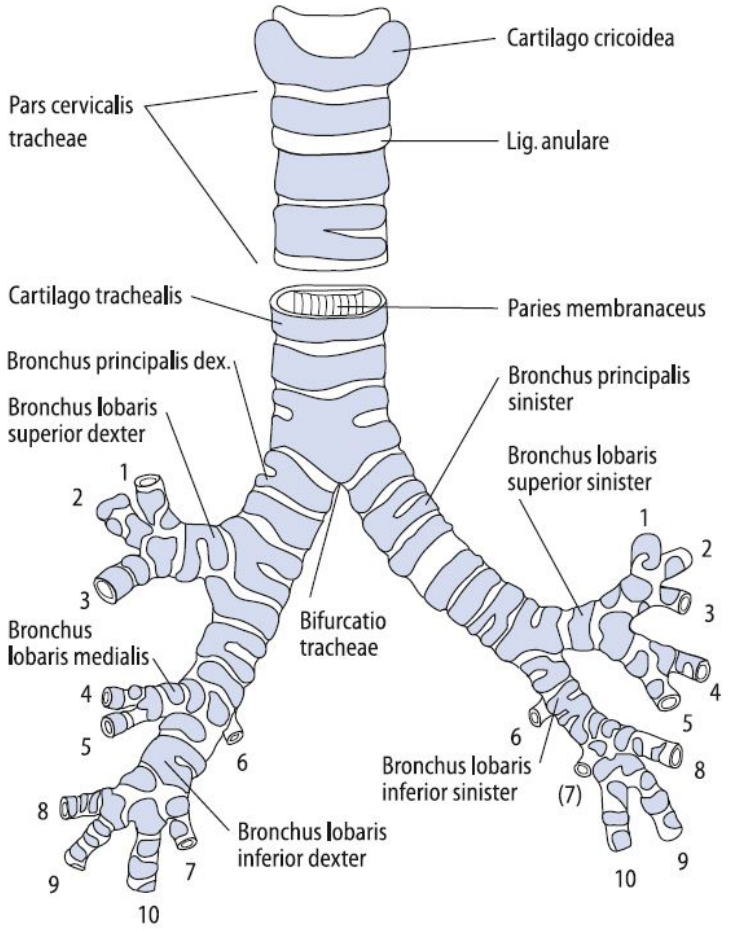


Fig. 2.2.1.: The bronchial tree starts at the subglottic part of the airconducting system. The *pars cervicalis trachea* is built by cricoid cartillage. A first subdivision can be seen at the *bifurcatio tracheae*. From that point on the bronchial tree spreads into a left and right *bronchus principalis*, which again spread into *bronchi segmentalis*. Image taken from [32]

- **Air conducting structures**

  The airway system can be subdivided into the upper and the lower airways. The upper airway system starts at the border between surrounding world and the body, which is the cavity of the mouth or nose, reaches down the pharynx, which is the cave behind the tongue and ends at the epiglottis, as a part of the larynx. This is the point where trachea and oesophagus starts. We find the glottis, which contains the vocal chords right under the epiglottis. Apart from conducting air to the trachea, the upper airways also work as a humidifier and warmer of the inspired air.

  The lower airways (see Figure 2.2.1) start at the vocal chords (as part of the

Ramifications	Structure
0	trachea
1	bronchus principalis
2	bronchus lobaris
3	bronchus segmentalis
4	bronchus subsegmentalis
9-13	bronchiolus
15-17	bronchiolus terminalis
18-21	bronchiolus respiratorius
21-25	ductus alveolaris, sacculus alveolaris

Table 2.1.: Ramifications of the bronchial tree

larynx). The trachea, which has a diameter of 1.5 cm to 2.5 cm, conducts air for about 10 cm up to 12 cm, then the *bifurcatio* is reached - this is the point where the trachea splits into a left and a right primary or main bronchus also called *bronchus principalis*. These main bronchi further subdivide into the *bronchus lobaris* (or secondary) and the *bronchus segmentalis* and *subsegmentalis* (or tertiary). The main, secondary, and tertiary bronchi consist of cartilage, connective tissue, contain lots of seromucoid glands, and are surrounded by smooth muscles. These glands together with the respiratory ciliated epithelium provide a self cleaning function of the lower airways, as the secretion binds particles and is transported outwards via the ciliated epithelium. When the cartilageous structures vanish, we speak of bronchioli. They only have a diameter of about 1mm but still consist of ciliated epithelium and inherit so called mucoid goblet glands. Furthermore, they consist of neuroepithelial bodies, which are chemoreceptors to measure the composition of the breathing gas.

- **Gas exchange structures (see Figure 2.2.2)**
  As soon as the bronchiolis wall has vanished, one alveoli is next to each other. This is the breaking point between the air conducting- and the gas exchange part of the respiratory system. While the ducti still show smooth muscles surrounding them, these muscles are vanished at the sacculi. The alveoles have a diameter between 200 μm and 300 μm. Due to their polyedric structure a maximum of gas exchange surface is reached. These septa separating the alveoles are between 5 μm to 15 μm thick, contain nerve fibres, blood- and lymphatic vessels. These septa build up the so called *blood-air-barrier*, which

is the location of gas exchange.

2.2.2. Physiological- vs. Mechanical Assisted Breathing

Almost any problem occuring during mechanical ventilation arises from the differences to physiological breathing. Indeed, there are lots of noteworthy differences, in this chapter the most relevant ones are discussed.

Underpressure- vs. overpressure ventilation

One of the most important differences is the inversion of pressure between physiological breathing, where the air is soaked into the thorax by underpressure, wand mechanical ventilation, where lung is inflated with overpressure. It is obvious that this pressure inversion leads to a tremendous changing of forces acting within the lungs parenchyme. It is necessary to keep the acting forces as low as possible and therefore to balance the needed air intake or inspiratory volume with the pressure that acts on the lung (see subsection 2.2.3). Too high pressure peaks will lead to an overinflation of alveoli which will lead to barotrauma as discribed in section 2.1.

Airway-modifications

Allthough ICU patients can also be mechanically ventilated through a mask, which has to be sealed airtight to the patients nose and mouth, most of them are ventilated through an endotracheal tube. This kind of airway management circumvents some natural barriers:

- Under physiological circumstances, the vocal chords work as a clasp. Since the function of this closing mechanism is circumvent by the endotracheal tube, which passes them, the function of it is also disabled. This, in turn, would lead to a collapse of the lung (further information see section 2.1). To prevent this, a positive endexpiratory pressure (PEEP) level has to be set.

- As discribed in section 2.2.1, the intrapulmonal epithelium has a self-cleaning and immunologic function. Since a tube also circumvents this at least partly, pathogenic material is able to enter the lung and settle there. This is one reason why especially long term intubation increases the risk of pneumonia (or

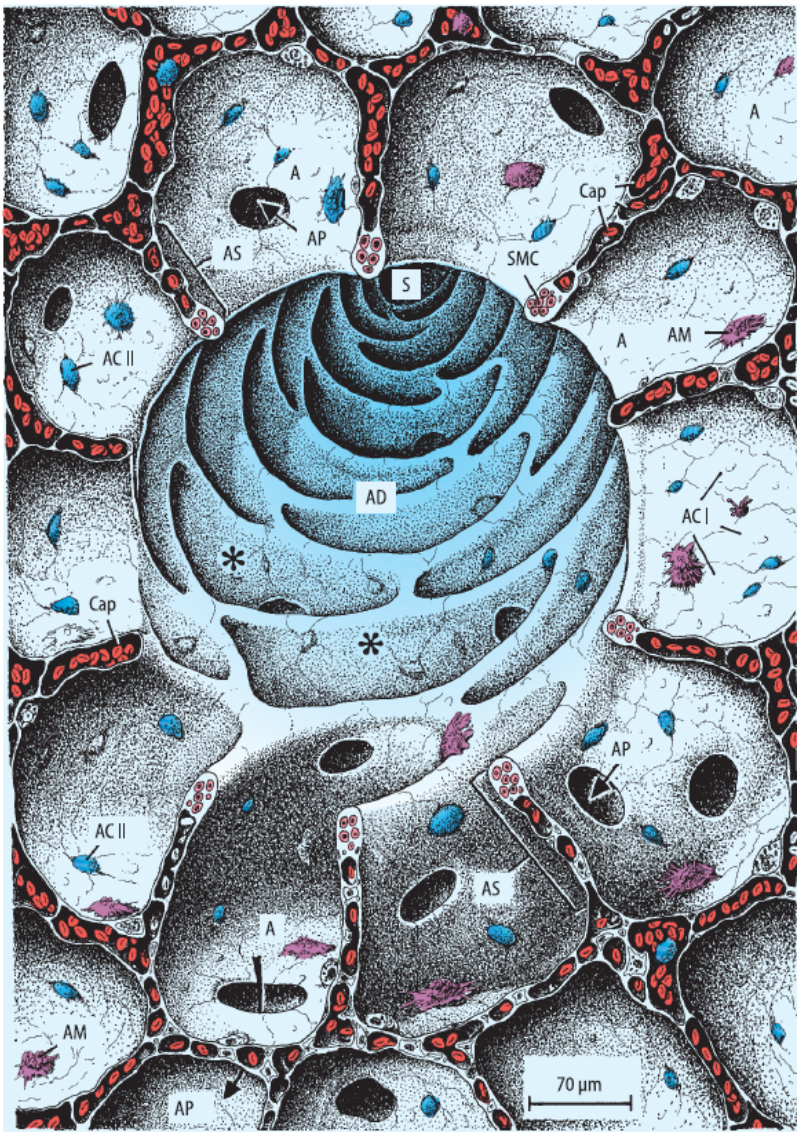


Fig. 2.2.2.: Showing a *ductus alveolaris* (AD), which ends in a *sacculus alveolaris* (S) in the back. * shows the opening of an *alveole* (A). *Alveolar septum* (AS), *smooth muscle cells* (SMC), *capillaries* (Cap), *alveolar macrophages* (AM) for immuno defence; *Pores* (P) connect the alveoles for a more homogenous ventilation. *Pneumocytes type 1* (ACI) build the main inner surface, *pneumocytes type II* (ACII) lie inbetween them and are crucial for surfactant production - a surface-active substance which is crucial to keep the alveols open especially during expiration, otherwise they would stick together, which in turn generate shear forces. Image taken from [30].

ventilator induced pneumonia (VIP)), which may cause serious complications and may even lead to death of an ICU patient.

- Another common issue of long term intubation is tissue damage of the trachea due to the balloon (also called *cuff*), which holds the tube in the right position. This cuff is under pressure and therefore also exerts pressure on the epithelium of the trachea. This leads to a local change of perfusion and may lead to necrosis of the trachea, which makes further operative interventions, such as the implantation of a tracheostoma, necessary.

2.2.3. Pressure- vs. volume-controlled ventilation

Studies have compared pressure- to volume-controlled ventilation regarding the risk of ventilator induced lung injury. The results seem to indicate that there is no general answer to be given to the question, which mode should be preferred. The favoured ventilation mode highly depends on the patients problems. This becomes obvious if we compare a patient who suffers from pulmonary fibrosis to another who suffers from a penetrating trauma of a lung lobe. In the first case of a pulmonary fibrosis, a disease which reduces the lungs elasticity and therefore its compliance to ventilation, it might be more helpful to choose a volume controlled ventilation mode and to check the patient for ventilator associated lung injury in the sense of a daily routine. In the second case of a penetrating trauma of a lung lobe, volume will also escape to the thorax cavity. Since this volume would not be involved in gas exchange, pressure controlled ventilation might be more suitable in this case. Indeed, there is no general recommendation regarding the ventilation mode [33].

2.2.4. Assisted Spontaneous Breathing

Between taking full control over a patient's ventilation and a patient, who is able to sufficiently breathe on his own, there is intermediate condition, in which a certain assistance is needed to breathe sufficiently, although the patient is fit enough to do some of the breathing-work on his/her own. This can happen, when *weaning* a patient from the respirator. Let us assume that a patient is ventilated over a period of four weeks due to critical illness. Let us further assume, the patient had to be in deep sedation during this time - this would make intubation and therefore ventilation necessary. During this recovering time of four weeks, the patient will loose muscles strength, since he does not use them - therefore she/he will also lose

muscle strength for breathing. This is one example where assisted spontaneous breathing (ASB) modes come to use. To gain muscle power, the assistance will be reduced over some days or even weeks until the patient will be able to do all of the needed breathing-work sufficiently.

2.2.5. Conventional and Variable-Pressure Support Ventilation

The ventilation methods applied in this clinical trial are the conventionally used *Spontaneous-Continuous Positive Airway Pressure/Pressure Support* (SPN-CPAP/PS) and an advanced setting of this mode called *Variation of Pressure Support in a Randomized Fashion* (Variable PS).
SPN-CPAP/PS is basically an assisted spontaneous breathing ventilation mode as discribed in subsection 2.2.4.

2.3. Heart Rate Variability

Since the main outcome parameter of this study is related to heart rate variability a general overview of this term is given in the following section. After describing some basics of heart anatomy and its working principle, a brief description of the nervous system and the crosslinks between heart and nervous system will be presented. Furthermore, basics of ECG and the calculation principles of HRV will be introduced.

2.3.1. Physiological Background

To capture the term of heart rate variability (HRV) a brief look at the relevant anatomical and physiological aspects of the human heart as well as at the nervous system has to be taken.

Hearts Anatomy and Function

The human heart can be divided into a right and a left half, which are both divided into an atrium and a ventricle. The left half of the heart pumps a blood poor in oxygen content through the lung, with a pressure from about 0 mmHg to about 25 mmHg, whereas the left half of the heart pumps the oxygenated blood with a maximum pressure of about 120 mmHg.

The primal electrical impulse generator for contraction of the atrial chamber and the ventricle is called sinus node and located in the area of the right atrial chamber. This node works in an autonomous way. The electrical impulses are propagated to the left atrial chamber and the ventricles through a complex network of nerve fibres. The propagation of the electrical impulse to the myocard muscle leads to a coordinated contraction - blood is pumped through the lung- and the body-circle.

The nervous system

Almost every body function is initiated and controlled by electrical impulses delivered by nervous fibres. The human nervous system can be separated into the central (CNS) and the peripheral nervous system. The CNS consists of the brain and the fibres, which build the spinal chord. Everything else is part of the peripheral system. Furthermore, we have to distinguish between afferent fibres, which transfer peripheral information to the CNS from efferent fibres, which in turn transmit central commands to e.g. muscle fibres or organs. In addition, the nervous system is

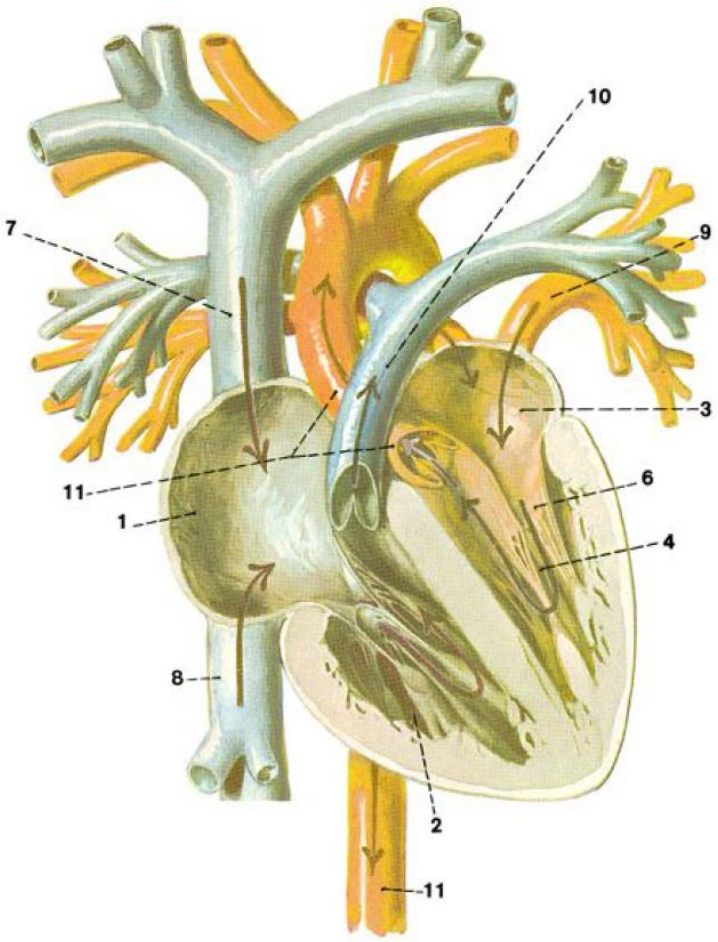


Fig. 2.3.1.: Blood poor in oxygen flows into the heart through the *vena cava superior* (7) and the *vena cava inferior* (8) and enters the right atrium (1). It is then pumped by the right ventricle (2) through the *truncus pulmonalis* (10) into the lung, where it is enriched with oxygen and carbondioxide is emitted to the air. Blood is then transported back to the left atrium (3) by the *venea pulmonalis* (9). It is pumped through the *valva mitralis* into the left ventricle (4). From there it is powerfully pumped into the *aorta* (11). Image taken from [34]

separated into the somatic and the autonomic nervous system (ANS). The somatic system is under voluntary influence - e.g. movement of limbs - whereas the ANS is not voluntarily controllable and inherits functions like renal hormon production, digesting and so on.
Since heart rate is not under voluntary influence in general, this work is focused on the autonomic nervous system regulation. All ANS functions can be discribed using two antagonists: The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Both systems are crucial for regulating and maintaining the homeostasis. This is for instance done by setting peripheral vessels resistance, as well as hearts minute volume (HMV), and in- or decreasing glandal activity. While the SNS is responsible for every initiated function, which is necessary for the known "fight or flight" functions, the PNS regulates the "rest and digest" parts. The most outstanding parasympathetic nerve is the vagus nerve, which is actually the 10^{th} cranial nerve, which springs from the myelencephalon and innervates more structures than any other nerve (this was eponymously, since the latin word *vagare* has the meaning of "roaming"). Most organs are actually innervated sympathetic as well as parasympathetic.

Interaction of cardiovascular and nerval regulation

There are lots of interaction points of the cardiovascular and the nervous system - in this section only examples will be discussed, the interested reader finds further details in [35].
All interactions work with any kind of feedback-mechanism.For better understanding, the *baroreflex* will be described in detail, since this is one feedback mechanism, which plays a crucial role in heart rate variability and respiration. To maintain homoeostasis is one of the main goals of any feedback regulating mechanism. The goal of the baroreflex is to maintain a certain bloodpressure level. A continuous blood pressure level is important to guarantee proper organ perfusion, since nutrients need to be delivered and waste products or produced messengers a.s.o. have to be removed from the organ. Baroreceptors are placed at certain points on the vascular system (e.g. in the aortic arch and the carotid sinus). Between the media and the adventitia layer of these vessels afferent nerve fibres are located, which are excited depending on of the mechanical strain on the vessel. The frequency of the nervous impulses depends on the absolute strain but also the temporal change - it can be seen as a proportional-differential behaviour. Thus, all crucial cardiac infor-

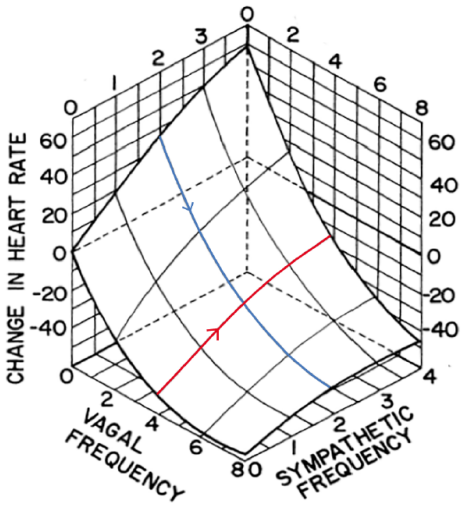


Fig. 2.3.2.: Effect of sympathetic and the parasympathetic nervous system on the heart rate. Image adapted from [36]

mation (e.g. frequence, mean pressure, stroke volume and -power) are measured by these receptors. On one hand the barereceptors inhibit sympathetic fibres while on the other stimulating vagal fibres. Therefore, a higher activation of baroreceptros through higher blood pressure would lead to stronger inhibition of sympathetic fibres and on the other hand rise vagal activity, which in turn leads to downregulation of heart frequency, inotropy, and the tone of peripheral resistance vessels.
Obviously, every fluctuation of blood pressure leads to a fluctuation of heart rate. Therefore, every breathing manoeuvre, which changes the thoracic volume and therefore the intrathoracic vessels blood pressure, leads to rythmic changes of heart rate. This mechanism will be discussed later in more detail.

Dependence of heart rate on the autonomous nervous system

As discribed in the section above, the heart frequency depends on the impulses generated by the sinus node. This pacemaker is under autonomous nervous system influence. Since body stress as well as phsycological stress affects the SNS and processes like digesting influences the vagal tone, all these factors also influence heart rate and therefore its variability (see Figure 2.3.2).

The role of the parasympathetic tone in critically ill or perioperative patients

Wenkebach was the first to find out that there is a crosslink between the variability of heart rate and the ANS [37].

Since there is hardly any body function which is not influenced by the PNS, it would go beyond the scope of this work to list every single benefit of a higher parasympathetic tone. However, studies show a correlation between a healthy ANS and the overall clinical outcome of a patient, which implies ICU-staying-days, morbidity, 30-days mortality a.s.o. [10, 38].

Electro Cardiogram

The following section gives a systematic overview of the basics of the electro cardiogram (ECG). The very interested reader finds further information in [39].
The ECG is one of the most important tools of clinical routine monitoring in anaesthesia and intensive care patients. It enables physicians to draw their conclusions about a patient's heart conduction system. The signal is detected via electrodes, which are positioned on the patient's body surface. Between these electrodes, a potential difference can be measured, which is influenced by the electrical activities of the heart. Any electrical impulse, which is propagated by the nerve fibres, will change the electrical dipole between two electrodes. These changes in space and time axis are captured on the patients monitor.
As shown in Figure 2.3.3, physiological ECG shows a certain pattern of ups and downs. These are alphabetically named P-wave, Q-spike, R-peak, S-peak, and T-wave. Each of these has a corresponding activity of the cycle of the heart.
The P-wave detects the activation of both (left and right) atrial chambers, which is naturally followed by a subsequent contraction of them. The PQ-interval is the phase of the heart cylce, when both atria are maximally excited and no further charge is distributed - this phase is essential in order to fill the chambers with blood and is enabled by the atrio-ventricular node. The QRS-complex corresponds to the excitation of the ventricles and therefore with the pump function of the heart, since this is the part of the heart cycle, where blood is distributed to the lung- and the body-circle. Taking a closer look at this complex shows that the Q-spike represents the signal propagation through the Bundle of His, whereas the R and the S-peak correspond to the actual chamber contraction. The T-wave displays the repolarisation of the chambers, which is crucial for them to be excitable again.

The actual acquisition of data is done by placing electrodes in a certain manner as shown in 2.3.5a and 2.3.5b. Since the captured signal is a potential difference between two electrodes, the waveform depends on the exact positioning of the elec-

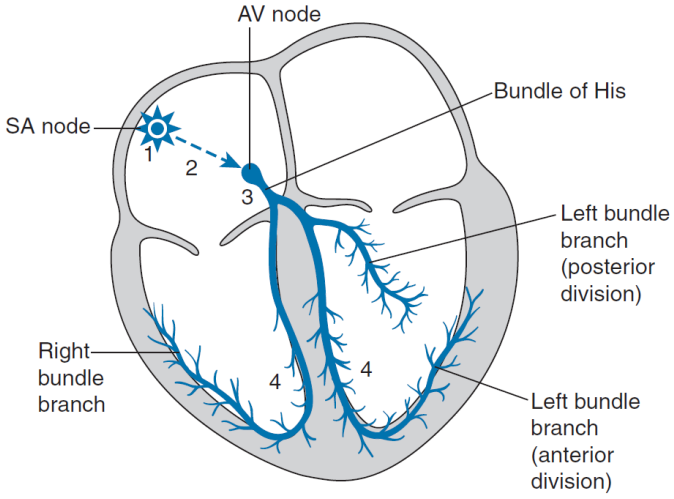


Fig. 2.3.3.: Illustrating a humans heart conduction pathways. Image taken from [39]

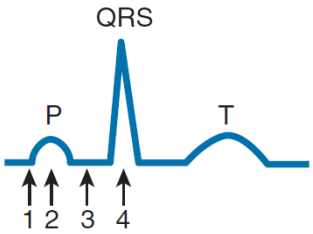
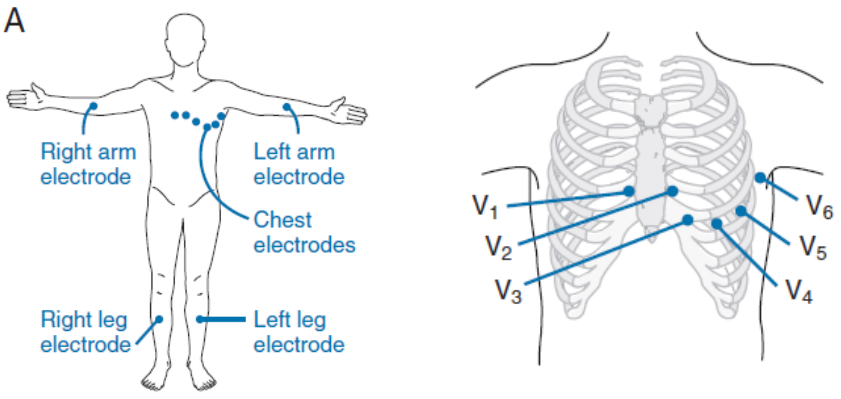


Fig. 2.3.4.: (1) begin of the impulse at the sinus node; (2) electrical impulse traverses the atrial chambers; (3) conduction through the Bundle of His; (4) ventricles excited. Image taken from [39]



(a) (b)

Fig. 2.3.5.: Electrode placement of ECG-electrodes on limbs for Einthoven and Goldberger derivations (a) and for chest wall derivations (V_1-V_6) for Wilson derivation (b). Images taken from [39]

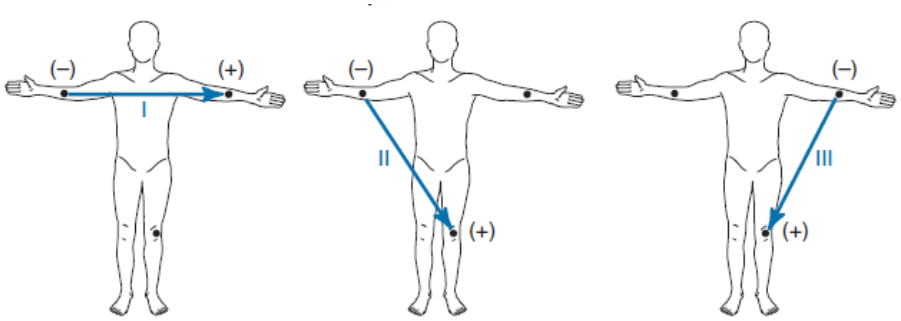


Fig. 2.3.6.: Explanation of Einthovens ECG, which are also called *limb leads*: lead I is the vector from the right to the left arm; leads II direction is from the right arm to the left leg; lead III points from the left arm to the left leg. Image taken from [39]

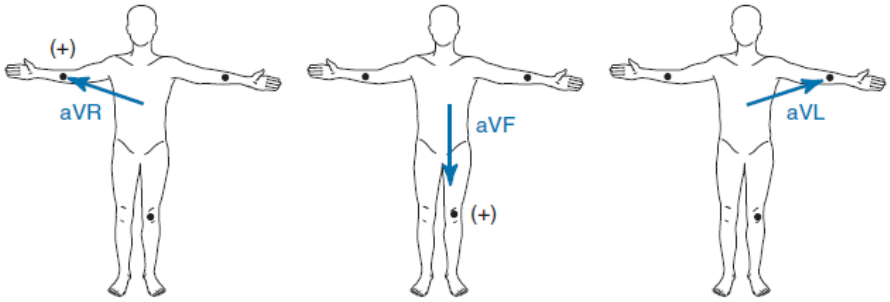


Fig. 2.3.7.: Goldberger derivations are also known as *augmented limb leads*. Derived from the same leads as the Einthoven triangle, they use *Goldbergs central terminal* as the negative pole. Image taken from [39]

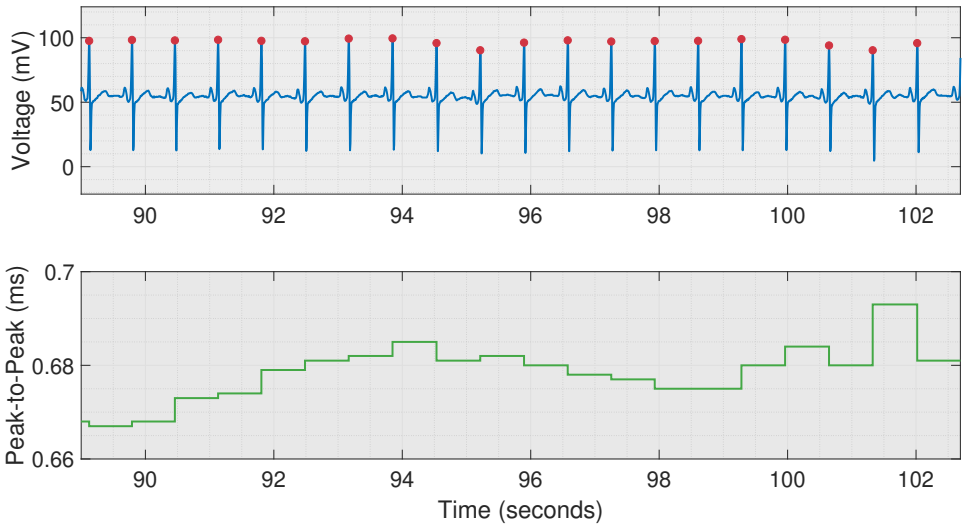
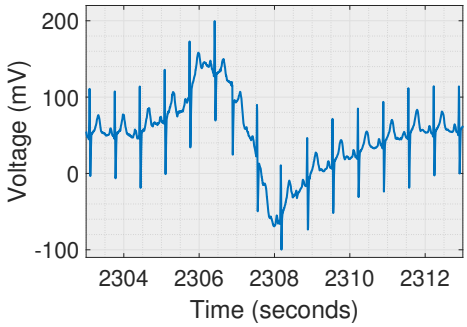


Fig. 2.3.8.: The graph shows an artefact free ECG, as one would see it using the MATLAB code for signal processing: the red dots are generated by the automatic R-peak detection. The green graph shows the corresponding time between two R-peaks, also known as *interbeat interval*. All HRV parameters are calculated from this peak-to-peak time.

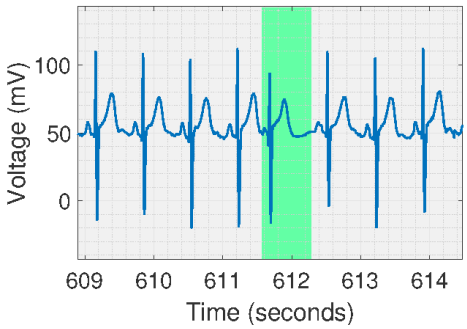
trodes. In clinical routine the 12-lead derivation usually gives information about all electrical activity of the patient's heart in a horizontal plane and with electrodes placed on arms and legs in a vertical plane. While Einthoven derivations (I-III) measure the potential difference between two limbs (as seen in Figure 2.3.6), the Goldberger derivations (aV_F, aV_L, aV_R) measure the potential difference between an electrode and the middle of the other two remaining electrodes. To further improve ECGs qualities as a diagnostic tool, the Wilson derivations can be measured with 6 additional electrodes as seen in 2.3.5b - this mode is used especially in diagnosing and screening cardiac diseases.

2.3.2. Artefact Signals

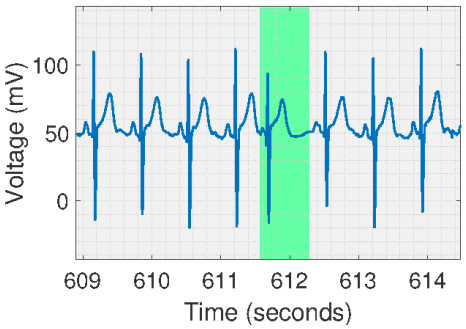
An ECG lead as shown in Figure 2.3.4 is only theoretically possible, not even a perfect ECG would look like that. A very artefact free ECG signal is shown in Figure 2.3.8. Indeed not every recorded ECG looks like that over the whole measurement period, which may be traced back to different artefacts. The most important ones are described in Figure 2.3.9.



(a) The captured deflection of the ECG baseline is related to movement of the patient. Depending on the movement pattern these parts of the ECG sometimes had to be excluded from HRV analysis, since an accurate detection of R-peaks is no more possible.



(b) This ECG shows a supraventricular extrasystole (marked green). In opposite to a ventricular extrasystole as shown in (c) one can see an atrial excitation (P-wave) prior to the ventricular excitation.



(c) The green marked non sinus-rhythm is a ventricular extrasystole. There is no P-wave prior to the chamber-excitement.

Fig. 2.3.9.: The ECGs above show the most frequent occuring signal abnormalities of the patients included in this study: movement artefacts (a) and increased rate of supraventricular (b) or ventricular (c) extrasystoles.

2.3.3. Cardiac Fitness

The meaning of *cardiac fitness* strongly depends on the context. In any case, cardiac fitness could be understood as the capability of the heart or the cardiovascular system to respond to external stimuli or any circulatory challange (e.g. increase of heart minute volume). The higher the degree of possible reaction, the better and the healthier. Certainly we think about intensive care unit patients, which are mostly severly ill and have lots of comorbidities and not about top athletes, but the definition of cardiac fitness is the same, only the challenge of the heart is different. Higher cardiac fitness is associated with a high HRV [40]. To give more concrete examples, studies demonstrated that the parasympathetic tone is higher in trained than in untrained participants [41, 42]. Especially endurance workouts increase the parasysmpathetic tone in rest and therefore may contribute to a lower mortality [43].

2.3.4. Time- and Frequency-Domains of Heart Rate Variability

The following subsection gives a brief overview of time- and frequency domains of HRV and is based on [8]. The interested reader finds further information there.

Heart Rate

The basic variable to determine the HRV is the heart rate (HR), which describes the interval between two consecutive heartbeats as seen in Figure 2.3.8. It can be calculated by dividing 60 by the beat-to-beat (RR) interval in seconds. This interval can also be determinded by other methods than ECG (e.g. arterial blood pressure monitoring), but measuring the distance from one R-peak to the following one is most precise. HR is heavily influenced by respiration patterns (known as physiological sinus arythmia), by autonomous- and central nervous system (CNS) respectively, and by very slowly changing processes like those regulated by hormones etc.

Heart Rate Variability

In physiological ECG a variability of the beat-to-beat-interval-duration can be measured. HRV indicates the ability of a patient's cardiovascular system to react to external stimuli. Consequently, a lack of HRV indicates a missing ability of cardiovascular responseability. This correlation was first observed in 1914 by Wenkebach,

who found out that a patient with higher HRV has a healthier heart than another patient with a lower HRV [37]. In 1978 Wolf et al. found out that HRV is suitable as an important marker for the clinical outcome of patients of heart intensive-care-units. In the 1980s HRV was first aknowledged as an important clinical marker, since a relation of morbidity and myocardial infarct has been proved [13]. These findings were followed by several studies, which were able to demonstrate a significant correlation between HRV, certain heart diseases, and the overall autonomic health [15, 10, 44].

Linear time domain analysis

The most basic measures of HRV are calculated by either measuring the distance between two conscetive normal-to-normal (NN) R-peaks or the alteration of the difference between following NN-intervals.

- ***SDNN***: The standard deviation from normal-to-normal measures the variance of HRV in ms. It reflects oscillations of all frequences.

- ***RMSSD***: The root of mean squared differences of successive NN intervals, which is also measured in ms and reflects high frequency oscillations, which are related to the autonomous nervous system parasympathetic activites.

- ***pNN50***: The number of successive interval differences, which have a higher than 50 ms difference divided by the total number of intervals in %. This measure also rather reflects higher frequency components.

Non-linear time domain analysis

The non-linear time domain measures allow us to make quantifications about the unpredictability of a time series. The following list refers to [45] and briefly describes describe the most important measures briefly:

- ***SD1***: The standard deviation in the Pointcaré plot perpendicular to the line of identity. It is a measure for the beat to beat variability. It is identical to the linear RMSSD measure. In this work, we will therefore refer to the RMSSD.

- ***SD2***: The standard deviation in the Pointcaré plot along to the line of identity. It is a measure for the long-term beat to beat interval variability.

- ***SD12***: The calculated quotient of SD1 and SD2. It is a measure for the unpredictability of the beat to beat time series. It is correlated with the LF-HF-Ratio (see Frequency domain analysis below).

Frequency domain analysis

Frequency domain measures are of far higher complexity than time domain measures. To carry through this analysis, a Fast-Fourier-Transformation has to be done at first. In a second step, a power spectral density (PSD) plot is created to determine the power of a certain frequence within the signal. It is measured in ms^2. In this master thesis, the following frequency domains were used:

- **HF**: The high frequency components are in a range from 0.15 Hz to 0.4 Hz. They represent the parasympathetic components of the ANS.
- **LF**: The low frequency components are in a range from 0.04 Hz to 0.15 Hz and represent the sympathetic activity of ANS.
- **LF-HF-Ratio**: Is an often discussed measure and represents the sympatho-vagal-balance. If that is suitable or not, is part of ongoing discussions.
- **VLF**: The very low frequency components in a range from 0.003 Hz to 0.04 Hz
- **ULF**: The ultra low frequency components in a range below 0.003 Hz represent - together with VLF-components - processes which are influenced by e.g. hormones.
- **TP**: The total power sums up the power of all components up to a frequency of 0.4 Hz and can be understood as a overall-ANS-measure.

3. Methods

The following chapter is intended to describe the way of acquiring the data which lead to the results of this thesis. This is separated in blocks: the first block is about the recording of data, whereas the second block is about the analysis of biosignals.

3.1. Measurement of Heart Rate Variability

In a joint study of the Medical University of Vienna and the Vienna University of Technology, all the data for this master thesis were recorded. This clinical trial was carried out at intensive care units (9D, 13B1, 13B2) of the "Vienna General Hospital" (AKH). The measurements were done between 4 and 7 p.m. in order to guarantee the same conditions regarding the day-night-rythm, which is controlled by the ANS, among all patients. The recording, bedside-work, and analysing was carried out by the author of this thesis. The ethics committee of the Medical University of Vienna agreed to the execution of this clinical trial (EK Nr. 1827/2017).

3.2. Study Population

To perform the present study, an overall population of $N = 52$ patients was determined according to the inclusion criteria which were submitted to the ethics committee before starting recruiting patients. A sample size calculation was carried out. Basis for this sample size calculation were preliminary data for the primary endpoint, the high frequency components (HF) of heart rate variability. We assume a mean HF of about $49\,\mathrm{ms}^2$ for the conventional mode of mechanical ventilation. An increase of an average $10\,\mathrm{ms}^2$ (to $59\,\mathrm{ms}^2$) for the variable pressure support mechanical ventilation was assumed. For sample size calculation, the standard deviation of the difference was set to $25\,\mathrm{ms}^2$. When the sample size is 52, a one-sample t-test with a 0.05 two-sided significance level will have 80 % power to detect the assumed effect. Empirical knowledge of eventual intervention-related drop-out of patients from the

Number of patients	14
male	9
female	5
Age	$61 \pm 12,7$
BMI	$23,9 \pm 15,7$
Procedure Site	
Pulmonology	5
General surgery	4
Vascular surgery	1
Inflammatory	2
Trauma	2

Table 3.1.: Epidemiology of included patients. Not all patients were analysed regarding their HRV, but secondary outcome parameters were evaluated either (for further information see chapter 4).

study leads to a sample size of $N = 60$ patients (drop outs due to technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest, and cardiopulmonary reanimation).
The study includes subjects between 18-80 years undergoing therapy at an anesthesiological ICU (ICUs: 9D, 13B1, 13C2). No absent sinus rhythm and no active implanted pacemaker or defibrillator is allowed.

Inclusion criteria

- patients undergoing therapy at an ICU
- patients aged between 18 and 80 years
- patients intubated and ventilated on SPN-CPAP/PS mode
- patients with sinus rhythm in ECG

Exclusion criteria

- patients aged under 18 or over 80 years
- patients with active heart pacemaker/defibrillator
- patients with absent sinus rhythm in ECG
- patients with severe autonomous nervous system disease
- women, who are already known to be pregnant before taking part in this study

However, due to technical reasons a problem in the observation of the main outcome parameter (high frequency components of HRV) emerged - that there was not even a trend of influence on the HF components between the two treatments. Therefore, the study was stopped after 15 patients. The 15 patients were used for an exploratory analysis. After validating the recorded ECG and calculating the peak to peak intervals, a few more patients were excluded due to impossible HRV-patterns, which may be traced back to arrhythmic events. Finally, only 7 patients could be analysed with respect to HRV. Nevertheless, all other observed physiologic and respiratory parameters of all 15 patients could be analysed.

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3.3. Protocol

Individuals were recruited at three ICUs of the general hospital in Vienna. These ICUs were chosen to receive a software update for their in daily clinical use respirators (*Evita Infinity V500*). The respirators were already able to perform the ventilation mode SPN-CPAP/PS (for further information see subsection 3.4.1). After installation of the mentioned software update, they were also able to perform variable pressure support ventilation as an advanced setting of assisted spontaneous breathing (SPN-CPAP/PS), which will be described in detail in subsection 3.4.2. The ICUs were regularly screened for patients which were includable according to the inclusion criteria listed in the section above. After recruiting the patient, contact to the on-duty doctor and the nursing staff which is responsible for this patient, was established. After coordination with the attendants (e.g. necessary rearrangement of the patient, planned medicinal therapy), the randomisation of the treatment order was performed with a suitable tool ("*Randomizer*") made available by the Medical University of Vienna. The patient was only included if no bolus-therapy was necessary within the whole measurement period. Patients received all drugs with a perfusor at equal rate during the measurement. In addition rearrangement of the patient's body position, which in long term is necessary to prevent pressure points, was not carried out by the nursing staff during the measurement. Furthermore, protocol steps are found in the section Measurement Setup below.

3.4. Measurement Setup

The measurement-procedure of every single patient was started by connecting the respirator (*Evita Infinity V500* by Dräger) and the patient's monitor (*Delta Inifinity Monitor* by Dräger) via ethernet, which automatically transmitted all respirator data to the monitor interface. All monitor data of the patient were automatically streamed via the Infinity Gateway by Dräger to the Dräger network. This was followed by starting the recording of all data with *VREACT* (*Vital-signs REal-time Analysis for Clinical Translation*) [46]. A stopwatch was started simultaneously with the click on the "*Record*"-button in order to set a time scale for the later following processing of the biosignals. Depending on the patients randomisation, the ventilator mode was set to "*Variable-PS*" or stayed unchanged on "*SPN-CPAP/PS*" - the time of the stopwatch was noted if the ventilators mode was changed. After 5 minutes of the first ventilation-phase (VPS or SPN-CPAP/PS), 10 millilitres of arterial blood were won through the arterial catheter, at the same time ventilator and physiological parameters were noted according to the consent form (see chapter A). Before switching the ventilator mode after 60 minutes, a second blood gas analysis (BGA) was carried out and the above mentioned parameters were recorded again. These steps were repeated during the second ventilation period, which started after 60 minutes - for higher accuracy of the signal analysis the current time of the stopwatch was noted again.
After finishing the second ventilation period, the ventilator was reset to its default setting. The recording in *VREACT* was stopped and finally the respirator and patients monitor were disconnected.
To prevent the loss of any relevant patient data, possibly important for further processing, the patients data were removed from the stations computer and kept safe.

3.4.1. Spontaneous-Continous Positive Airway Pressure/Pressure Support

One of the used ventilation modes is called "*Spontaneous-Continuous Positive Airway Pressure/Pressure Support*" (further referred to as SPN-CPAP/PS or abbreviated as SPN). This mode can be seen as a reference ventilation mode for patients, who need assistance while breathing spontaneously [32]. This mode is commonly used at ICUs world wide especially within the weaning-process. This mode can

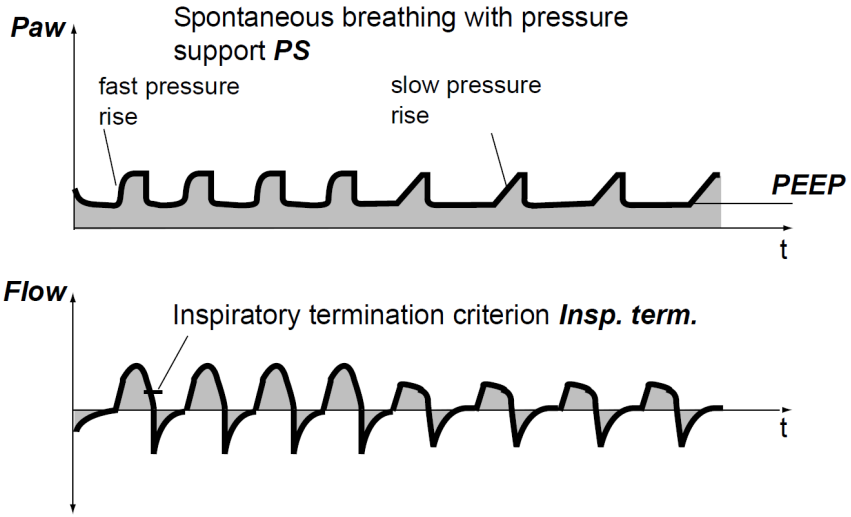

Fig. 3.4.1.: If the patients breathing effort is sufficient, a preset pressure support will be applied by the ventilator in order to facilitate the breathing effort of the patient. Image taken from [47].

be used for intubated patients but could also be applied through a mask, which has to be fixed air sealed to the patient's face. In this thesis, only intubated or patients with a tracheostoma were recorded. Each inspiratory effort of the patient herself/himself, which meets the trigger-criteria - a preset inspiratory flow, which has to be produced by the patient - will lead to a pressure support by the ventilator. The amount of this support has to be set by the physician, usually by setting a maximum inspiratory pressure and the volume, which has to be shifted per minute (so called *minute volume*). Like in all other pressure-controlled ventilation-modes, the tidal volume depends on the difference of the upper pressure-level P_{supp} and the set positive endexpiratory pressure (PEEP). The time needed for the pressure increase is set by the parameter *ramp* - a higher ramp would lead to a higher mechanical stress of lung tissue, whereas a lower ramp will lead to a higher quotient of inspiratory to expiratory time. The pressure support will be stopped as soon as the patients inspiratory flow is smaller than the maximum inspiratory flow or if the support-time becomes bigger than the maximum inspiratory time. Nevertheless, a default PEEP will prevent a collapse of lung structure, which would occur naturally due to the missing valve function of the anatomical structures, which are bypassed with the endotracheal tube.

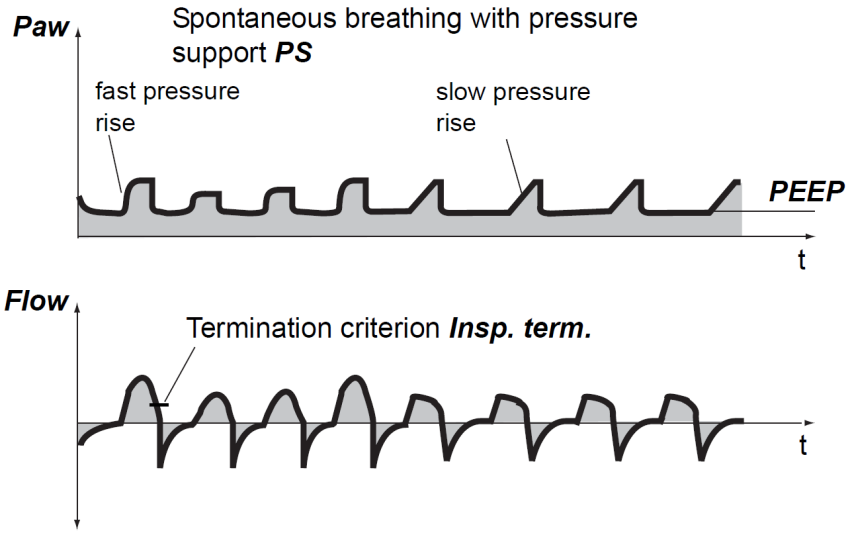

Fig. 3.4.2.: Variable PS works on the same basis as SPN-CPAP/PS but differs the with every breath applied pressure support within a preset range, without exceeding the maximum pressure or falling below the PEEP level. Image taken from [47].

3.4.2. Variable Pressure Support

This mode is an advanced setting of the SPN-CPAP/PS ventilation mode, which is at the moment only obtainable by Dräger. It is only a software modification only and can be installed on every respirator by Dräger, which is able to perform the SPN-CPAP/PS mode. It has the same rationale but the pressure support differs from breath to breath within a beforehand defined range. This has the purpose to simulate a more physiological breathing by a higher variation of tidal volumes and therefore intrathoracic pressure and should thus result in different improvements of the patient's condition. The difference of pressure application and the promised resulting variation of tidal volumes as compared to classical assisted spontaneous breathing is shown in Figure 3.4.1 and Figure 3.4.2. The parameters, which have to be set by the physician are the same but in addition to that a variation coefficient has to be set. The amount of this variation around the set mean pressure support, P_{supp}, is set by the pressure variability (*Press.var.*) from 0 to 100 %. The minimal variation is limited by the PEEP, whereas the maximum is restricted by the maximum airway pressure, P_{max}.

3.5. Data Analysis

3.5.1. Preprocessing

For analysing HRV, certain steps were necessary to be done in advance. This work was accomplished after recording the data using MATLAB (The MathWorks Inc., Natrick, MA, U.S.A.). All the steps necessary for adequate HRV analysis are discribed in the following section.

3.5.2. Handling of Recorded Data

As mentioned in section section 3.4, all the data displayed on the patient's monitor were recorded with *VREACT*. The tool saved all data in comma separated values (csv) files - for each recording one VitalSamples file and one WaveSamples file was created automatically. The VitalSamples file contains all the values, which are calculated by the monitor, such as heart rate, arterial oxygen saturation, SpO_2, etc.. The WaveSamples file contains files like the different ECG-leads or the arterial pulse wave.
Before the signal could have been further processed in MATLAB, it was necessary to transform the raw data obtained with VREACT into a file format, which could be properly analysed by this program.

1. Since VREACT records in UTF-16 format, which can not be used with MATLAB, the files had to be converted to UTF-8 prior to anything else with *UTF Cast Express*.

2. All data from the batched csv file were merged in MATLAB in order to generate one single file for each patient.

3. All files were checked if the signals which had to be analysed (e.g. the ECG-II-lead for HRV determination), were available.

All these steps had to be performed with every single patient.

3.5.3. Preprocessing of the Electro Cardiogram Signal

Due to some unknown technical problem, it turned out that the ECG signal was lost while recording in a range of milliseconds. This led to single samples of the originally 200 Hz ECG to be -15000 mV, which can be seen as obvious artefacts.

After making sure that these artefacts were not related to any movement of the patient or missing contact of the ECG electrodes, these samples were automatically detected and replaced by the mean of the foregoing and the following sample by a so called *one dimensional median filter*.
Allthough the original recorded ECG, which was measured with 200 Hz, would be accurate to perform a HRV analysis [8], the signal was re-sampled with a low-pass interpolating filter up to 1 kHz. This interpolation method first inserts a set number of zeros between the known two samples and then a symmetric finite impulse response with the *Nyquist frequency* with the input as the cut-off frequency.

3.5.4. Heart Rate Extraction

Heart rate is a value determined by certain amplitudes or durations in a signal like ECG. In this case, HR is determined by first analysing the peak to peak time, which makes an automatic R-peak detection necessary.
The R-peak detection was performed with a tool, which is, on the one hand, able to detect R-peaks of an underlying ECG automatically and on the other hand enables the user to manually add peaks as well as remove single peaks or even whole areas of artefacts. This algorithm first calculates a probability density function over the histogram of the gradients between successive samples. The time between two consecutive R-peaks was estimated from this function, which, in turn, was used to detect the actual position of these peaks in the original ECG. This automatic detection of peaks was followed by a manual validation and only correct detected R-peaks were used for the further processing of the ECG signal. Almost every ECG shows abnormalities, as described in subsection 2.3.2, within a recording time of two hours (up to 5 extrasystoles within a time of 24 hours is even seen as physiological). Nevertheless, these abnormalities had to be corrected to carry out a proper HRV analysis. Hence, single R-peaks or even larger artefact areas (for example, artefacts caused by movement of the patient (see Figure 2.3.9a)) were excluded manually from further signal analysis. This is followed by replacing the NN intervals of these artefact areas with the previous true NN interval, which leads to a corrected NN interval signal.
With these revised peak-to-peak intervals, the actual heart rate was calculated in beats per minute as

$$HR_i = \frac{60}{NN_i} \tag{3.1}$$

where i indicates the number of the observed interval.

3.5.5. Heart Rate Variability Analysis

The error cleaned HR signal was used to determine different HRV parameters. As one can see in subsection 2.3.1, there are parameters which depend on each other more or less directly, whereas others do not. For the underlying thesis, linear time domains as well as frequency domains were calculated and analysed in order to understand most of the interactions between mechanical ventilation and the autonomous nervous system. We focused on temporal changes of these domains between the two different ventilation modes of each patient. All HRV parameters were calculated with a time window of 5 minutes and an overlap of 80 %, which meets a time of 4 minutes.
All time domain parameters are calculated directly from the heart rate and are therefore as well given in milliseconds as well. Within the time-domains, we analysed the standard deviation from peak-to-peak, *SDNN*, and the root mean square of successive difference, *RMSSD*. The underlying formulas for calculating these parameters are shown in Equation 3.2 and Equation 3.3.

$$SDNN = \sqrt{\frac{1}{n}\sum_{i=0}^{n}(NN_i - \overline{NN})} \tag{3.2}$$

$$RMSSD = \sqrt{\frac{1}{n}\sum_{i=0}^{n}(NN_i - NN_{i-1})^2} \tag{3.3}$$

To perform the analysis of frequency domains, a couple of steps had to be done. At first, the peak-to-peak intervals had to be interpolated to a frequency of 3 Hz, which is methodically reasonable, since the smallest changes in HR are still much slower and the highest frequency of interest for the analysis is 0.4 Hz. This was followed by a Welch transformation of the NN interval into the frequency domain. With this transformation method, the underlying signal is splitted into overlapping segments, for which the power spectral density (PSD) is then calculated using the discrete time Fourier transformation. To reduce the variance of the estimated PSD, the local time estimates are then averaged. Finally, the power of certain frequency bands was summed up to calculate the HRV parameters, which in this case were total

power (TP), high frequency (HF), and low frequency (LF). All of these frequency domains have the unit of ms^2.

3.6. Signal Analysis

In the previous sections, the recording, filtering, and validation of the biosignals was described. The following chapter will show with what sort of statistical methods these recorded signals were evaluated.
The data-sets containing all recorded patients were merged patientwise in MATLAB. The medians of the calculated HRV parameters for each ventilation period were saved to a table, which in a next step was imported to RStudio (Version 1.1.456 – © 2009-2018 RStudio, Inc.) as a csv file. Further statistical analysis, as described in the following section, was performed with RStudio.

3.6.1. Preparing of the Biosignals

As described in subsection 3.5.2, all Wave- and VitalSamples were saved in one single file for each patient. The first step for the final analysis was to calculate all relevant parameters of time- and frequency domains for each patient and for each ventilation mode. For each treatment, the median of the HRV parameters was calculated and saved to a table. For the respirator data, the mean over each hour of treatment was calculated and saved to a separate table. The blood gas analysis results were manually transcribed into a table.

3.6.2. Statistics

To compare the results of both treatments, first for the parameters of HRV, the median value over the whole treatment period (60 minutes) was calculated for each patient separately for both treatments. Due to a missing normal distribution of resulting median HRV parameters, a Wilcoxon signed rank test was performed to compare both treatments. Respirator data were assumed to be normally distributed and therefore a two sided t-test for paired samples was done with these parameters. With the intention of conveying an impression of the blood gases developement, all BGA results (1,2,3 and 4) were furthermore described with boxplots, taking the randomisation order into account. Due to the small sample sizes and exploratory character of the study no formal statistical test was performed to investigate the

influence of the randomisation order. For an overall comparison of the two treatment groups with respect to the blood gas parameters, the mean of the two measured blood gas parameters per patient was calculated for each treatment. A two-sided t-test for paired samples was used to compare the blood gas values between the treatment groups. Due to the exploratory character of the study,12 the significance level was set to 0.05 (see Figure 4.3.1).

4. Results

For every single included patient, a large number of variables has been recorded. Due to critical illness of some patients, it became obvious that some patients were not suitable for HRV analysis. Since these patients could either way be analysed regarding all other recorded parameters, the results-section is separated into blocks: HRV-analysis, respiration-analysis, and blood gas analysis. Within these blocks, a different number of patients was included due to problems in the measurement of some parameters as described in section 3.2, which will be further explained in chapter 5.

4.1. Heart Rate Variability

In this block, most of the recruited patients had to be excluded due to partly irrational HRV-patterns (to get an idea of this pattern take a look at A.2.1a, A.2.1b or A.2.1d). An HRV analysis was carried out for $N_{\mathrm{HRV}} = 7$ patients. For each patient, the median over the whole treatment period was calculated seperately for both treatments. To compare both treatments, boxplots were drawn and individual measurements are shown (see Figure 4.1.2). The boxplots generally showed for all HRV parameters skew distributions with outliers. Therefore, Wilcoxon signed rank tests were performed (for *SDNN*, *RMSSD*, *TP*, *HF*, *LF*, *LF*-*HF*-Ratio). For all measured parameters, no significant difference between SPN-CPAP/PS and VPS was found (all $p > 0,05$).

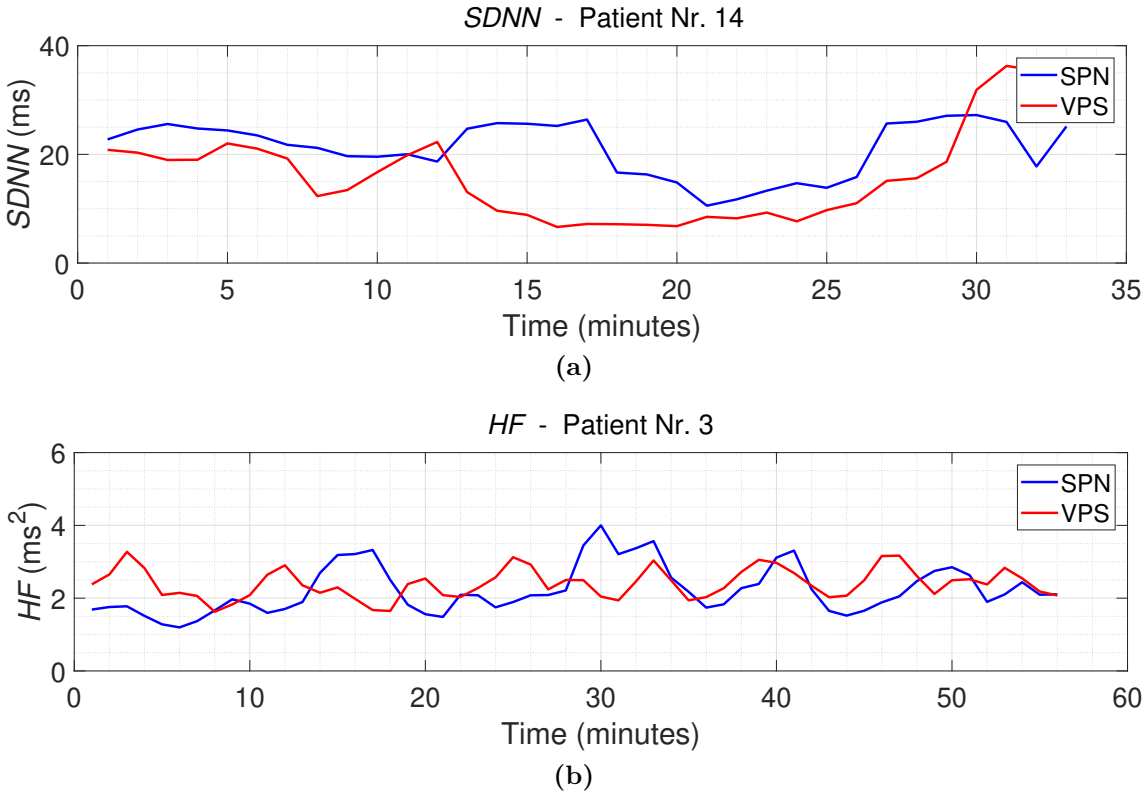

Fig. 4.1.1.: These courses of HRV parameters *SDNN* and *HF* also show grafically, what is the result of statistical analysis: there seems to be no relevant differences regarding these parameters between variable (VPS) and conventional (SPN-CPAP/PS) pressure support mechanical ventilation. For detailed information and the other plots please see appendix chapter A.

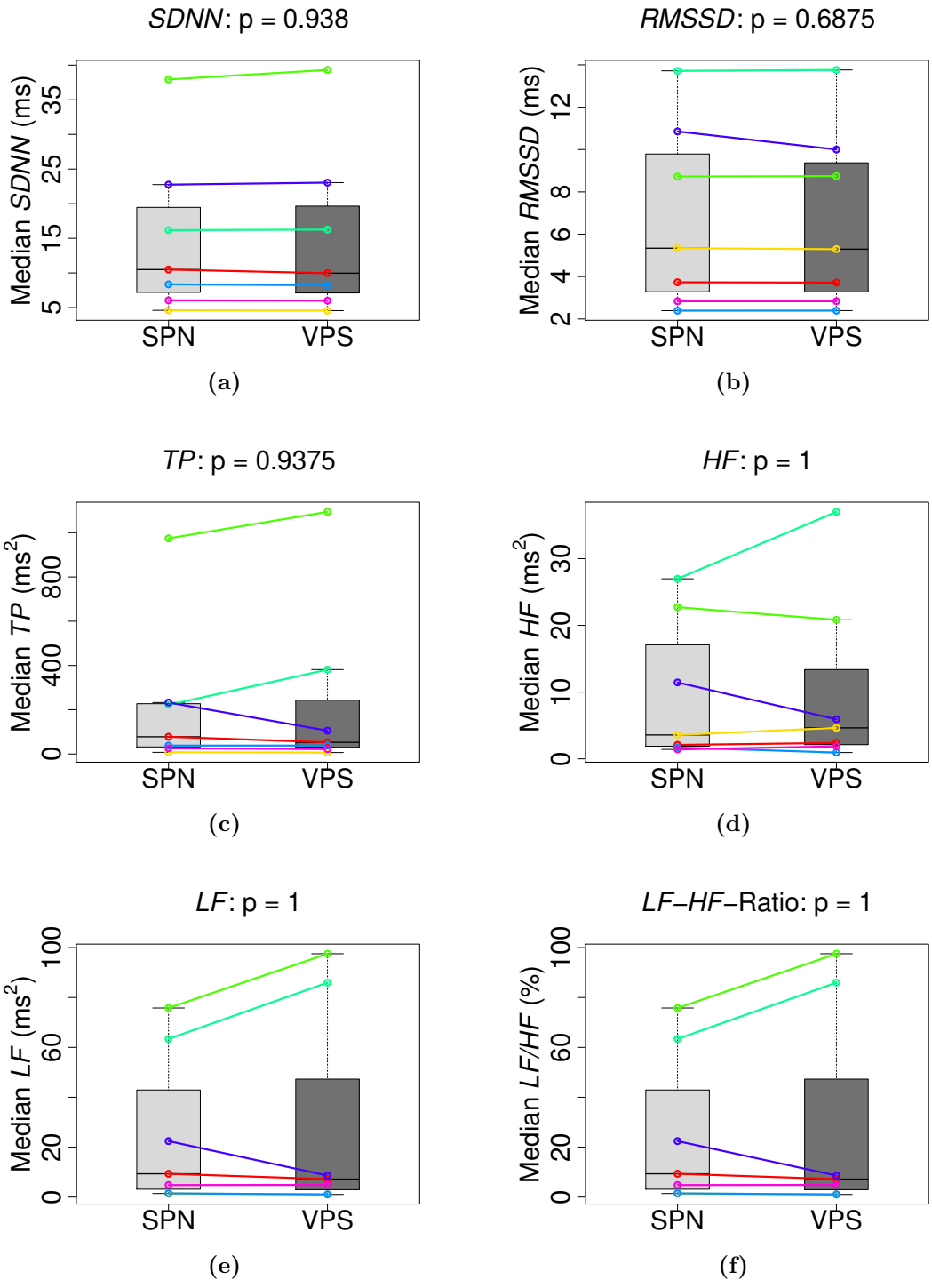

Fig. 4.1.2.: Comparing the mean over one hour of each treatment of respiratory parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS). Statistically tested with a Wilcoxon signed rank test. The coloured lines show the course of every single patient.

4.2. Mechanical Ventilation and Physiological Parameters

Since the analysis of respiration-variables does not depend on any criteria which is relevant for analysis of HRV patterns, we were able to include a number of $N_{\text{Ventilator/Physiological}} = 13$ patients to the analysis of mechanical ventilation variables - one patient had to be excluded due to loss of connection during the measurement. For each patient, the median over the whole treatment period was calculated seperately for both treatments. To compare both treatments, boxplots were drawn and individual measurements are shown (see Figure 4.2.1). If the boxplots showed a skew distribution with possible outliers, Wilcoxon signed rank tests were performed (for mean and standard deviation of tidal volumes, v_{T}, maximum inspiratory, *PIP*, and mean airway pressure, *MAwP*, respiratory frequency, *RF*, and arterial mean pressure, *MAP*. For all measured respirator parameters, no significant difference between SPN-CPAP/PS and VPS was found (all $p > 0,05$). For the *MAP*, a significant smaller value was found for the VPS treatment with $\text{p} = 0.00398$. However, one has to be aware of this finding, because this parameter was defined as secondary parameter in the planning phase of the trial.

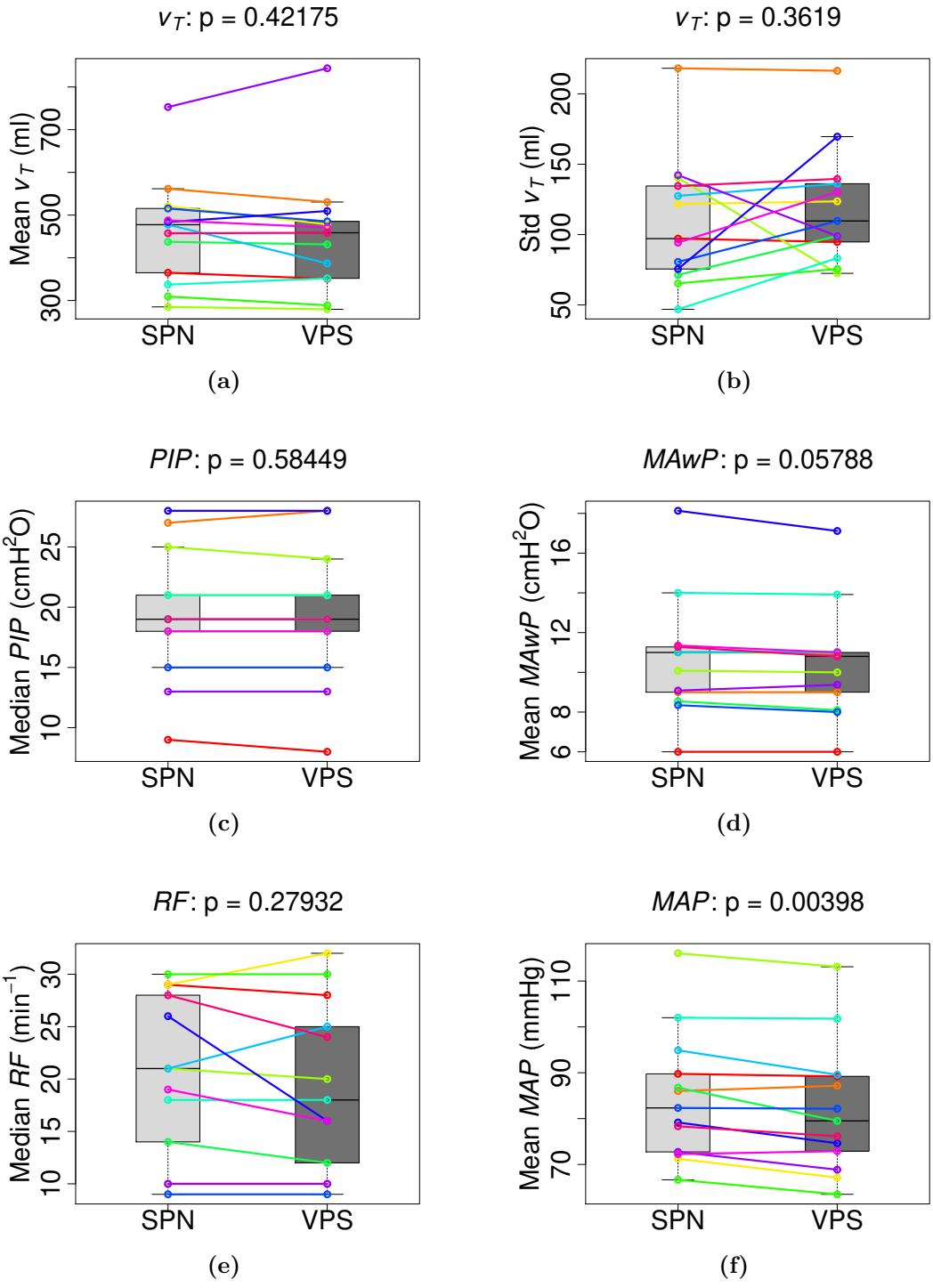

Fig. 4.2.1.: Comparing the mean over one hour of each treatment of respiratory parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS). Statistically tested with a Wilcoxon signed rank test. The coloured lines show the course of every single patient.

4.3. Blood Gas Analysis

We included $N_{\mathrm{BGA}} = 13$ patients in this group. For each patient, the mean over the two measurement parameters per patient was calculated for both separately. To compare both treatments, boxplots were drawn and individual measurements are shown (see Figure 4.1.2). Furthermore, paired t-tests were calculated. If the boxplots showed a skew distribution with possible outliers, Wilcoxon signed rank tests were performed (for base, pH, partial pressure of carbon dioxide, pCO_2, partial pressure of oxygen, pO_2, concentration of haemoglobin, haematocrit, arterial bloods oxygen saturation, sO_2, and concentrations of potassium, sodium, calcium, chloride, glucose and lactate). For all measured parameters, no significant difference between SPN-CPAP/PS and VPS was found (all $p > 0{,}05$).
The visualisation of blood gases was carried out in two blocks, each with 2 subgroups:

- In order to detect global changes in blood gases, we plotted an overview over the means of every treatment without taking the randomisation into account (see Figure 4.3.1).

- With the intention to detect any changes in variables with the switch of the ventilation mode, an analysis of the changes in blood gas variables was carried out between the 2^{nd} and 3^{rd} BGA. The order of randomisation (SPN-VPS or VPS-SPN) was taken into account (see Figure 4.3.2). The randomization ordering does not seem to have an influence on the difference between treatment groups. However, due to the small sample size, the interpretation of the data with respect to the ordering was difficult. Furthermore, all 4 measurements were plotted (see Figure A.3.1 in Appendix).

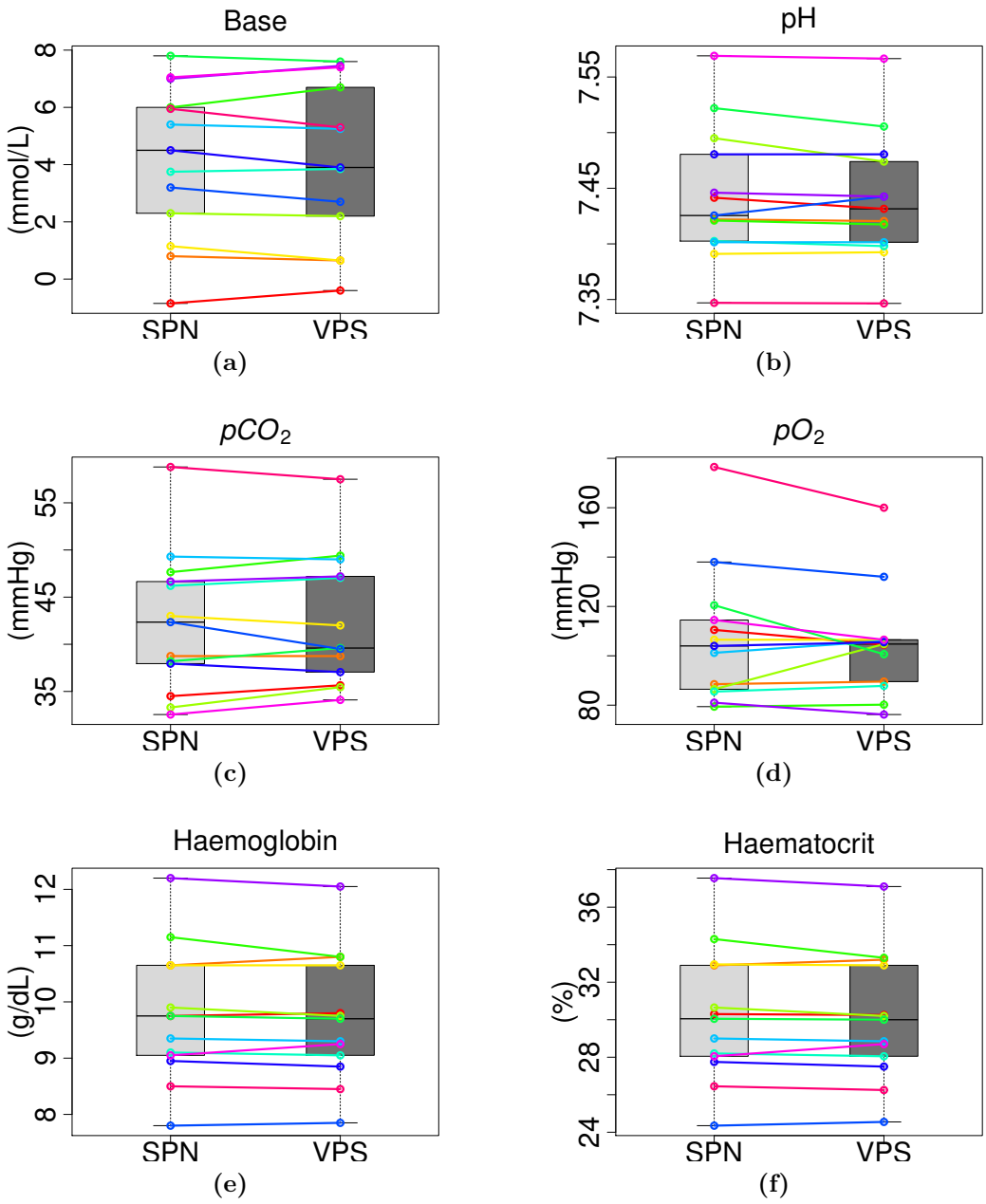

Fig. 4.3.1.: Part A; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

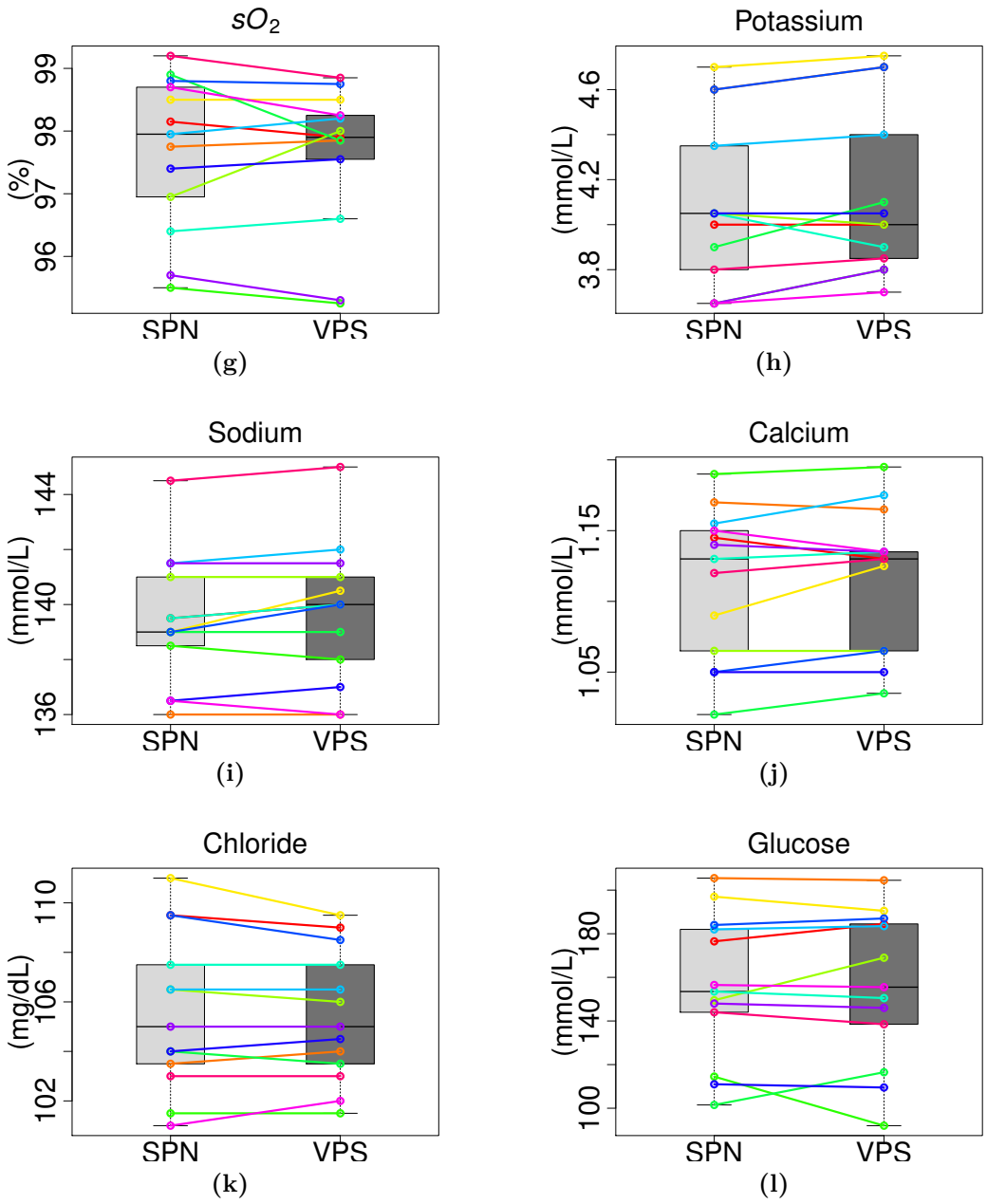

Fig. 4.3.1.: Part B; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

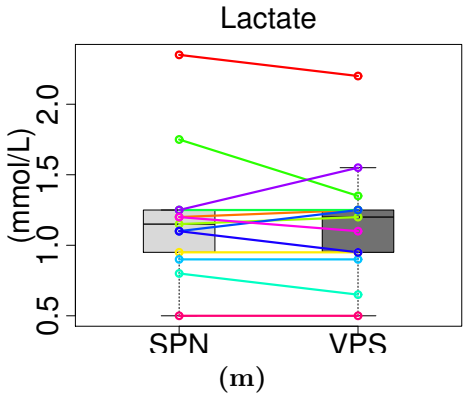

Fig. 4.3.1.: Part C; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

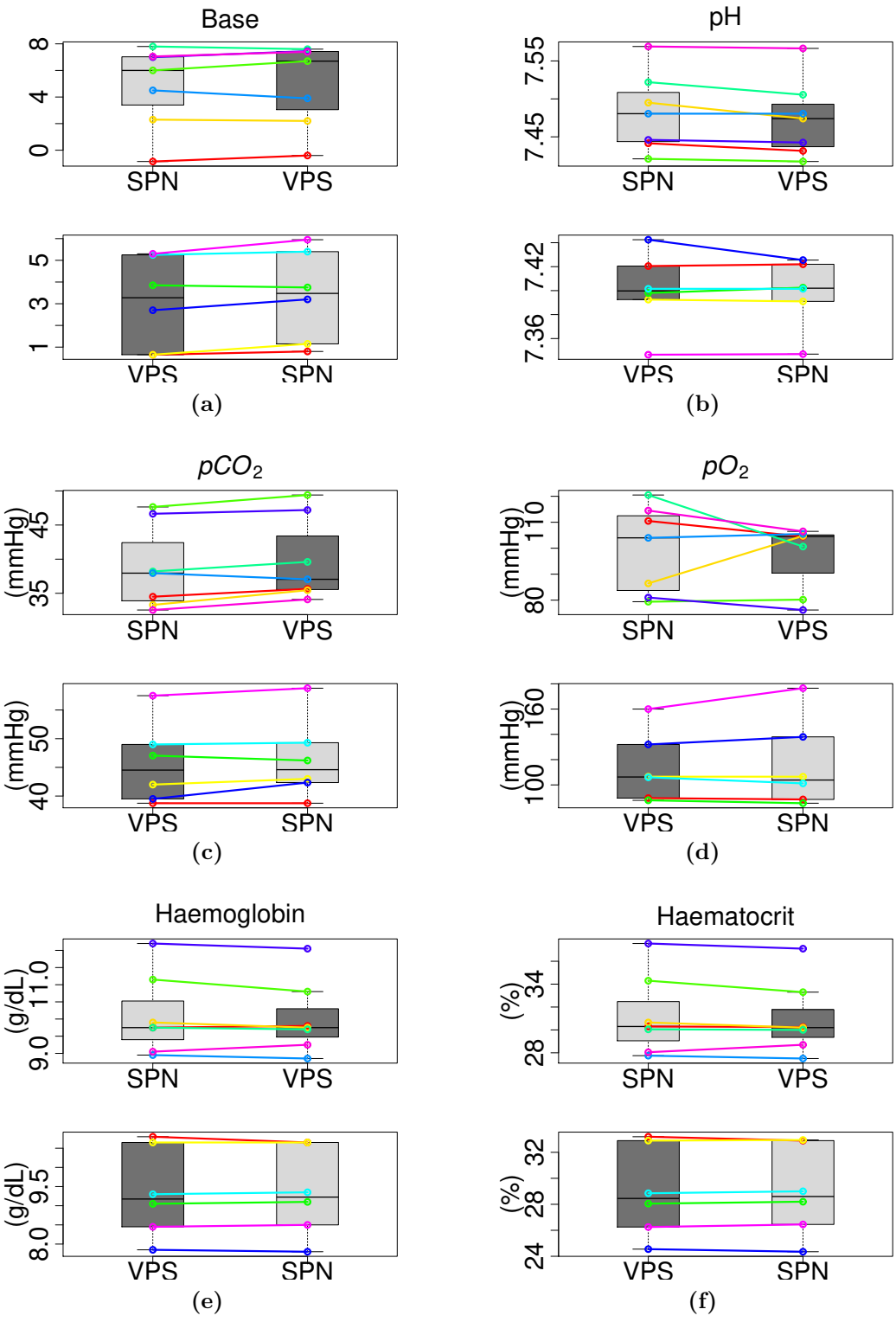

Fig. 4.3.2.: Part A; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

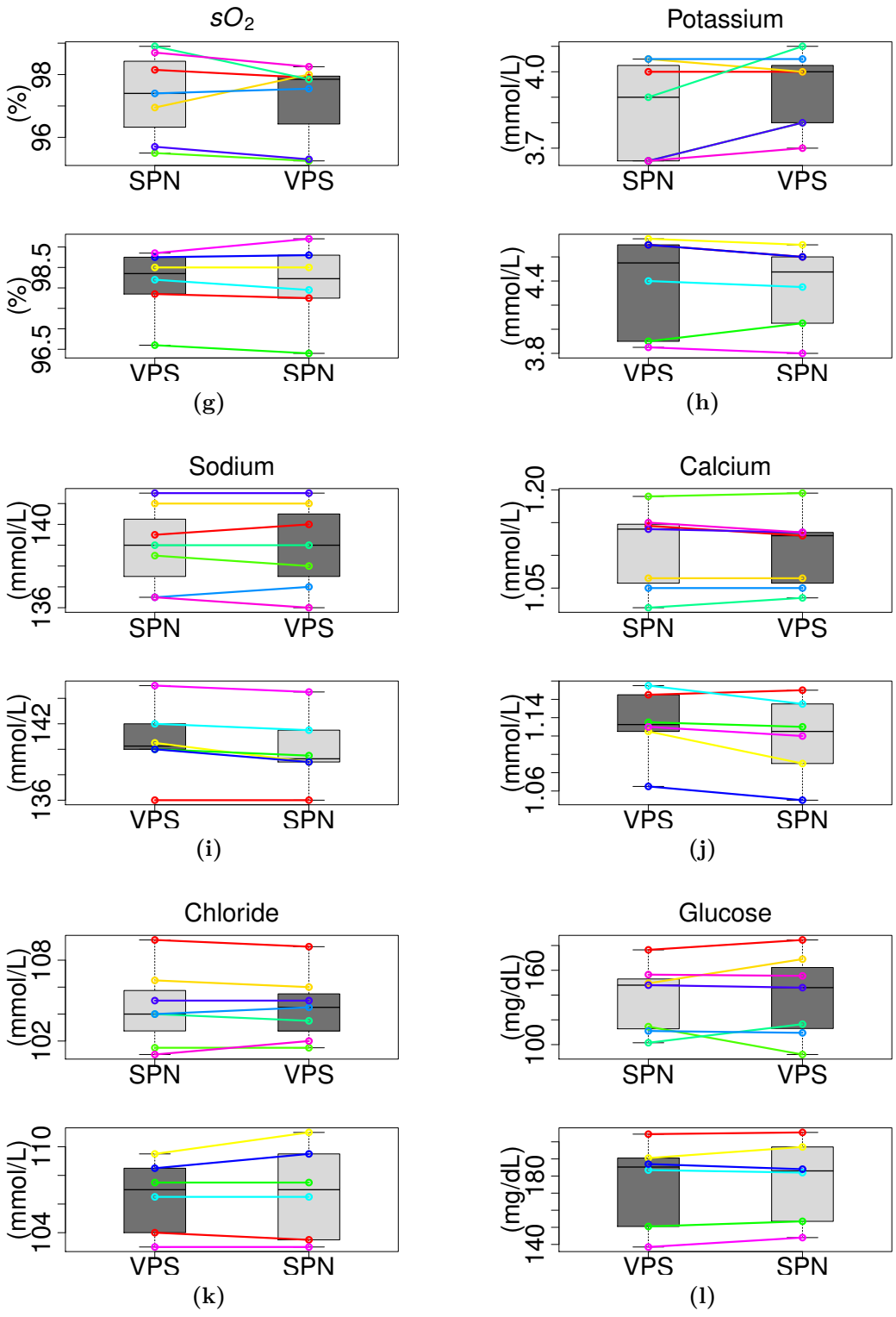

Fig. 4.3.2.: Part B; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

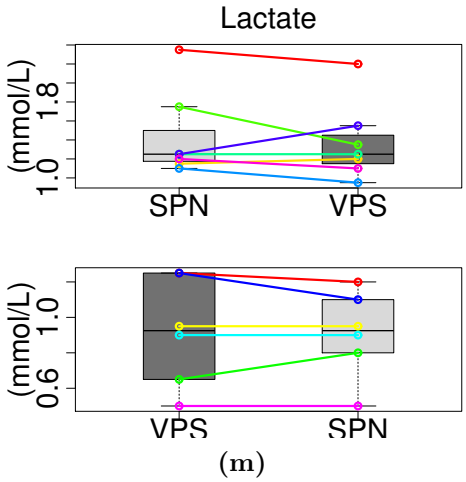

Fig. 4.3.2.: Part C; Comparing the mean over one hour of each treatment of BGA parameters between SPN-CPAP/PS (SPN) and Variable PS (VPS) without respect to the randomisation order. Statistically tested with a paired t-test, there is no variable with $p < 0.05$. The coloured lines show the course of every single patient.

5. Discussion

The aim of this work was to further investigate interactions between heart and lungs by comparing the admission of a novel ventilation mode called *"variable pressure support mechanical ventilation"* with a conventional pressure support mechanical ventilation (SPN-CPAP/PS) regarding their influence on heart rate variability. Since the manufacturer of this novel ventilation mode proposes that a more physiological breathing would be enabled for the patient, we furthermore evaluated the activity of the autonomous nervous system and compared the autonomic states, assessed by HRV, between the conventional and the variable pressure support ventilation, since a higher parasympathetic activity would mean a lot of advantages regarding the overall outcome of the patient [15, 10, 37].

The measurements for this study were performed in selected ICUs of the general hospital of Vienna during normal intensive care duty. Due to this, patients of different pathogenesis were included in this study (e.g. polytrauma, status post lung transplantation, status post liver transplantation). Further degrees of freedom were gender (5 female, 9 male), age (mean $61 \pm 12,7$), height and weight (which lead to a mean BMI of $(23,9 \pm 15,7)$. These factors led to a heterogeneous study population. The heterogeneity was further increased by the multi morbidity of most ICU patients, which was necessary to avoid selection bias. Furthermore, this heterogeneity was important, since many degrees of freedom (such as gender and age) are related to certain HRV related behaviour [48, 49, 50].

Detection of R-peaks and artefact cleaning of the ECG had to be performed before computing HRV parameters. The R-peak detection was performed automatically and was manually validated. Due to the omitted interventions on the patient during the 2 hour measurement, the signal quality was very constant and good. Only single samples were wrong due to connection problems of the Dräger network - the algorithm for signal processing was therefore extended to detect these samples and a medianfilter was used to repair these parts of the ECG. Furthermore, ECG artefacts, which occurred due to spontaneous movement of the patient, were manually detected and excluded - an automatisation of this step could be planned for further

studies in order to save time. ECG abnormalities (e.g. extrasystoles) also had to be detected and excluded manually. As this takes a lot of time, performing this step automatically would be more efficient. Therefore, an extending of existing algorithms should be taken into account, however, this would be very time-consuming.
Only 7 out of 14 included patients were taken into account for HRV analysis due to impossible HRV patterns. Nevertheless, blood gases of all included patients were evaluated and respirator data of 13 patients were analysed (one patient of the respirator-analysis group had to be excluded due to loss of signal).
The statistical analysis of time (*SDNN*, *RMSSD*) and frequency domains (TP, LF, HF, LF-HF-Ratio) of HRV shows no significant differences between the novel VPS and the conventional SPN-CPAP/PS groups. Figure 4.2.1b shows that there is no significant higher variation of tidal volumes between both groups - nevertheless, it has to be mentioned that the visual assessment of the boxplots indicates an increase of variation. Maybe a follow up study with a study design fitting for the question of tidal volume variation could provide insight into this.
To our interest, mean airway pressure was significantly lower in VPS as compared to the conventional SPN-CPAP/PS group (see Figure 4.2.1d). Moreover, the maximum inspiratory pressure seems to have a decreasing tendency (see Figure 4.2.1c). These two facts might indicate a better compliance of lung tissue to variable pressure support ventilation, in accordance with known literature [51]. To evaluate a possible positive influence in terms of lung protective ventilation of variable pressure support on maximum and mean airway pressure, further research has to be done. This could be done in a far simpler setting, which would lead to a higher number of includable patients. Blood gas analysis results do not show any significant differences between both groups. It is certainly not astonishing that blood cells do not react to a different ventilation mode, especially not in a short period of one hour. Nevertheless, we could not detect any difference regarding oxygen saturation, partial pressure of oxygen or partial pressure of carbon dioxide in arterial blood, which stands in contrast to known literature, which showed an improvement of regional lung aeration and higher perfusion during variable pressure support ventilation [19]. To our interest, the arterial mean pressure (*MAP*) shows a high significant decrease in variable pressure support mechanical ventilation as compared to SPN-CPAP/PS, although no other parameters (such as drug therapy) changed within the whole measurement period (see Figure 4.2.1f). If a decreasing MAP turns out in a higher number of patients with variable pressure support, it could be seen as an evidence based indicator to think about using variable pressure support especially for pa-

tients with heart failure. Further studies, which deal with the relevance of variable pressure support mechanical ventilation and its influence on blood pressure, could performed in the near future.

It should be mentioned that performing a two hour measurement with a patient of an intensive care unit is related to many challenges, and when such challenges could not be overcome in some cases these patients had to be excluded. Two hours of measurement were necessary to detect very low frequent changes in heart rate variability and therefore necessary to perform this study properly. Nevertheless, intensive care unit patients suffer from severe illness, which makes it almost impossible to have a steady state setting for two hours. In addition, it has to be recalled that patients, which are breathing already spontaneously are in a state of reduced vigilance, but not necessarily unconscious (one patient was watching television - but he had to be excluded due to many extrasystoles). Consequently, another problem arises when measuring the autonomous nervous systems activity: Patients might have a fluctuating awareness of their surrounding, which again will have tremendous impact on the autonomic state - without necessarily being dependant on the variable pressure support.

6. Conclusion and Outlook

With the intention to draw a conclusion of this study, it can be said that variable pressure support mechanical ventilation did not show any improvement of heart rate variability compared to conventional pressure support mechanical ventilation. Furthermore, we were not able to detect any positive impact on the autonomous nervous system (low-to-high-frequency-ratio (see Figure 4.1.2f)), more precisely an increase of the parasympathetic tone (high frequency domains of HRV (see Figure 4.1.2d)), which would have had a very positive impact on the general outcome of an intensive care unit patient [10]. The systematic variation of tidal volumes under variable pressure support mechanical ventilation, which is promised by the manufacturer, could not be shown statistically in this trial. Nevertheless, when looking at Figure 4.2.1b, one can see that there might be a trend to higher variation of v_T.

Perhaps it would be a rational step to do research on the impact of variable pressure support on the applied tidal volumes. This could be done in a much simpler setting with shorter periods of measurement and without paying attention to an underlying sinus rhythm, which is not present in many cases. With these two modifications of inclusion criteria, this kind of clinical trial could be carried out faster.

The systematic decrease in mean arterial blood pressure was a random result. The connection between variable pressure support and decreasing mean arterial blood pressure has not been target of research yet. Therefore, this finding should be further investigated, since lowering mean arterial pressure could be of interest in patients with the tendency to need higher doses of antihypertensives.

Another interesting future study would be the admission of variable tidal volumes (via volume controlled ventilation) to relaxated patients (e.g. in an intraoperative setting) with a subsequent evaluation of HRV parameters.

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A. Appendix

A.1. Consent Form

Patienteninformation für nicht einwilligungsfähige Patienten zur Teilnahme an der klinischen Prüfung

Herzratenvariabilität während mechanisch druckunterstützter Beatmung – ein Vergleich zwischen konventioneller und variabler druckunterstützter Beatmung: eine Cross-Over Studie

Sehr geehrte Patientin, sehr geehrter Patient!

Sie wurden während Ihres Aufenthaltes auf der Intensivstation in eine wissenschaftliche klinische Studie eingeschlossen. Aufgrund Ihres gesundheitlichen Zustandes war es uns damals nicht möglich, Sie um Ihr Einverständnis zu ersuchen.

Ihre Teilnahme an dieser klinischen Prüfung erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Prüfungen sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Prüfung ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Prüfung schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Prüfarzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Prüfung vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Prüfung im Klaren sind.

Zu dieser klinischen Prüfung, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

Was ist der Zweck der klinischen Prüfung?

Inhalt dieser Studie ist die Erforschung der Belastung auf das Herzkreislaufsystem, während Sie an eine Maschine, welche Ihre Atemtätigkeit unterstützt bzw. gegebenenfalls übernimmt (medizinisch Beatmung), angeschlossen sind.

Insbesondere wollen wir überprüfen, ob Ihre Herzratenvariabilität, ein Maß für die Änderung ihrer Herzfrequenz, ansteigt, wenn Sie mit dem Beatmungsmodus „variable druckunterstützte Beatmung“ beatmet werden. Dieser Beatmungsmodus unterscheidet sich zu konventionellen druckunterstützten Beatmung (SPN-CPAP/PS) nur dadurch, dass die Tiefe der Atemhübe nicht immer gleich ist, sondern über die Zeit leicht variiert.

Folgende Maßnahme wurde ausschließlich aus Studiengründen durchgeführt:

- Umstellung zwischen den Beatmungsmethoden „*Variable PS*“ (Variation der Druckunterstützung bei der Beatmung) und „*SPN-CPAP/PS“* (keine Variation der Druckunterstützung bei der Beatmung)

- Messung der Herzratenvariabilität über ein im Rahmen der klinischen Routine angelegtes Elektrokardiogramm (EKG). Die Bestimmung der Herzratenvariabilität erfordert demnach keine zusätzlichen Maßnahmen am Patienten.
- 4 Blutgasanalysen im Verlauf der Messung, welche über eine, im Rahmen der klinischen Routine gelegten, arteriellen Verweilkanüle durchgeführt werden. Blutgasanalysen von arteriellem Blut sind ebenfalls Teil der Routinemaßnahmen. Durch die Studie werden ihnen insgesamt maximal 8ml Blut für diese Analyse abgenommen.

Insgesamt wurde maximal eine Messung mit beiden Beatmungsmethoden durchgeführt: maximal 2 Stunden an einem Tag.

Wie wurde die Messung durchgeführt?

Um die vorgenommenen Messungen durchführen zu können, mussten wir keine neuen Geräte an- oder bereits im Einsatz befindliche Geräte abschließen. Es kam zu keiner Unterbrechung Ihrer Therapie oder elektronischen Patientenüberwachung.

Die Spontanatmung mit kontinuierlichem positiven Druckniveau mit oder ohne Druckunterstützung (SPN-CPAP/PS) wird häufig während der Entwöhnung des Patienten vom Beatmungsgerät angewendet. Dabei wird die Spontanatmung des Patienten druckunterstützt, was die Atemanstrengung reduziert und ein kollabieren der Lunge durch ein kontinuierlich positives Druckniveau verhindert. Die Beatmungsmethode „*Variabler PS*“ (VPS) ist eine zusätzliche Gerätefunktion, die mit der Beatmungsmethode SPN-CPAP/PS kombiniert werden kann. VPS ist eine bereits zugelassene Gerätefunktion der Evita Infinity V500 Beatmungseinheit von Dräger™.

Bei der Aktivierung von VPS wird bei jedem Atemzug unterschiedlich hohe Druckunterstützung appliziert. Wie groß der Unterschied der einzelnen Unterstützungen ist, sowie der mittlere und maximale Beatmungsdruck werden voreingestellt. So entstehen bei jedem Atemzug unterschiedlich hohe Beatmungsdrücke und Atemzugsvolumina. Dabei wird durch das voreingestellte kontinuierliche Druckniveau auch eine untere Grenze der Druckvariation gewährleistet. Die Herzratenvariabilität (HRV) wurde im Rahmen der Erfassung Ihres Überwachungs-EKG von einem Computer berechnet. Für die Bestimmung der (HRV) war also keine Veränderung Ihrer Überwachung notwendig.

Worin liegt der Nutzen Ihrer Teilnahme an dieser klinischen Prüfung?

Mit der Anwendung der VPS war möglicherweise eine verbesserte Anreicherung mit Sauerstoff und eine Umverteilung des Blutflusses durch das Lungengewebe möglich. Neben diesem individuellen Nutzen hoffen wir, dass die Ergebnisse der klinischen Prüfung zu Erkenntnissen über die Belastung des Herzkreislaufsystems beatmeter Patienten beitragen. Sollte sich bestätigen, dass die Anwendung von VPS die Herzkreislaufbelastung senkt, könnte dies zu einer Verbesserung der Therapie und somit zu besseren Überlebenschancen vieler beatmungspflichtiger Patienten führen.

Studien belegen, dass durch die Verwendung von VPS keinerlei Nachteile gegenüber konventioneller druckunterstützter Beatmung wie SPN-CPAP/PS zu erwarten sind.

Versicherung

Als Teilnehmer an dieser klinischen Prüfung besteht für Sie der gesetzlich vorgeschriebene Versicherungsschutz (Personenschadenversicherung gemäß § 47 Medizinproduktegesetz) der alle Schäden abdeckt, die an Ihrem Leben oder Ihrer Gesundheit durch die an Ihnen durchgeführten Maßnahmen der klinischen Prüfung verursacht werden können; ausgenommen sind genetische Schäden. Die Versicherung wurde für Sie bei der Zürich Versicherungs-Aktiengesellschaft, Schwarzenbergplatz 15, A-1010 Wien, Tel: 08000 – 80 80 80 unter der Polizzennummer 07229622-2 abgeschlossen. Auf Wunsch können Sie in die Versicherungsunterlagen Einsicht nehmen.

Im Schadensfall können Sie sich direkt an den Versicherer wenden und Ihre Ansprüche selbständig geltend machen. Für den Versicherungsvertrag ist österreichisches Recht anwendbar, die Versicherungsansprüche sind in Österreich einklagbar.

Um den Versicherungsschutz nicht zu gefährden

- dürfen Sie sich während der Dauer der klinischen Prüfung einer anderen medizinischen Behandlung nur im Einvernehmen mit Ihrem behandelnden Prüfarzt, unterziehen (ausgenommen davon sind Notfälle). Dies gilt auch für die zusätzliche Einnahme von Medikamenten.
- müssen Sie sich dem behandelnden Prüfarzt - oder der oben genannten Versicherungsgesellschaft - eine Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte, unverzüglich mitteilen.

Zur Unterstützung können Sie sich auch an die Patientenanwaltschaft, Patientenvertretung oder Patientenombudsschaft wenden (Adresse: Schönbrunner Straße 108, 1050 Wien. Telefonnummer: +43 15871204. Fax: +43 1586 3699. E-Mail: post@wpa.wien.gv.at).

In welcher Weise werden die im Rahmen dieser klinischen Prüfung gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas Anderes vorgesehen ist, haben nur die Prüfer und deren Mitarbeiter, sowie in- und ausländische Gesundheitsbehörden Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten im In- und Ausland erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Prüfung werden Sie nicht namentlich genannt.

Die Daten werden für ein Jahr aufbewahrt, um diese für allfällige weitere wissenschaftliche Fragestellung im Bereich der Anästhesie und Intensivmedizin zur Verfügung zu haben. Innerhalb dieses Jahres werden die gesamten Daten von Maximilian Schnetzinger, BSc sicher und unter Berücksichtigung der Sensibilität der Daten, entsprechend der „Good scientific Practice“ Richtlinien der Medizinischen Universität Wien, verwahrt.

Wir weisen ausdrücklich darauf hin, dass eine Weiterverwendung Ihrer Daten im Rahmen eines neuen Forschungsprojektes, nur nach vorheriger Genehmigung des Projektes durch die zuständige Ethikkommission möglich ist.

Die im Rahmen der 4 Blutgasanalysen abgenommenen Blutproben werden unmittelbar nach der Analyse verworfen. Die Blutproben werden also nicht für andere Zwecke gelagert oder verwendet.

Des Weiteren können Sie Ihre Zustimmung zur Teilnahme an dieser oder Folgestudien jederzeit ohne Angabe von Gründen widerrufen und verlangen, dass ihre aufgezeichneten Daten vernichtet werden. Es entstehen für Sie dadurch keinerlei Nachteile.

Falls Sie Fragen im Zusammenhang mit der klinischen Prüfung haben, können Sie sich jederzeit an folgende Ärzte wenden:

Name der Kontaktperson:	Assoc. Prof. PD Dr.med. Klaus Ulrich Klein
ständig erreichbar unter:	+43 676 5302505

Einwilligungserklärung

Name des Patienten in Blockbuchstaben: ……..
Geboren am …….. Code: ……

Ich bin von Herrn / Frau ..... ausführlich und verständlich über die variable druckunterstützte Beatmung und die Messung der Herzratenvariabilität sowie die Abnahme von arteriellen Blutproben mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Prüfung, die bestehende Versicherung sowie die sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 4 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich willige ein, dass die von mir erhobenen Daten und Blutproben für die Studie „Herzratenvariabilität während mechanisch druckunterstützter Beatmung – ein Vergleich zwischen konventioneller und variabler druckunterstützter Beatmung: eine Cross-Over Studie“ verwendet werden.
Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Prüfung ermittelten Daten gespeichert werden. Mir ist bekannt, dass zur Überprüfung der Richtigkeit der Datenaufzeichnung Beauftragte der zuständigen Behörden, der Ethikkommission und ggf. des Auftraggebers beim Prüfarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen dürfen.
Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes 2000 beachtet.

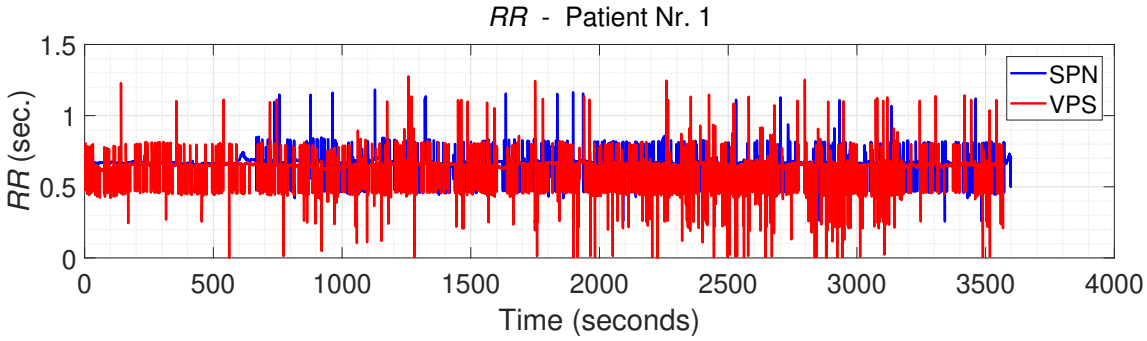
Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

……..
(Datum und Unterschrift des Patienten)

……..
(Datum Name und Unterschrift des verantwortlichen Prüfers)

A.2. Raw Data

A.2.1. Excluded Patients



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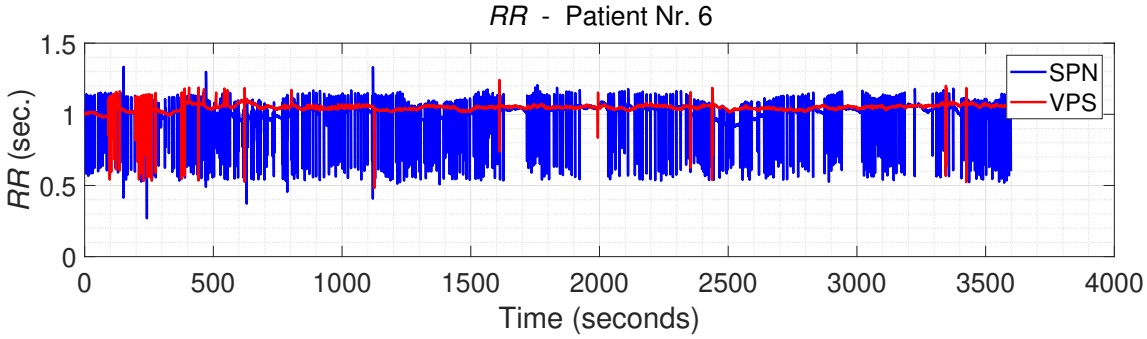

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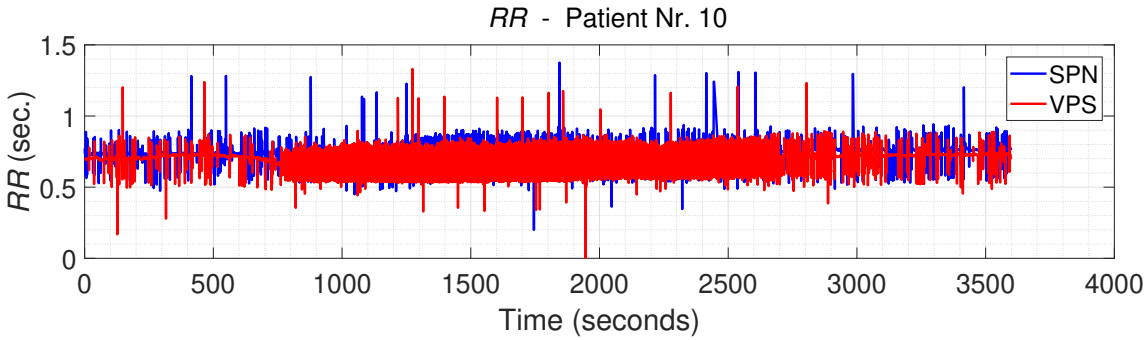

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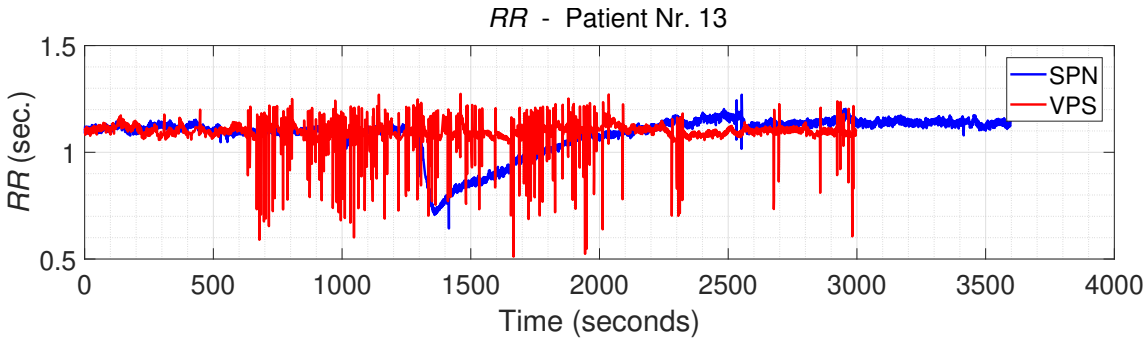

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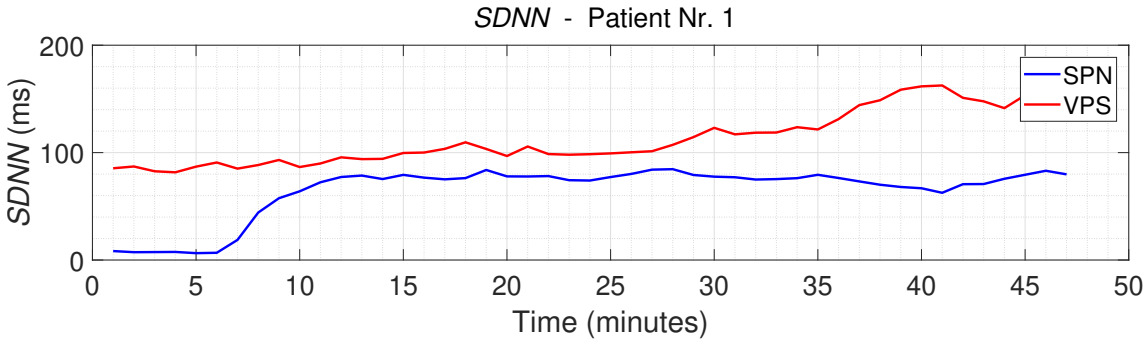
Fig. A.2.1.: RR intervals of patients excluded from HRV analysis.



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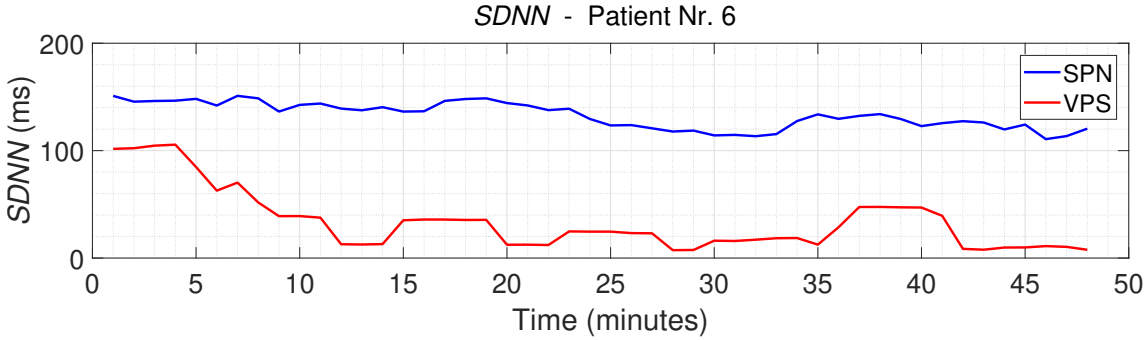

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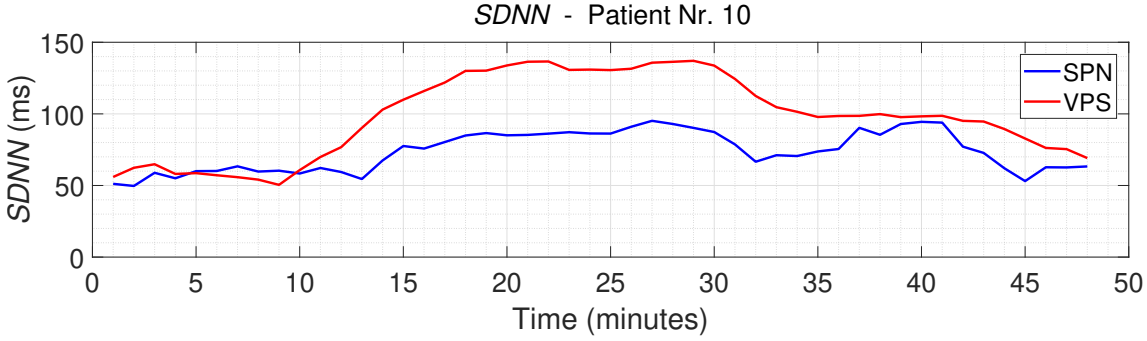

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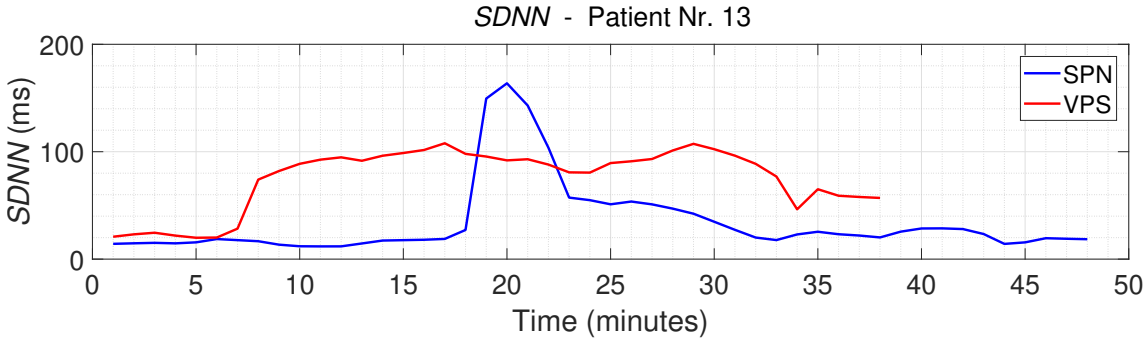

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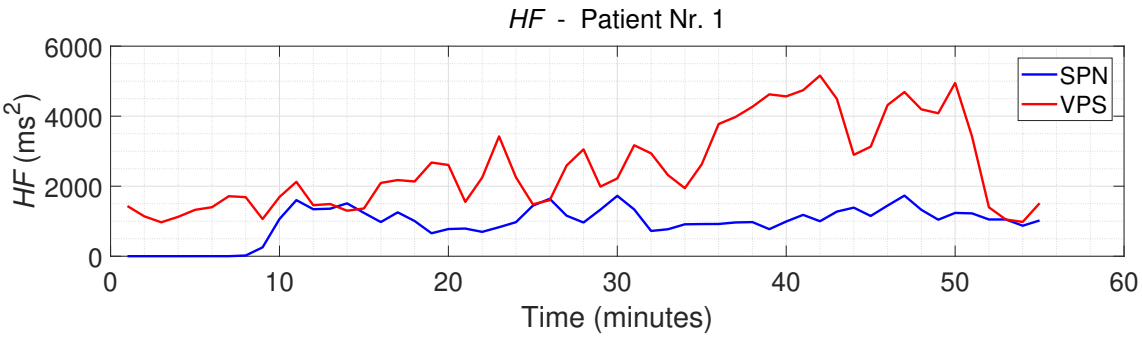
Fig. A.2.2.: Standard deviation of RR-Intervals of patients excluded from HRV analysis.



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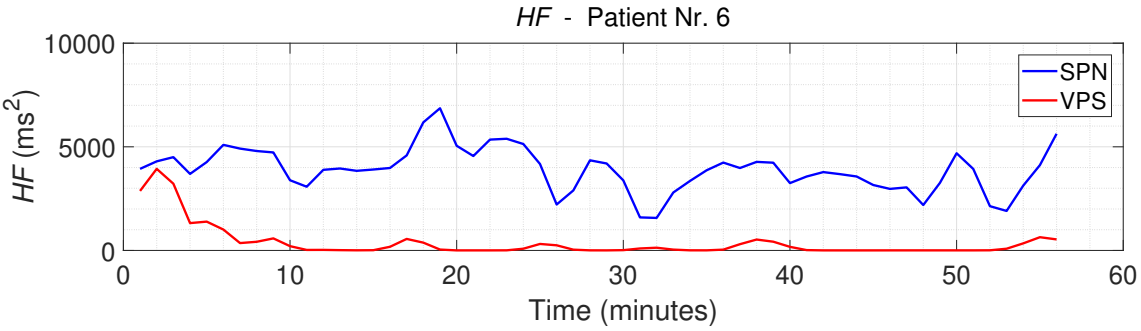

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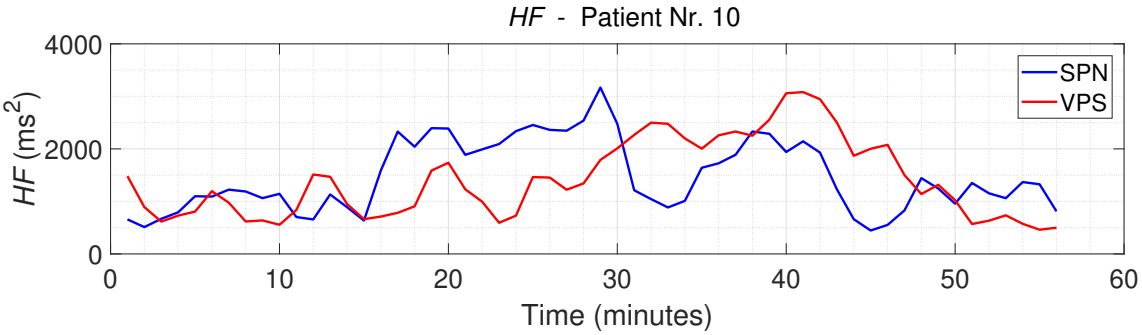

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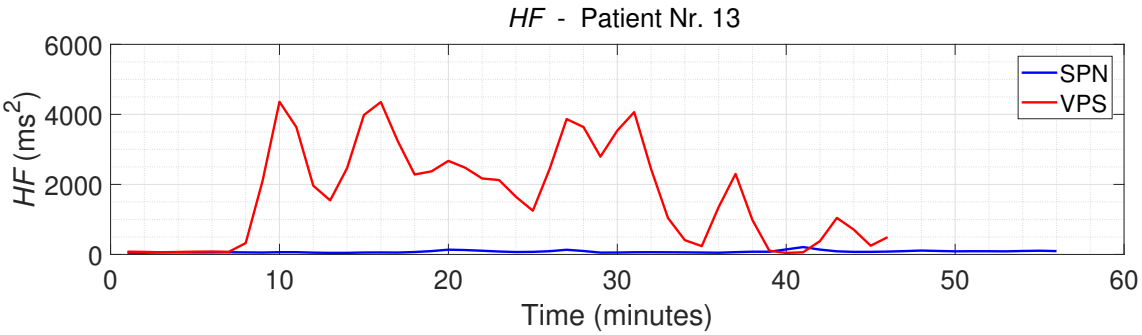

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Fig. A.2.3.: High frequency components of HRV of patients excluded from HRV analysis.

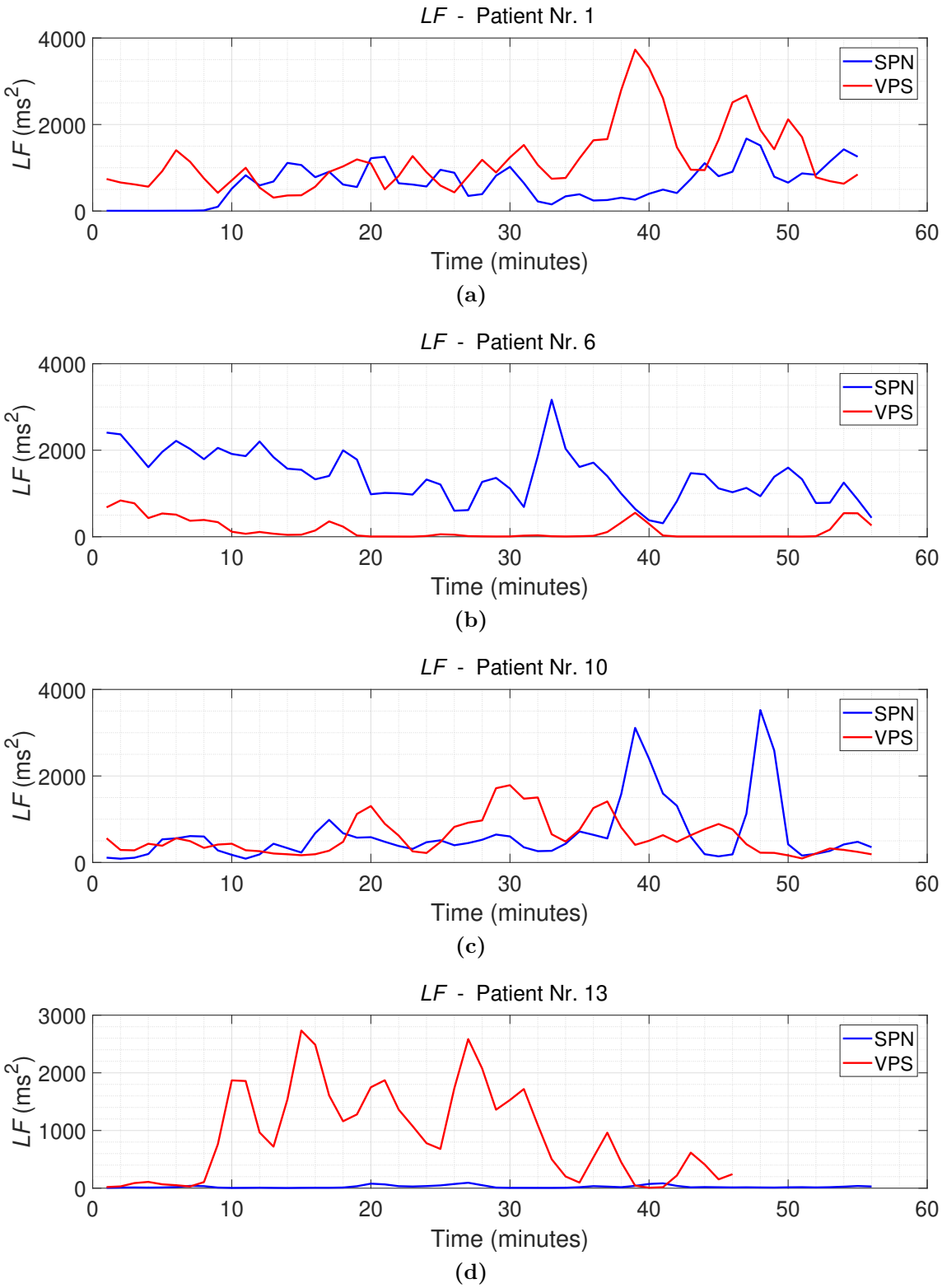
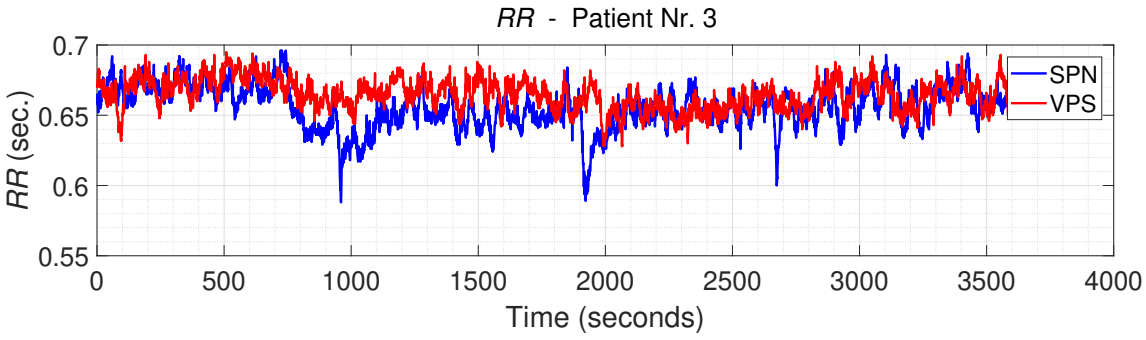


Fig. A.2.4.: Low frequency components of HRV of patients excluded from HRV analysis.

A.2.2. Included Patients



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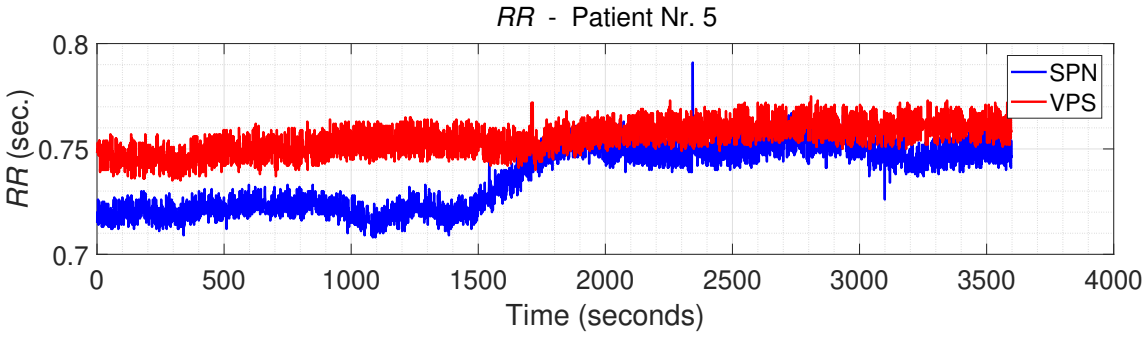

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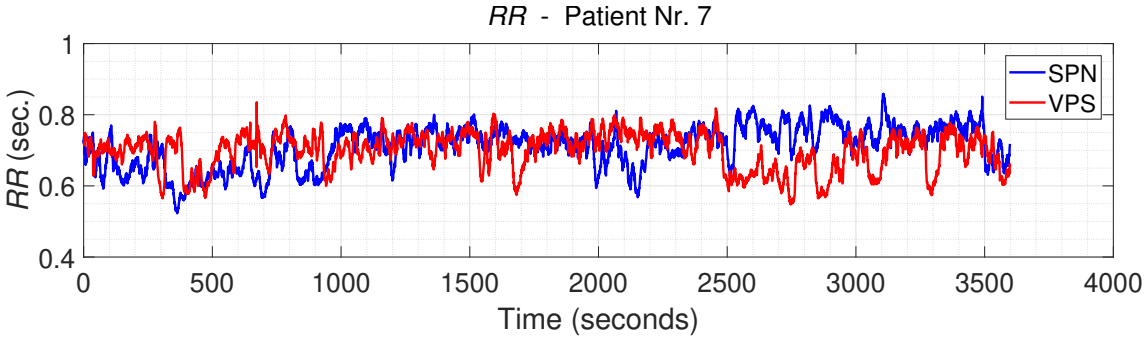

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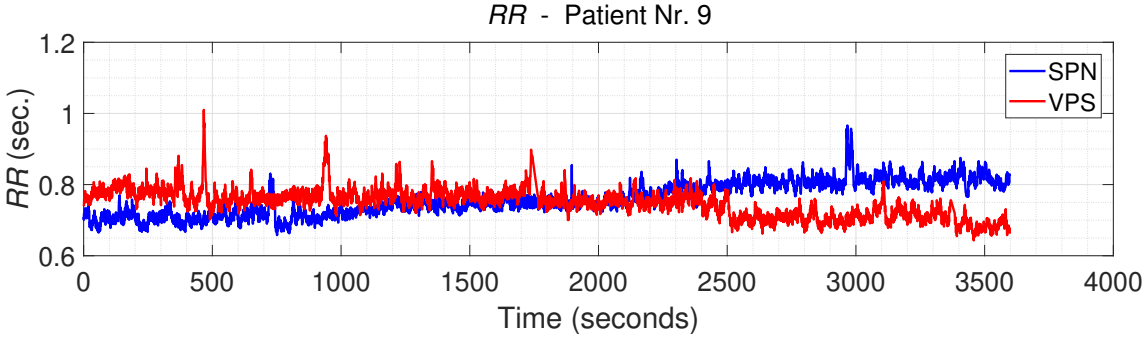

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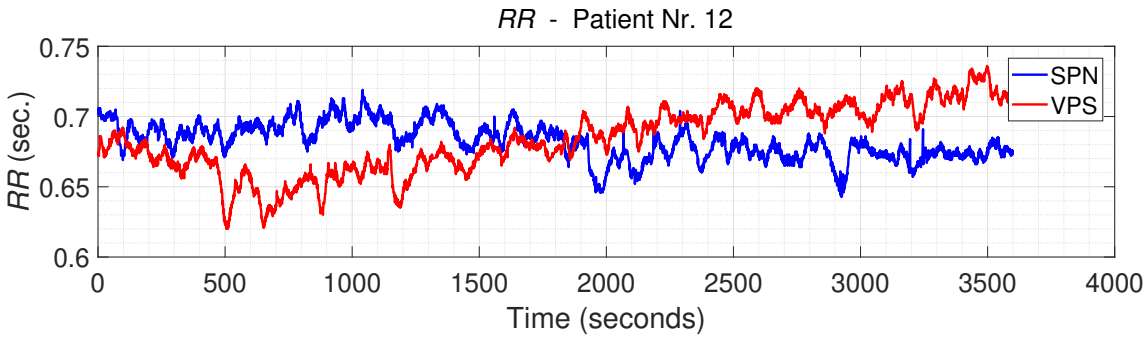

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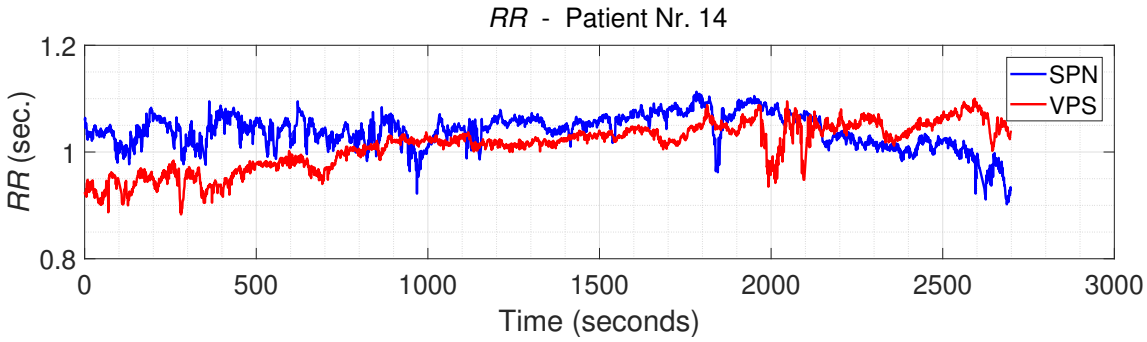

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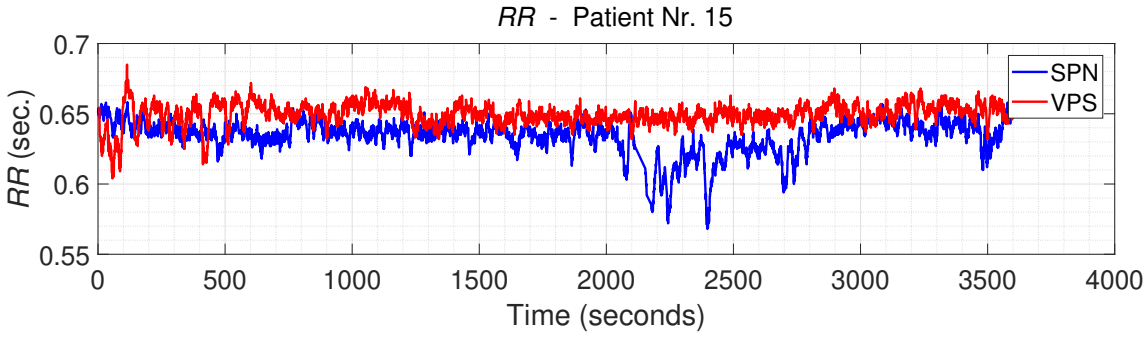
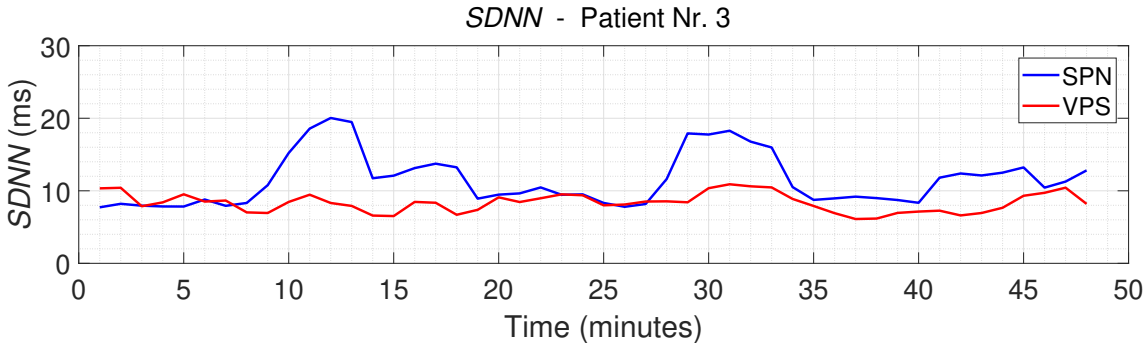
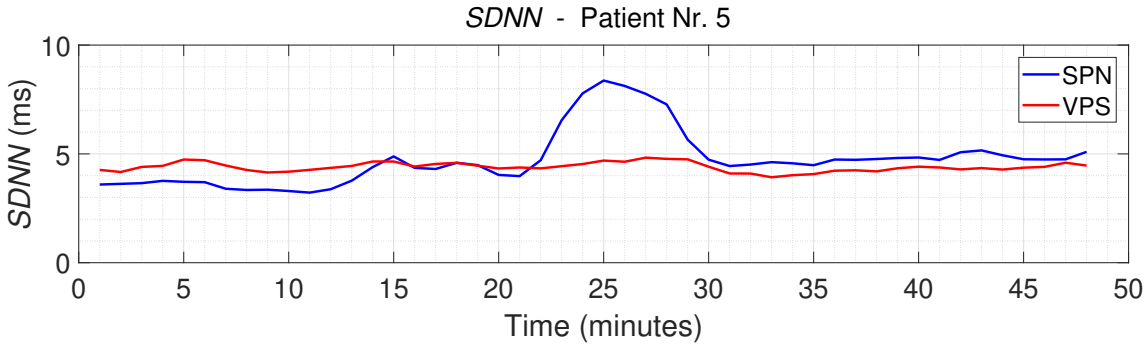


(g)

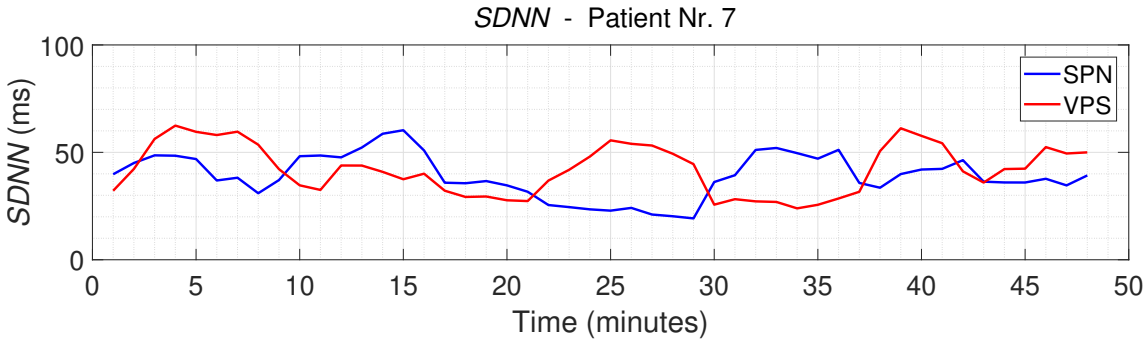
Fig. A.2.4.: RR intervals of patients included to HRV analysis.


SDNN - Patient Nr. 3
SDNN (ms)
Time (minutes)
SPN
VPS

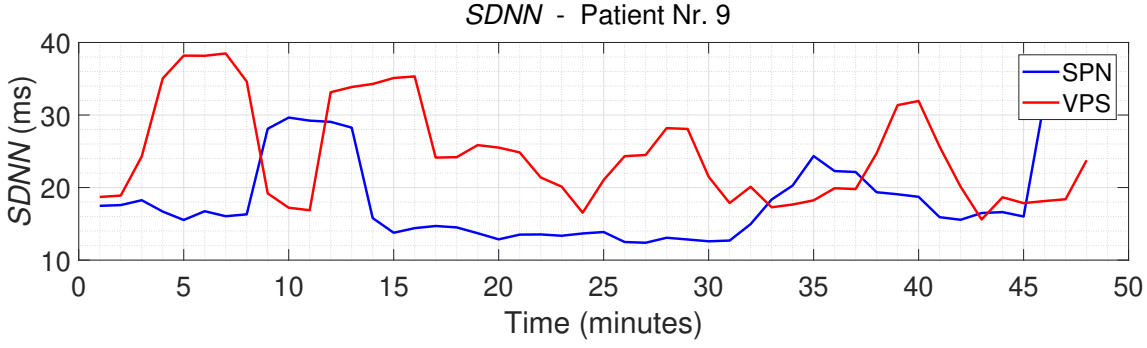
(a)


SDNN - Patient Nr. 5
SDNN (ms)
Time (minutes)
SPN
VPS

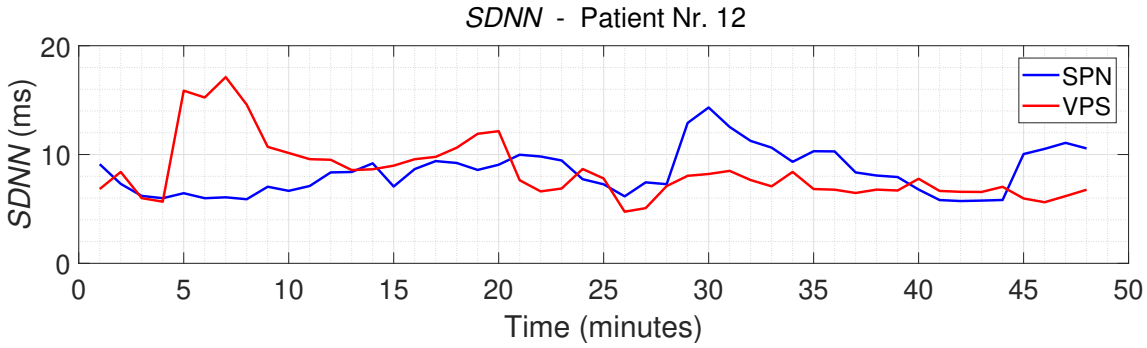
(b)


SDNN - Patient Nr. 7
SDNN (ms)
Time (minutes)
SPN
VPS

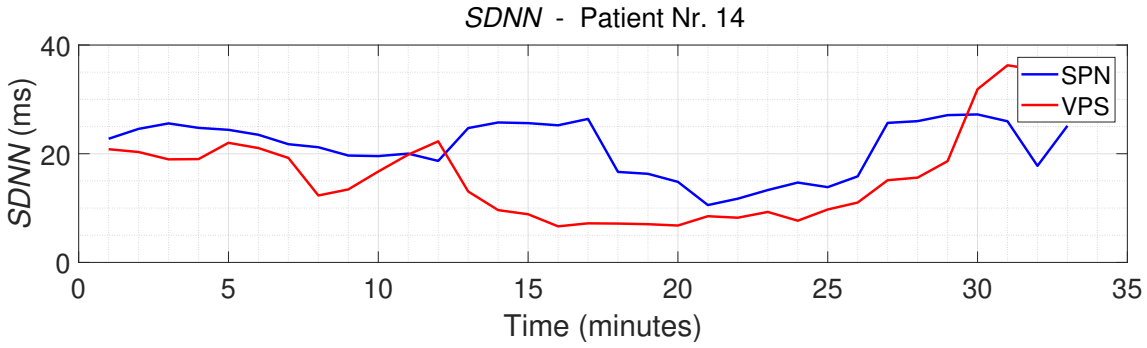
(c)


SDNN - Patient Nr. 9
SDNN (ms)
Time (minutes)
SPN
VPS

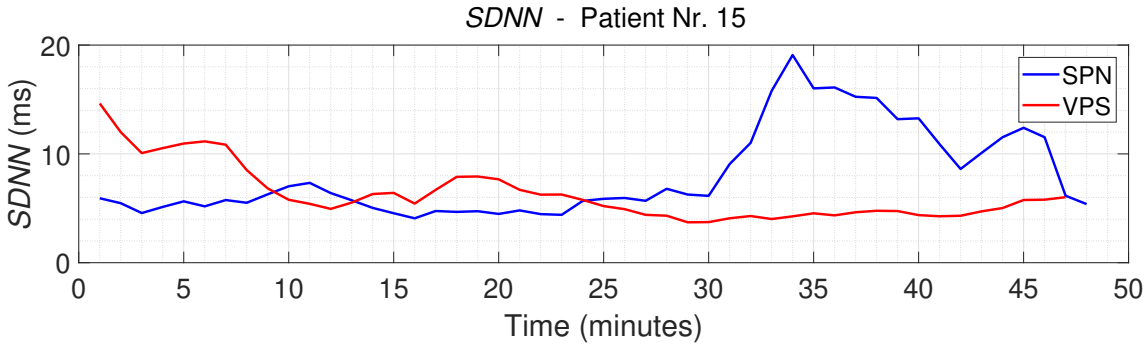
(d)



(e)

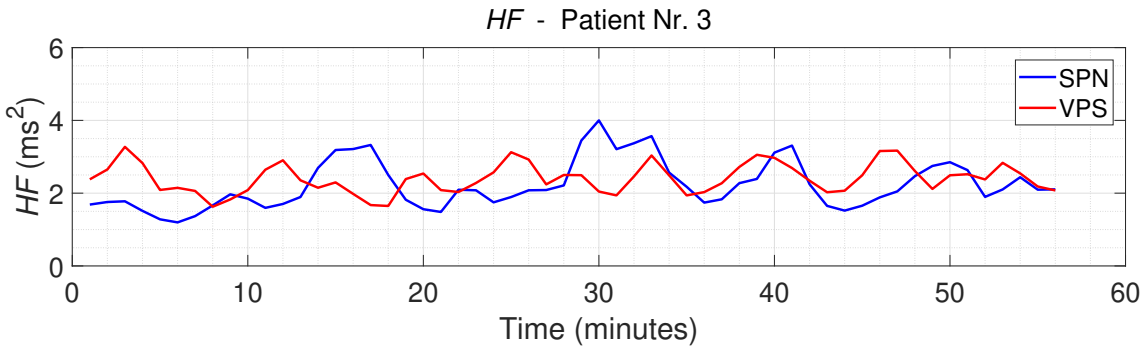


(f)

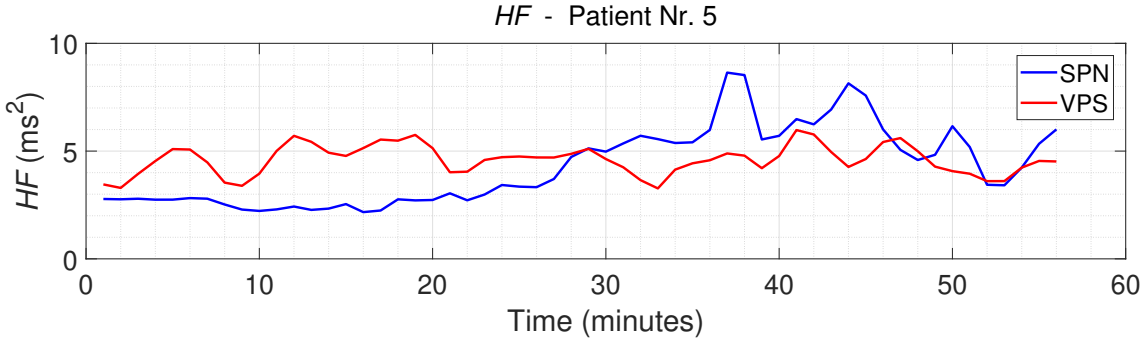


(g)

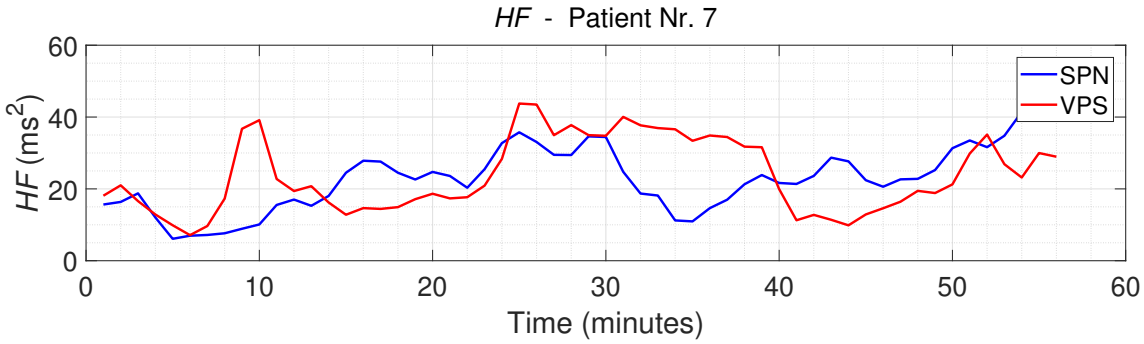
Fig. A.2.4.: Standard deviation of RR-Intervals of patients included to HRV analysis.


HF - Patient Nr. 3
HF (ms2)
Time (minutes)
SPN
VPS
0
2
4
6
0
10
20
30
40
50
60

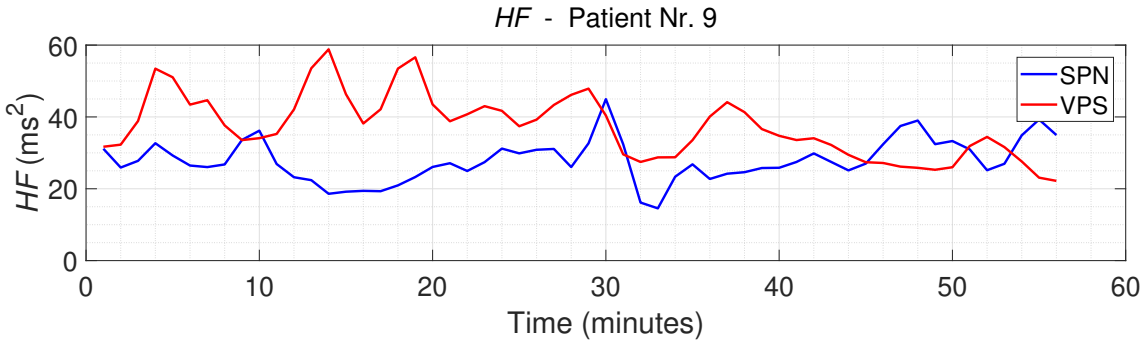
(a)


HF - Patient Nr. 5
HF (ms2)
Time (minutes)
SPN
VPS
0
5
10
0
10
20
30
40
50
60

(b)


HF - Patient Nr. 7
HF (ms2)
Time (minutes)
SPN
VPS
0
20
40
60
0
10
20
30
40
50
60

(c)


HF - Patient Nr. 9
HF (ms2)
Time (minutes)
SPN
VPS
0
20
40
60
0
10
20
30
40
50
60

(d)

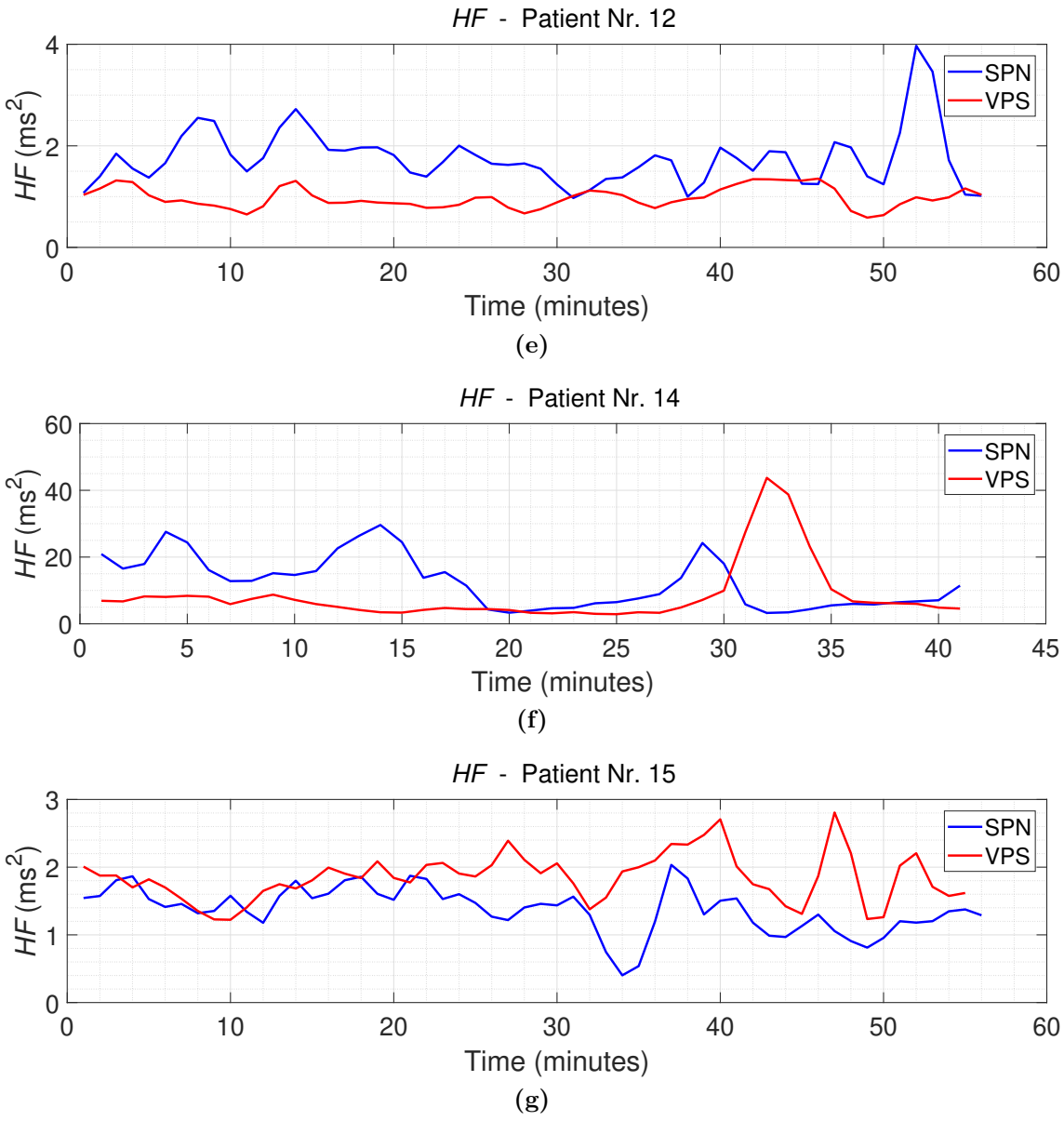
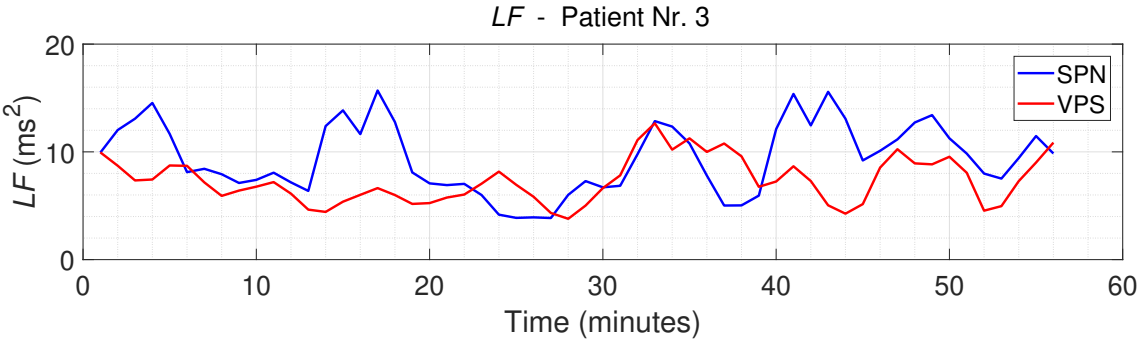
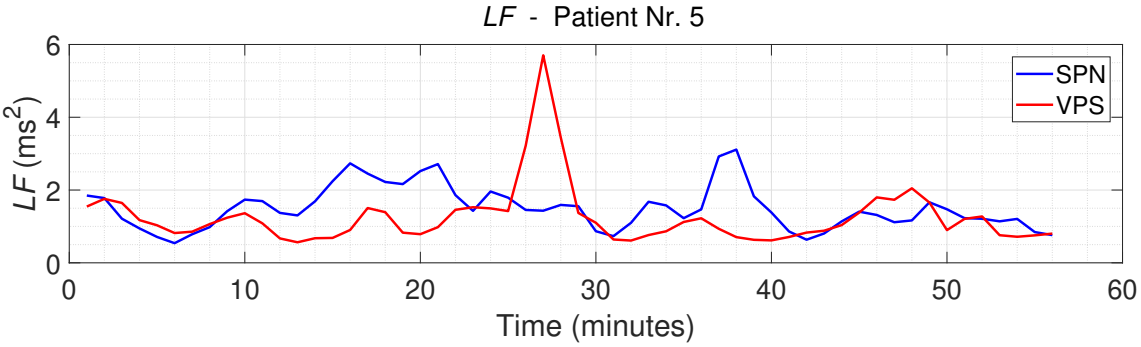


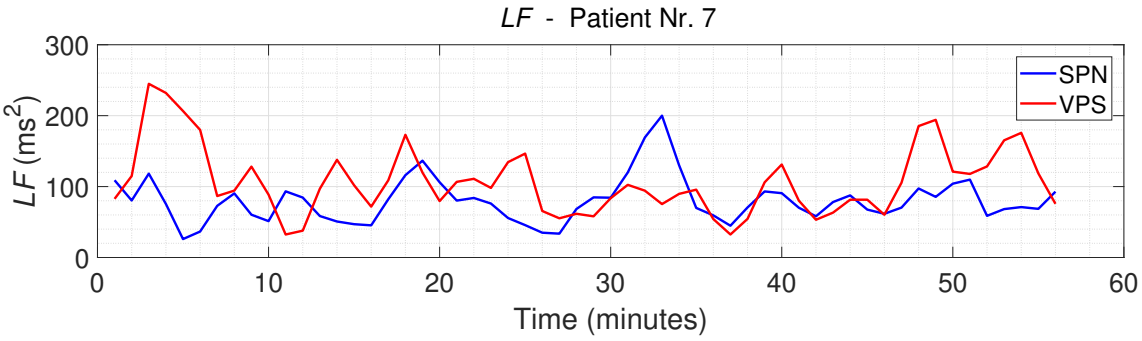
Fig. A.2.4.: High frequency components of HRV of patients included to HRV analysis.


LF - Patient Nr. 3
LF (ms2)
Time (minutes)
SPN
VPS
0
10
20
30
40
50
60

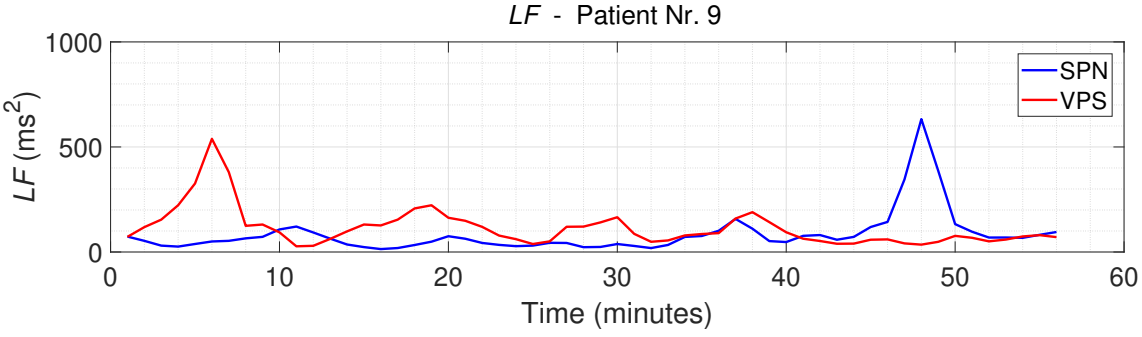
(a)


LF - Patient Nr. 5
LF (ms2)
Time (minutes)
SPN
VPS
0
2
4
6
10
20
30
40
50
60

(b)


LF - Patient Nr. 7
LF (ms2)
Time (minutes)
SPN
VPS
0
100
200
300
10
20
30
40
50
60

(c)


LF - Patient Nr. 9
LF (ms2)
Time (minutes)
SPN
VPS
0
500
1000
10
20
30
40
50
60

(d)

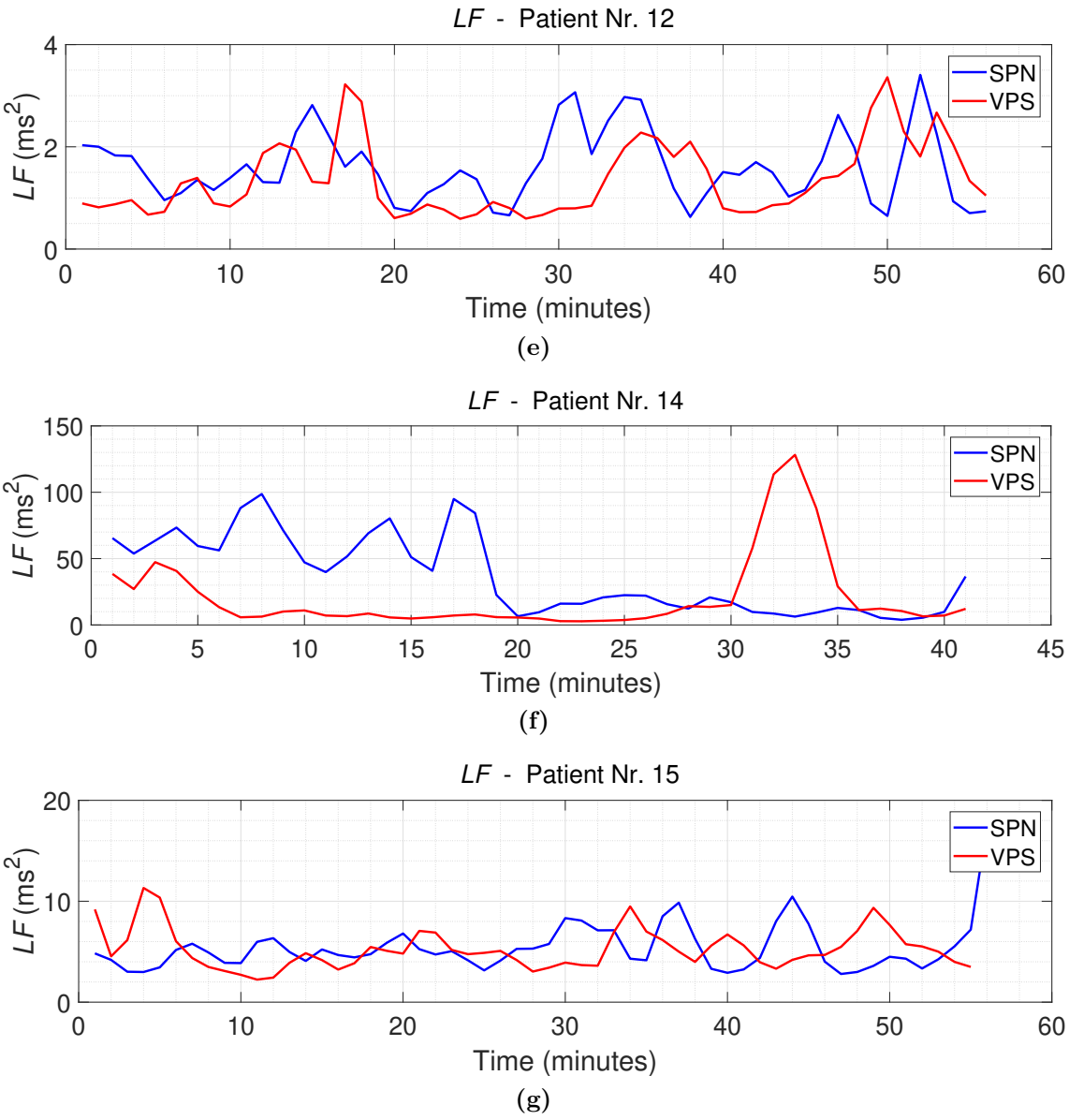
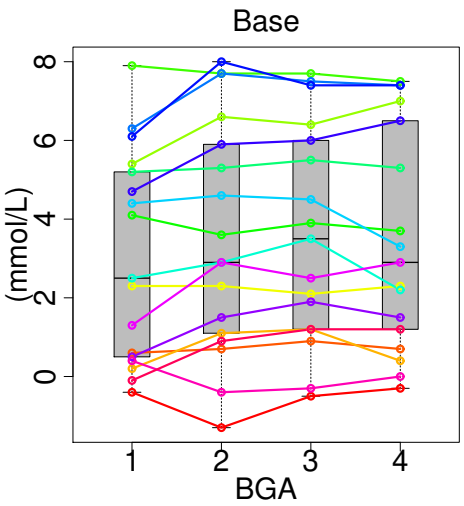
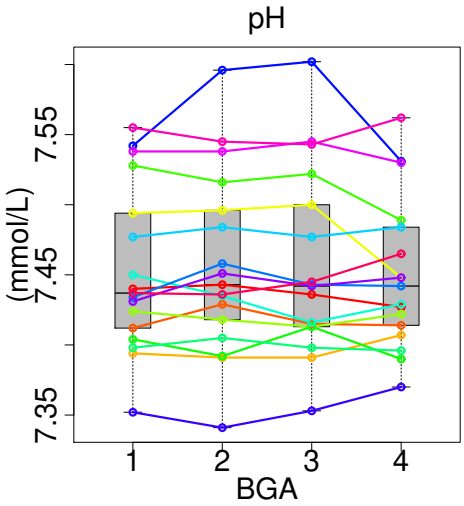


Fig. A.2.4.: Low frequency components of HRV of patients included to HRV analysis.

A.3. Blood Gas Analysis Raw Data



(a)



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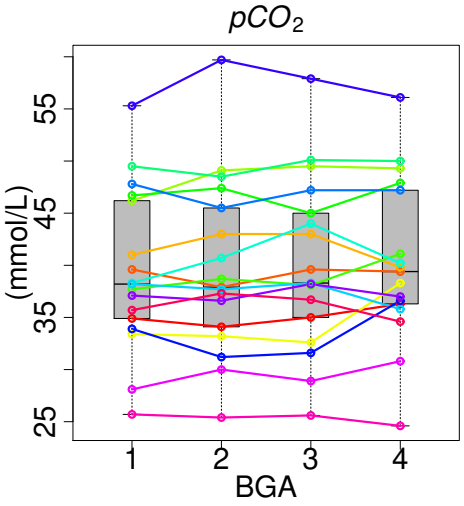
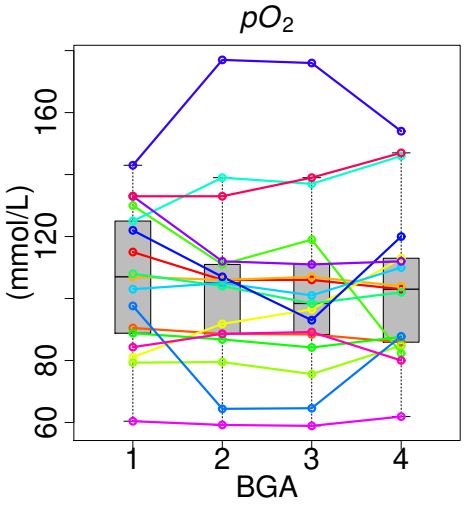
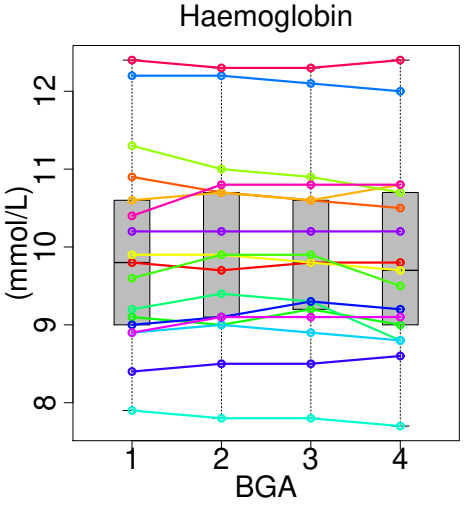


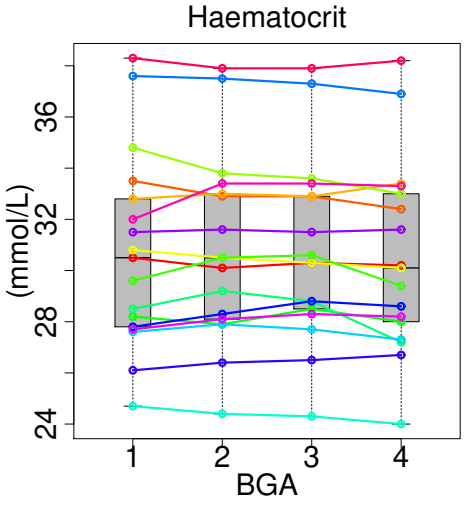
(c)



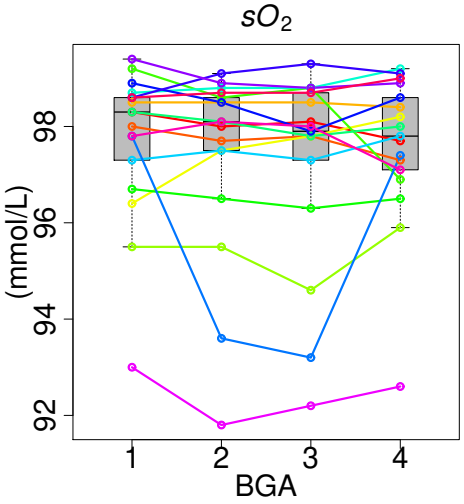
(d)



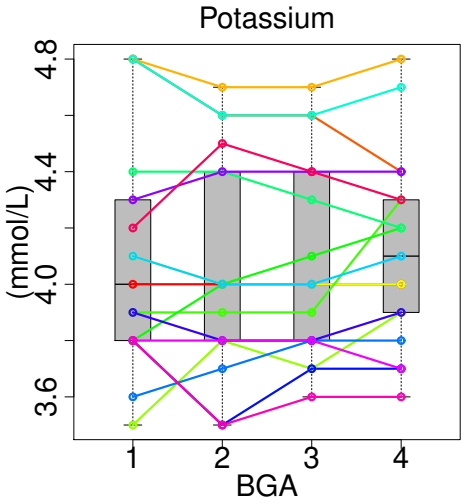
(e)



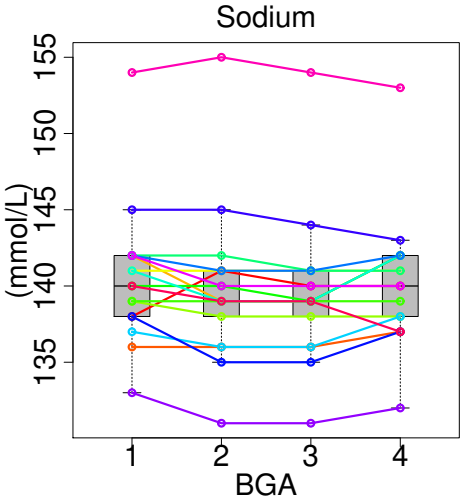
(f)


sO_2
(mmol/L)
92
94
96
98
1
2
3
4
BGA

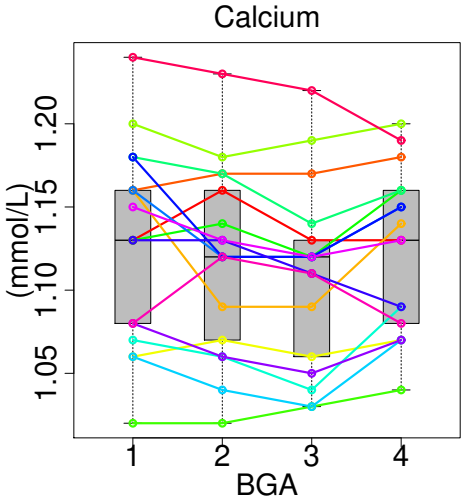
(g)


Potassium
(mmol/L)
3.6
4.0
4.4
4.8
1
2
3
4
BGA

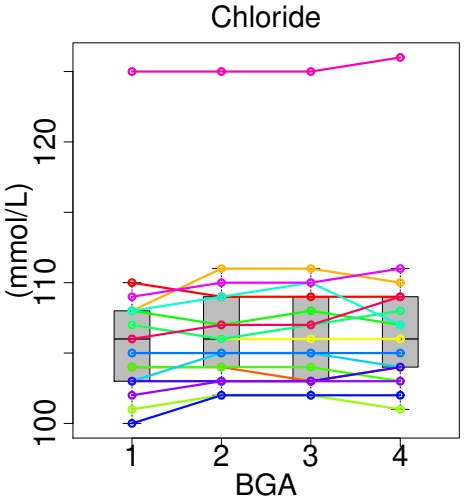
(h)


Sodium
(mmol/L)
135
140
145
150
155
1
2
3
4
BGA

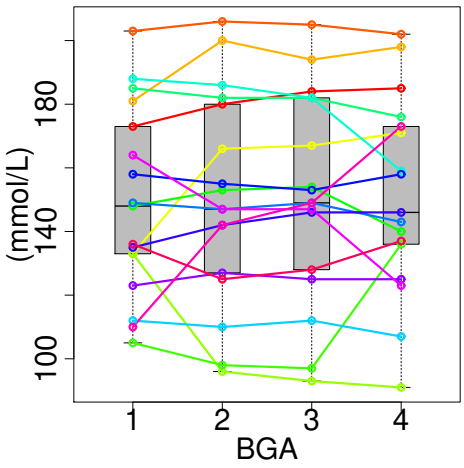
(i)


Calcium
(mmol/L)
1.05
1.10
1.15
1.20
1
2
3
4
BGA

(j)


Chloride
(mmol/L)
100
110
120
1
2
3
4
BGA

(k)


Glucose
(mmol/L)
100
140
180
1
2
3
4
BGA

(l)

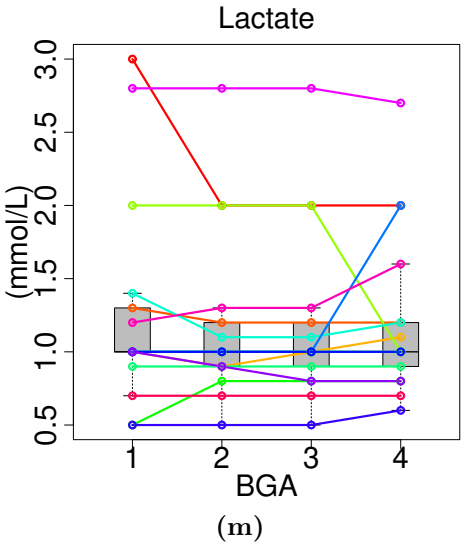


Fig. A.3.1.: Comparing the derived blood gaseses (1 at minute 5, 2 at minute 60, 3 at minute 65 and 4 at minute 120 of the two hour measurement) without respect to the randomisation of SPN-CPAP/PS and Variable PS

A.4. Tables

Pat.Nr.	cBase_1	pH_1	pCO2_1	pO2_1	ctHb_1	Hctc_1	sO2_1	cK_1	cNa_1	cCa_1	cCl_1	cGlu_1	cLac_1
1	-0,4	7,440	34,9	115,0	9,8	30,5	98,3	4,0	138	1,13	110	173	3
2	0,6	7,412	39,6	90,5	10,9	33,5	98,0	4,8	136	1,16	104	203	1,3
3	0,2	7,394	41,0	107,0	10,6	32,8	98,5	4,8	142	1,16	108	181	1,0
4	2,3	7,494	33,4	81,1	9,9	30,8	96,4	4,1	141	1,06	107	133	1
5	5,4	7,424	46,2	79,3	11,3	34,8	95,5	3,5	139	1,20	101	133	2
6	7,9	7,528	37,7	130,0	9,6	29,6	99,2	3,9	139	1,02	104	105	1
7	4,1	7,404	46,7	88,8	9,1	28,2	96,7	3,8	140	1,13	108	148	0,5
9	5,2	7,398	49,5	108,0	9,2	28,5	98,3	4,4	142	1,18	107	185	0,9
10	2,5	7,450	38,3	125,0	7,9	24,7	98,7	4,8	141	1,07	108	188	1,4
11	4,4	7,477	38,2	103,0	8,9	27,6	97,3	4,1	137	1,06	103	112	1
12	6,3	7,434	47,8	97,6	12,2	37,6	97,8	3,6	142	1,16	105	149	1
14	6,1	7,542	33,9	122,0	9,0	27,8	98,9	3,8	138	1,18	100	158	1
15	4,7	7,352	55,3	143,0	8,4	26,1	98,6	3,9	145	1,13	103	135	0,5

Table A.1.: Data of all the first blood gas analysis after 5 minutes of measurement of all patients, without taking the randomisation order into account.

Pat.Nr.	cBase_2	pH_2	pCO2_2	pO2_2	ctHb_2	Hctc_2	sO2_2	cK_2	cNa_2	cCa_2	cCl_2	cGlu_2	cLac_2
1	-1,3	7,443	34,1	106,0	9,7	30,1	98,0	4,0	141	1,16	109	180	2
2	0,7	7,429	37,9	88,6	10,7	32,9	97,7	4,6	136	1,17	104	206	1,2
3	1,1	7,391	43,0	106,0	10,7	33,0	98,5	4,7	139	1,09	111	200	0,9
4	2,3	7,496	33,2	91,8	9,9	30,5	97,5	4,0	141	1,07	106	166	1
5	6,6	7,418	49,1	79,5	11,0	33,8	95,5	3,8	138	1,18	102	96	2
6	7,7	7,516	38,7	111,0	9,9	30,5	98,6	3,9	139	1,02	104	98	1
7	3,6	7,392	47,4	86,8	9,0	27,9	96,5	4,0	140	1,14	107	153	0,8
9	5,3	7,405	48,5	104,0	9,4	29,2	98,1	4,4	142	1,17	106	182	0,9
10	2,9	7,435	40,7	139,0	7,8	24,4	98,8	4,6	139	1,06	109	186	1,1
11	4,6	7,484	37,7	105,0	9,0	27,9	97,5	4,0	136	1,04	105	110	1
12	7,7	7,458	45,5	64,4	12,2	37,5	93,6	3,7	141	1,12	105	147	1
14	8,0	7,596	31,2	107,0	9,1	28,3	98,5	3,5	135	1,12	102	155	1
15	5,9	7,341	59,7	177,0	8,5	26,4	99,1	3,8	145	1,13	103	142	0,5

Table A.2.: Data of all the second blood gas analysis after 60 minutes of measurement of all patients, without taking the randomisation order into account.

Pat.Nr.	cBase_3	pH_3	pCO2_3	pO2_3	ctHb_3	Hctc_3	sO2_3	cK_3	cNa_3	cCa_3	cCl_3	cGlu_3	cLac_3
1	-0,5	7,436	35,0	106,0	9,8	30,3	98,1	4,0	140	1,13	109	184	2
2	0,9	7,415	39,6	88,4	10,6	32,9	97,8	4,6	136	1,17	103	205	1,2
3	1,2	7,391	43,0	107,0	10,6	32,9	98,5	4,7	139	1,09	111	194	1,0
4	2,1	7,500	32,6	96,5	9,8	30,3	97,8	4,0	141	1,06	106	167	1
5	6,4	7,413	49,5	75,6	10,9	33,6	94,6	3,7	138	1,19	102	93	2
6	7,7	7,522	38,1	119,0	9,9	30,6	98,8	3,9	139	1,03	104	97	1
7	3,9	7,413	45,0	84,2	9,2	28,5	96,3	4,1	139	1,12	108	154	0,8
9	5,5	7,398	50,1	98,4	9,3	28,8	97,8	4,3	141	1,14	107	182	0,9
10	3,5	7,416	44,0	137,0	7,8	24,3	98,8	4,6	139	1,04	110	182	1,1
11	4,5	7,477	38,3	101,0	8,9	27,7	97,3	4,0	136	1,03	105	112	1
12	7,5	7,443	47,2	64,6	12,1	37,3	93,2	3,8	141	1,12	105	149	1
14	7,4	7,602	31,6	93,0	9,3	28,8	97,9	3,7	135	1,12	102	153	1
15	6,0	7,353	57,9	176,0	8,5	26,5	99,3	3,8	144	1,11	103	146	0,5

Table A.3.: Data of all the third blood gas analysis after 65 minutes of measurement of all patients, without taking the randomisation order into account.

Pat.Nr.	cBase_4	pH_4	pCO2_4	pO2_4	ctHb_4	Hctc_4	sO2_4	cK_4	cNa_4	cCa_4	cCl_4	cGlu_4	cLac_4
1	-0,3	7,427	36,3	103,0	9,8	30,2	97,7	4,0	140	1,13	109	185	2
2	0,7	7,414	39,4	85,9	10,5	32,4	97,3	4,4	137	1,18	104	202	1,2
3	0,4	7,407	39,8	104,0	10,8	33,4	98,4	4,8	142	1,14	110	198	1,1
4	2,3	7,448	38,3	113,0	9,7	30,1	98,2	4,0	141	1,07	106	171	1
5	7,0	7,422	49,3	84,8	10,7	33,0	95,9	3,9	138	1,20	101	91	1
6	7,5	7,489	41,1	82,3	9,5	29,4	96,9	4,3	139	1,04	103	136	1
7	3,7	7,390	47,9	87,6	9,0	28,0	96,5	4,2	142	1,16	107	140	0,8
9	5,3	7,396	50,0	102,0	8,8	27,2	98,0	4,2	141	1,16	108	176	0,9
10	2,2	7,429	40,2	146,0	7,7	24,0	99,2	4,7	142	1,09	107	159	1,2
11	3,3	7,484	35,8	110,0	8,8	27,3	97,8	4,1	138	1,07	104	107	1
12	7,4	7,442	47,2	87,8	12,0	36,9	97,4	3,8	142	1,15	105	143	2
14	7,4	7,531	36,6	120,0	9,2	28,6	98,6	3,7	137	1,15	102	158	1
15	6,5	7,370	56,1	154,0	8,6	26,7	99,1	3,9	143	1,09	104	146	0,6

Table A.4.: Data of all the fourth blood gas analysis after 120 minutes of measurement of all patients, without taking the randomisation order into account.