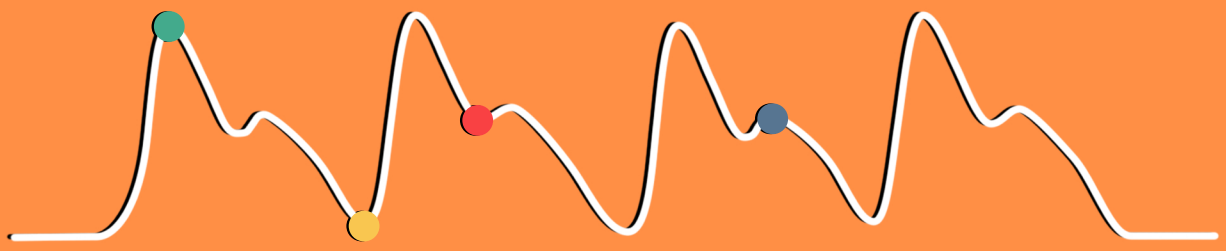
THE PREDICTION OF EARLY SEPSIS WITH WEARABLE DEVICES

P.F. ENGELBERT



University of Twente.

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The prediction of early sepsis with wearable devices

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Acknowledgments

Nine years ago, I started my study career in Enschede with the study technical mathematics. After a few months, I realized that this was not the right study for me and I made the switch to technical medicine. A decision that I have never regretted. The combination of the technical and medical aspects was perfect for me and I have enjoyed the things I have learned. A year and a half ago, I did a short internship at the emergency department of the UMCG and I liked the topic and atmosphere so much that I decided to come back and to do my master graduation research at this department. Now this graduation year is coming to an end and before I present my graduation thesis I would like to thank everyone that made this year possible and have helped me with this research and/or my personal growth.

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Abstract

Objective. Sepsis is a life-threatening organ dysfunction with a mortality rate of 15-25%. Early recognition and timely treatment are necessary to improve the outcome of this infectious disease. The aim of this research is to investigate the potential of novel features extracted from continuously measured photoplethysmography (PPG) and diaphragm electromyography (EMG) as early signs in the prediction of clinical deterioration in ward patients with severe infections. Our hypothesis is that these novel features may be earlier signs of deterioration than the traditional vital signs.

Methods. This research is divided into two sub-studies, where the first sub-study investigated the feasibility of the two chosen wearable devices in the desired study population and the second sub-study consisted of long-term measurements to find out which features are early signs of deterioration. In the second sub-study, the primary goal is to find out whether the parameters were able to distinguish deteriorating and non-deteriorating patients at the general ward up to six hours before the nurse's check-up. The secondary goal is to investigate whether it is possible to predict the overall clinical outcome based on measurements of the first 36 hours after hospital admission.

Results. The feasibility study showed that the chosen wearable devices have met the required yield of more than 60%. The precision and accuracy of the PPG device still left room for improvements and due to limitations in the reference method, the precision and accuracy of the EMG device could not be fully investigated. However, these limitations did not seem to influence the outcome of the long-term study much, as seventeen of the nineteen features gave significant differences in the primary outcome. Five of these features showed significant differences up to six hours before the nurse's check-up. In the secondary outcome, seven of the nineteen features were significantly different and six features showed promising differences.

Conclusion. Based on the results of the long-term study, it can be concluded that several of these features show differences up to six hours before the nurse's check-up and that four features showed significantly differences at the first four hours of recording. This indicates that continuously measured PPG and diaphragm EMG can indeed be of added value in the prediction of clinical deterioration. However, before these wearables can be implemented for clinical usage, the wearables and validation methods need to be improved and more research is needed to make a prediction algorithms based on the features used in this research.

Contents

List of Abbreviations

AI	Augmentation Index
APG	Acceleration Plethysmography
AUC	Area Under the Curve
DAMP	Danger-Associated Molecular Pattern
DPA	Diastolic Peak Amplitude
ECG	Electrocardiography
ED	Emergency Department
EHR	Electronic Health Record
EMG	Electromyography
fs	Sample Frequency
HR	Heart Rate
HRV	Heart Rate Variation
HTA	Health Technology Assessment
ICU	Intenvise Care Unit
IPA	Inflection Point Area
MEWS	Modified Early Warning Score
MU	Motor Unit
MUAP	Motor Unit Action Potential
MWI	Moving-window integration
NF-kb	Nuclear Factor-kb
PAMP	Pathogen-Associated Molecular Pattern
PMN	Polymorphonuclear leukocyte
PPG	Photoplethysmography
PPR	Pattern Recognition Receptor
PtP	Peak-to-Peak
qSOFA	quick Sequential Organ Failure Assessment
RA	Relative Amplitude
RI	Reflection Index
RR	Respiratory Rate
SCCM	Society of Critical Care Medicine
SIRS	Systemic Inflammatory Response Syndrome
SNR	Signal-to-Noise Ratio
SOFA	Sequential Organ Failure Assessment
SPA	Systolic Peak Amplitude
SQI	Signal Quality Index
Te	Expiratory Time
Ti	Inspiratory Time
TPR	Total Peripheral Resistance
TS	Template Subtraction
UMCG	University Medical Center Groningen

Chapter 1

Introduction

Sepsis, a life-threatening organ dysfunction induced by an infection, is a common, deadly, and expensive disease.[1–3] With a mortality rate of 15-25%, sepsis is associated with 11 million deaths worldwide in 2018, which is almost 20% of all global deaths.[4–6] Therefore, sepsis carries a large global burden of disease. The cost of sepsis care is increasing over the last few years. For inpatient admissions and skilled nursing facility admissions the cost is estimated around $41.5 billion in the US in 2018, which is an increase of 40% in comparison to 2012.[7] Survivors of sepsis have an impaired quality of life and a higher mortality in the long-term.[8,9]

In order to improve the outcome, early recognition and timely treatment of sepsis are of utmost importance. Various strategies are being implemented in hospitals to accelerate this process, such as scoring systems to screen high-risk patients.[4,10] However, even with these strategies implemented a significant portion of the patients presented at the emergency department (ED) with a (suspected) infection will deteriorate.[11,12] An unpublished study at the ED of the University Medical Center Groningen (UMCG) showed that 22.5% of the ED patients deteriorated within 72 hours. Most of these deteriorations do not happen at the ED, but at the ward where patients are not continuously monitored. Their vital signs are only monitored during the repeating check-ups by the nurses.[13,14] These check-ups are done a few times per day and a change in vital signs can potentially go unnoticed for a few hours.[15,16] This can cause a delay in recognizing a deteriorating patient and is therefore increasing the risk of an unplanned intensive care unit (ICU) admission, associated with an increased mortality rate.[17,18]

To improve the recognition of a deteriorating patient at the ward, a lot of research is performed with wearable devices.[19] These devices allow easy and cheap continuously monitoring of vital signs.[20] Although continuously monitoring can reduce the time to detect deteriorating patients, there is still room for improvement. The notification algorithms of the wearable devices are based on the scoring systems used by the nurses, such as the Modified Early Warning Score (MEWS). These scoring systems only used the absolute values of the vital signs. Churpek et al. (2017) compared different scoring systems for patients outside the ICU and found that scores with the highest sensitivities had the lowest specificities and vice versa, making none of the scores a good predictor for deterioration.[21]

It is possible that the vital signs used in the scoring systems may not indicate the start of deterioration, but only reflect changes in a later stage of the deterioration. For example, decreasing oxygen saturation is currently an important signal for detecting respiratory failure and used in the MEWS. However, there is a potential time delay between the onset of a hypoxic event and a decrease in oxygen saturation.[22] This could mean that the oxygen saturation does not decrease at the start of respiratory distress, but changes when the body can no longer compensate for the distress.[23] Our hypothesis is that one of the first changes in respiratory distress would be an increase work of breathing to maintain the same amount of tidal volume and respiratory rate. Monitoring of the compensation mechanism, such as muscle activity of the respiratory muscles during respiratory

distress, may give an earlier sign of deterioration than the traditional vital signs.

1.1 Technical medical question

The aim of this research is to investigate the potential of early signs in the prediction of clinical deterioration in ward patients with severe infections. These early signs can presumably be measured using continuously measured respiratory muscle activity and blood volume changes. These physiological waveforms can be recorded with electromyography (EMG) of respiratory muscles and photoplethysmography (PPG). An easy and patient friendly way to measure these waveforms is with the use of wireless wearable devices. The main research question for this study is as follows:

How can PPG and diaphragm EMG be of added value in the prediction of clinical deterioration in ward patients with severe infections?

Two sub-questions are formulated to support this research question. The aim of first sub-question is to investigate the feasibility of the chosen wearable devices. The aim of the second sub-question is to assess the potential of the waveforms in detecting early signs of deterioration.

Sub-question 1

What is the feasibility of continuous diaphragm EMG and PPG waveform in patients with a severe infection at the ED and the ward?

Sub-question 2

Which features extracted from continuous diaphragm EMG and PPG are early signs of deterioration in patients with a severe infection?

1.2 Overall study design

This research was part of the Acutelines data- and biobank project of the UMCG. In short, Acutelines is a large scale project at the ED of UMCG to collect and store data and biomaterials of patients acutely admitted to the hospital. The goal of Acutelines is to form a data- and biobank with data and biomaterials of acute ill patients, in order to facilitate research to the pathophysiology, diagnosis, treatment and prognosis of severe diseases.

Each sub-question of this research was investigated as a sub-study. First, a feasibility study was performed to determine the usability of two wearable devices for measurements on acutely ill patients. After that, a long-term study was performed with the wearables to investigate the usage of PPG and diaphragm EMG in early recognition of deterioration in patients with severe infections.

1.3 Thesis structure

In order to better understand and interpret the research question and results, first the pathophysiology of sepsis and the technical contexts and the working mechanisms of the chosen waveform signal will be elaborated in Chapter 2. The chosen wearable devices will also be introduced in this chapter. The next chapter is about the feasibility study, the methods, results, discussion, and conclusion of this study will be discussed. Chapter 4 will describe the methods, results, discussion, and conclusion of the long-term study. The last chapter of this thesis is the overall conclusion of the research. The results of both sub-studies will be summarized and future recommendations will also be given in the last chapter.

Chapter 2

Background

2.1 Clinical background

Although sepsis has long been recognized, there was no clinical definition of sepsis until the late 20^{th} century. In 1991, a consensus statement was established by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) during a consensus conference.[24] They defined the criteria for Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis, and septic shock, where sepsis was defined as infection leading to the onset of SIRS (Table 2.1).

Table 2.1: Systemic Inflammatory Response Syndrome (SIRS) Criteria.

SIRS Criteria (Any 2 of the following)	Value
Heart rate	> 90
Respiratory rate	> 20
Temperature	> 38 or < 36
White blood cell count	$> 12000/\text{mm}^3$ or $< 4000/\text{mm}^3$ or 10% bandemia

Since then, the definitions were twice revised, with the latest revision in 2016 by a task force generated by the SCCM and the European Society of Intensive Care Medicine. They published the new consensus definitions, *Sepsis-3*, where sepsis is defined as a life-threatening organ dysfunction caused by a deregulated host response to infection.[1] In the Sepsis-3 definition, the terms SIRS and severe sepsis were eliminated. The authors recommended a new scoring system to define organ dysfunction, the Sequential Organ Failure Assessment (SOFA) score (Table 2.2), where a higher score is associated with an increased possibility of mortality. However, some components of SOFA (such as creatinine or bilirubin level) require laboratory testing and may therefore not be promptly to capture an organ dysfunction. Furthermore, other components of SOFA are complex to determine in a non-ICU setting. Therefore, a new and easier measure was described by the task force, the quick SOFA (qSOFA, Table 2.3). This modified version of the SOFA score has only three components and can quickly and repeatedly be assessed. The task force suggests that the qSOFA score is to be used to prompt clinicians for further investigation of organ dysfunction. However, an Australian study stated that, although qSOFA ≥ 2 has a high specificity, the poor sensitivity may limit this utility as a screening tool.[25]

Table 2.2: Sequential (sepsis-related) Organ Failure Assessment (SOFA) score

	SOFA score				
Organ Sytem	0	1	2	3	4
Respiratory PO2/FiO2, mmHg(kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation platelets, x $10^3/mm^3$	≥155	<155	<100	<50	<20
Liver, bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system, Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Renal creatinine, mL/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine ourput, mL/d				<500	<200

FiO2: fraction of inspired osygen; MAP: mean arterial pressure; PO2: partial presure of oxygen.

Table 2.3: quick Sequential (sepsis-Related) Organ Failure Assessment (qSOFA) score

Criteria	Points
Respiratory rate ≥22/min	1
Systolic blood pressure ≤100 mmHg	1
Change in mental status	1

2.1.1 Normal response to an infection

Before looking into the mechanisms that are involved in sepsis-induced organ failure, the normal response of the body to an infection needs to be explained. The normal host response to infection is a complex process that locates and controls bacterial invasion while initiating repair of damaged tissue. The response is initiated when innate immune cells recognize and bind to microbial components. The innate immune cells, particularly macrophages, have pattern recognition receptors (PRRs) on their surface. These PRRs recognize and bind to the pathogen-associated molecular patterns (PAMPs) of microorganisms.[26,27] PRRs can also recognize danger-associated molecular patterns (DAMPs), which are endogenous danger signals that are released during the inflammation.[28] Binding of PRRs to PAMPs or DAMPs initiates a series of effects.[29]

Firstly, it activates polymorphonuclear leukocytes (PMNs). These leukocytes will then aggregate to the vascular endothelium and migrate to the site of the infection.[30] There, the PMNs will release mediators that are responsible for vasodilation, hyperemia, and increased microvascular permeability.

Besides the activation of PMNs, the binding of immune cell surface receptors to microbial components also starts a signaling cascade that activates nuclear factor-kb (NF-kb), which is a protein complex that controls transcription of DNA, cytokine production and cell survival. The activated NF-kb induces the activation of a large set of genes, such as proinflammatory cytokines and nitric oxide.[31] These proinflammatory cytokines are responsible for various effects, including the recruitment of more PMNs and macrophages.

The overall response to infection is regulated by proinflammatory and anti-inflammatory mediators.[32–34] If the proinflammatory and anti-inflammatory mediators are in balance, the initial infection will be overcome, homeostasis will be restored, and healing of the injured tissue will be the end result.[35,36]

2.1.2 Transition to sepsis

However, when the release of proinflammatory mediators exceeds the boundaries of the local environment, the response becomes generalized, resulting is sepsis. The cause for the generalized response is uncertain, but it is most likely a multi-factorial cause. An uncontrolled production of proinflammatory mediators may be of influence.[37,38] When there is a large amount of proinflammatory mediators released at the local site, the mediators might migrate into the bloodstream. With the circulation of the blood, the proinflammatory mediators spread through the vascular system and create proinflammatory environments throughout the body. Furthermore, the micro-organisms responsible for the initial infection release components that contribute to the progression of a local infection to sepsis.[39] Elevated levels of bacterial cell wall components and bacterial products in the bloodstream are associated with sepsis and multiple organ dysfunction.[40,41] Another component in the generalization of a local infection may be the complement activation. The complement system helps clear pathogens from an organism.[42] In both animal and human sepsis studies evidence is found that complement activation has occurred, as reflected by appearance of complement activation products in the bloodstream. These complement activation products result, even in low concentrations, in intense proinflammatory activity.[43]

2.1.3 Effects of sepsis

The generalization of the initial infection can lead to cellular and vascular dysfunctions, which are the precursors to organ dysfunctions.[44,45] Any organ system can be affected by the consequences of sepsis. Usually multiple organs are affected and the mortality of sepsis is correlated with the number of organs that are affected.[46] In the clinical practice, the cardiovascular, respiratory, renal, neurological, hematological, and hepatic systems are most often affected and the organ failures of these systems are therefore also the most broadly studied. The underlying mechanisms of organ dysfunction are similar for all organs.[45] The focus of this research will be on the cardiovascular and respiratory dysfunctions, the specific mechanisms of these two systems will therefore be elaborated at the end of this section.

Mechanisms of organ dysfunction

One of the key mechanisms of organ dysfunction are the cellular abnormalities that occur as a result of sepsis. There are two main abnormalities: the activation of cell death pathways and dysfunction of the mitochondria.

The cell death pathways are activated either through direct interaction with pathogens or as a result of the pathophysiology of the inflammation. Four of the cell death pathways that are associated with sepsis are necrosis, pyrosis, apoptosis, and autophagocytosis.[47] Necrosis is a non-programmed cell death that can be triggered by factors released by a pathogen and it increases the local inflammation through extracellular release of DAMPs. Pyrosis is a programmed cell death by rapid rupture of the plasma membrane and also results in the release of DAMPs. Another programmed cell death is apoptosis, which is triggered by stress stimuli and mitochondrial products. The proinflammatory mediators present during sepsis delay apoptosis in activated macrophages and neutrophils. Autophagy is a natural process by which cytoplasmic substances or pathogens are swallowed by the autophagosome of the cell. The autophagosome is then fused with a lysosome to be degraded. During sepsis, autophagy is decreased. All these types of cell death pathways are prolonging or augmenting the inflammatory response and therefore contributing to the development of organ dysfunction.[48]

Another cellular abnormality contributing to organ dysfunction during sepsis is mitochondrial dysfunction. The mitochondrion is a key organelle for multiple essential cellular processes. Many mitochondrial functions are altered during sepsis. In septic patients, the mitochondrial morphology may change indicating that a mitochondrial energetic crisis may be involved in organ dysfunction. The energy production of the mitochondria is reduced and the affected mitochondria release

DAMPs, which further augment the immune response. Overall, the mitochondrial dysfunction leads to cytotoxicity and the development of organ dysfunction.[49]

Besides the cellular abnormalities, micro-circulatory alterations are also key mechanism in the pathogenesis of organ dysfunction.[50] As a result of an imbalance in coagulation and fibrinolytic systems, the formation of microthrombosis occurs. Microthrombosis clogs the capillaries, thereby reducing the number of functional capillaries. This increases the diffusion distance for oxygen and results in tissue hypoxia.[50]

The other key mechanism is an altered endothelial function. The endothelium is a single cell layer that lines the inner surface of blood vessels and the lymphatic system. It forms the barrier between the vessels and the tissue and has a major role in the vascular tone. Furthermore, the endothelium controls the blood flow and is involved in the immune response.[51] During sepsis the interactions between endothelial cells and activated PMNs may cause the normal cell-cell connections of the endothelium to disrupt. This will increase the permeability of the endothelium, resulting in the formation of protein-rich tissue edema. Furthermore, the glycocalyx is disrupted early in the sepsis process. The glycocalyx is a complex network of macromolecules that covers the apical side of the endothelium and regulates the microvascular tone and the endothelial permeability.[52] The disruption of the glycocalyx further increases the permeability of the endothelium and thus also the formation of edema. The formation of edema increases the diffusion distance for oxygen and decreases the amount of intervascular fluid.

Hemodynamic dysfunction

Hemodynamic dysfunction is the organ-specific dysfunction of sepsis for the cardiovascular system. However, the hemodynamic dysfunction affect all other organ systems and is therefore another important mechanism for multiple organ dysfunctions in sepsis.

The most common feature of hemodynamic dysfunction in patients with sepsis is hypotension. Hypotension is caused by multiple factors of the pathophysiology of sepsis. One factor is an unintended consequence of the release of vasoactive mediators. Their purpose is to improve the metabolic autoregulation by applying appropriate local vasodilation. However, with the generalization of the inflammatory mediators, the vasodilation is also generalized. Another factor is the formation of edema as a result of the increased endothelial permeability causing hypovolemia and aggravating the hypotension. As a result of the hypotension, the tissue perfusion is altered and increased lactate levels are found in the bloodstream.

Moreover, during sepsis, myocardial depressant factors are released in the bloodstream, causing myocardial dysfunction.[53] This myocardial dysfunction is associated with decreased left and right ventricular ejection fractions and decreased blood flow through the body.[54]

Respiratory dysfunction

As the lungs have a large microvascular surface, the endothelial and microvascular abnormalities during sepsis can lead to prominent lung injuries. In the pulmonary capillaries, the endothelial dysfunction disturbs the blood flow and enlarges the permeability, resulting in interstitial and alveolar edema. The edema results in a ventilation-perfusion mismatch and will lead to hypoxemia, hyperventilation, and ultimately to respiratory alkalosis, which will be amplified if there is also metabolic acidosis.[45] In severe cases where sepsis progresses in the lungs, the patient also develops acute respiratory distress syndrome and mechanical ventilation is often necessary.

2.2 Technical background

In this research, early signs of the hemodynamic and respiratory dysfunction in patients with infections will be investigated with continuously measured PPG and diaphragm EMG waveforms. An important part of this research are the two wearable devices used for the measurements and the

waveforms they measure. The first few months of this research, I have immersed myself in wearable devices and contacted multiple companies to discuss the possibilities to use their wearable devices for Acutelines. However, most companies did not want to share the raw signals of their wearables, which was a hard requirement for us. Therefore, their wearable devices were not an option for us. We found two companies who wanted to share the raw signals and collaborate with us on this project, DiagnOSAS and Sencure (previously known as ItoM Medical). Six months after the start of this research, both devices were delivered and ready to use for the sub studies.

OSAsense (DiagnOSAS B.V., Haaksbergen, The Netherlands) is a wearable pulse oximeter, that measures PPG signals. For the diaphragm EMG measurements the ExG measurement device from Sencure (Roden, The Netherlands) was used. The ExG measurement device will from now on be called 'Sencure'. The mechanisms behind PPG and EMG measurements, the influence of the cardiovascular and respiratory systems on these type of measurements, and the technical aspects of the devices and the measurements will now be explained.

2.2.1 Photoplethysmography

PPG is a simple technique to measure changes of blood volume in tissues.[55] The technology only requires a light source and a light detector. The light source illuminates the tissue and the light detector measures the intensity of the transmitted or reflected light. The intensity is dependent on the absorption of light, which is associated with the tissue perfusion. PPG waveform therefore reflects the blood movement in the vessels at the measuring site. For PPG measurements at the fingertip, the transmitting principle, where the light source is on one side of the fingertip and the light detector is on the other side, is most commonly used (see Figure 2.1).

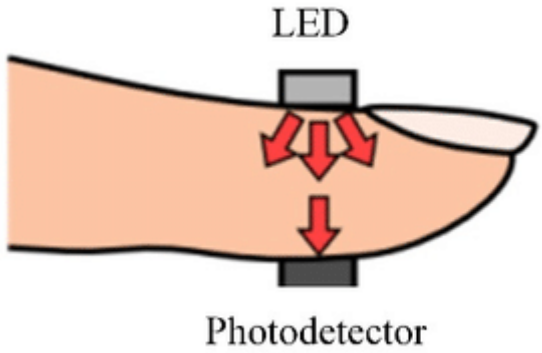


Figure 2.1: Transmitting principle of PPG.[56]

Red (∼700 nm) or infrared (780-1000 nm) are the most commonly used wavelengths in PPG technology, because the light absorption of blood at these wavelengths depends on the hemoglobin of red blood cells. Changes in the PPG signals are therefore a reflection of the blood volume changes, this part of the PPG is called 'AC', derived from alternating current in electrical circuits. When PPG waveform is mentioned, only the AC part of the PPG signal is meant. There is also a DC part in PPG signals, this is the unchanging background absorption and it depends on the non-pulsatile component of arterial blood, venous blood and other structures, such as thickness of the finger, color of skin, and amount of fat and muscle tissue, see figure 2.2.

The PPG waveform is influenced by various physiological systems. Although the origin of the different components of the PPG waveform are still not fully understood, it is known that the cardiovascular and respiratory systems influence the PPG waveform. The clearest influence of the cardiovascular system is the pulsatile AC component, which is synchronous with the heart rate. The rising edge of the waveform is defined as the anacrotic or systolic phase and the falling edge as

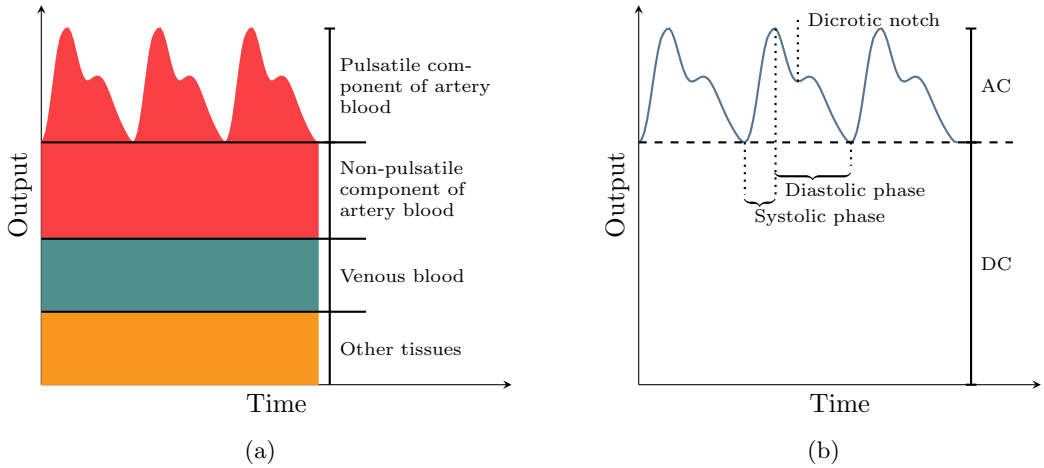


Figure 2.2: Example of PPG signal

the catacrotic or diastolic phase. In subjects with healthy compliant arteries, a dicrotic notch can be seen in the diastolic phase. In subjects with a degree of vasodilation, the dicrotic notch moves toward the baseline and can even disappear from the waveform.[57] Damping of the PPG waveform has been associated with an increased peripheral resistance and a reduction of vessel compliance.[58] Furthermore, the force of ventricular contraction could potentially be determined by the steepness of the slope of the systolic phase.[57]

The respiratory system can modulate the PPG waveform in three different ways, by amplitude modulation, baseline wander, and frequency modulation. Changes in intrathoracic pressure during inhalation causes reduced stroke volume, which is shown as amplitude modulation of the PPG waveform. The baseline wander is also a result of the changes in intrathoracic pressure transmitted through the arterial tree. Furthermore, deep breaths have been reported to cause vasoconstriction of peripheral arteries, which is also shown as baseline wander in PPG waveforms.[59] Frequency modulation is the manifestation of an increased or decreased HR during, respectively, inhalation and exhalation.[60]

Figure 2.3: OSAsense

OSAsense

The OSAsense is a wearable pulse oximeter and consists of a wristband with a monitor and a finger pulse oximeter, see Figure 2.3. The display of the wristband shows the saturation, heart rate and PPG waveform. Besides these parameters, the OSAsense also determines the acceleration of the wristband. The PPG signals are measured using red (660 nm) and infrared (910 nm) light and are determined by the amount of light transmitted through the fingertip, not the amount of absorbed light, which is in contradiction to clinically used bedside monitors.

In this research, the accelerometer data was measured with a sample frequency (fs) of 2 Hz. In the first eight measurements with the OSAsense the PPG signal was measured with an fs of 100 Hz. All other measurements with the OSAsense had an fs of 50 Hz for the PPG signals. The OSAsense does not measure the signals with a constant fs, the true fs of the PPG signals were in the range 98.6-100 Hz or 48.2-50 Hz. In the analysis of the PPG signals only the red light signals were used. The raw data from the devices was provided by the company.

2.2.2 Diaphragmatic electromyography

EMG is a technique that records the electrical potentials produced during muscle contractions. It uses electrodes placed on the skin or inserted in the muscle tissue. Surface EMG is most commonly used, because it is non-invasive and more easy to use than intramuscular EMG.

As said, EMG measures the electrical activity of muscles. This electrical activity originates from motor units (MUs), which are the functional entities of the neuromuscular system. Each MU is made up of a motor neuron and a group of muscle fibers. The central nervous system can stimulate the motor neuron, which then generates an action potential in all muscle fibers of the MU by releasing neurotransmitters. This will cause the muscle fibers to reorganize themselves in a way that shortens the muscle and the muscle will contract. The summation of these action potentials is called motor unit action potential (MUAP). The central nervous system can control the force of muscle contraction in two ways, by changing the number of activated MUs, spatial recruitment, or by changing the firing rate of the active MUs, temporal recruitment.[61]

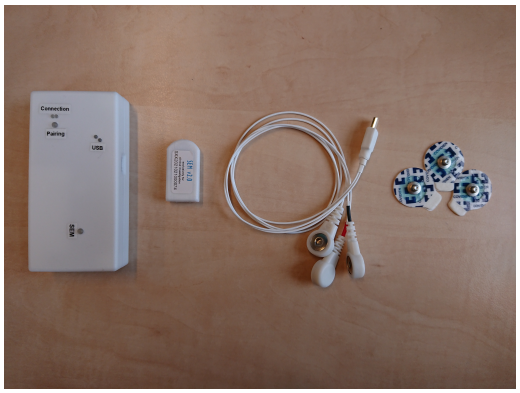
It is possible, with the use of intramuscular electrodes, to measure the individual MUAPs. Surface electrodes however are less sensitive for the individual electrical activity of MUs than intramuscular electrodes. EMG measurements with surface electrodes will therefore give the summation of all MUAPs of the underlying muscle tissue. When the muscle force increases, more MUAPs are created by spatial or temporal recruitment. This increase in MUAPs will result in a higher amplitude of the surface EMG signal. Amplitude features of surface EMG are therefore reflections of the actual degree of muscle activation.[61]

In this research diaphragmatic surface EMG is used. The diaphragm is a muscle that separates the thoracic cavity and the abdominal cavity and is the main muscle of respiration.[62] Surface EMG recordings of the diaphragm pose some challenges as the diaphragm is not a subcutaneous muscle. Loss of signal power occurs through the tissues interposed between the electrodes and the diaphragm. Correct electrode placement can reduce the amount of interstitial tissue and is therefore key.[62] Furthermore, due to the loss of signal power and interstitial tissue, there is a higher potential of interference of electrical signals from different muscles, such as the abdominal muscles and the heart. Signal processing and filtering can (partly) remove these interferences from the EMG signal.

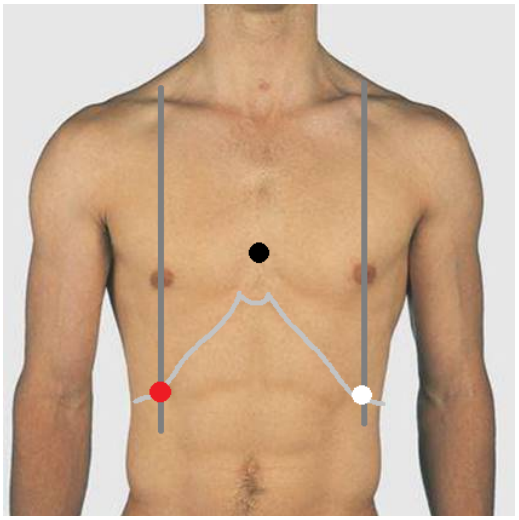
As the diaphragm is the main muscle involved in respiration, the respiratory system has a great influence on the diaphragmatic EMG signals. An increase in respiratory rate is achieved by activating the diaphragm more frequently. This increase frequency will also be visible in the EMG signals. Furthermore, an increase in diaphragm muscle activation or work of breathing will probably result in an increased EMG amplitude. The cardiovascular system only influences the diaphragmatic EMG measurements by the cardiac artifacts due to the heart contractions.

Sencure

The Sencure is an ExG measurement device and consists of a sensor electrical module with three electrodes and a docking station, shown in Figure 2.4a. The electrode placement is shown in Figure 2.4b. The red and white electrodes were placed right and left midclavicular on the costal margin and the third, reference, electrode is placed midsternal at the third intercostal space. The measured data are transferred via Bluetooth to the docking station, which is connected to a laptop. The Sencure measures the EMG of the diaphragm and accerolemeter data. The fs of these measurements was 500 Hz.



(a)



(b)

Figure 2.4: Sencure ExG measurement device. (a) From left to right: docking station, sensor electrical module, electrode cables, electrodes. (b) Electrode placements: red and white electrodes are placed right and left midclavicular on the costal margin and the black reference electrode is placed midsternal at the third intercostal space.

Chapter 3

Feasibility study

3.1 Method

3.1.1 Design

The feasibility study was the first part of this research and the objective was to assess whether the Sencure and OSAsense are suitable for measurements in the desired patient population. However, due to two months delay in the approval and delivery of the Sencure system, it was not possible to perform the feasibility measurements of the Sencure before the long-term measurements. Therefore, the feasibility of the Sencure was determined using only the data of the long-term study.

For the OSAsense, the feasibility measurements and the long-term measurements were used to determine its feasibility. The feasibility measurements were conducted before the long-term measurements. Waveform signals were collected for at least two hours at the ED with the OSAsense and the Philips IntelliVue MP70 (Philips, Eindhoven, the Netherlands) as reference. The measurements were ended when the patient was admitted to a ward or discharged to home.

As part of this sub-study, three medicine bachelor students performed a health technology assessment (HTA) of the two wearable devices. They used questionnaires to interview patients, nurses, and research assistants about their experiences with the devices.

3.1.2 Population

Twelve patients were included for measurements of the feasibility study only. These patients were admitted to the ED of the UMCG between 9:00 and 17:00 from February 2021 till March 2021. Fifteen patients of the long-term study were also included in the feasibility study. All these patients were admitted to the ED of the UMCG between 9:00 and 23:00 from April 2021 till May 2021. The additional in- and exclusion criteria are formulated as follows:

- Inclusion criteria:
  - Adult ($\geq$ 18 years)
  - One of the following (early) sepsis criteria of Acutelines:
    - Clinical suspicion of sepsis by the physician or nurse
    - Two or more qSOFA-criteria
    - Two or more SIRS-criteria
    - Blood cultures taken in combination with red/orange triage-color or admission by ambulance and yellow triage-color.
    - Temperature $<$ 35°C or $>$ 38°C in combination with red/orange triage-color or admission by ambulance and yellow triage-color

  - Urinary tract infection or pulmonary tract infection as suspected focus of the (early) sepsis

- Exclusion criteria
  - Known cardiac arrhythmias
  - Pacemakers, deep-brain stimulation, and other stimulation devices implanted under the skin in the thoracic or abdominal area
  - Comorbidities with known signal disturbance, such as pneumothorax and ascites

The exclusion criteria were chosen to reduce the amount of artifacts or noise in the measurements. A proven or suspected COVID-19 infection was not an exclusion criterion for this research, as these patients are part of the desired population with pulmonary infections. These patients were included following the Acutelines protocol for patients in isolation.

3.1.3 Data preprocessing

The data preprocessing steps for the PPG and EMG signals are described below. For both signals, first a flowchart is shown with a summary of the preprocessing steps and after that a detailed description of all the steps will be given.

PPG

The four main steps in the PPG preprocessing, shown in Figure 3.1, are basic preprocessing, a first quality check, point of interest detection and a second quality check based on a signal quality index (SQI).

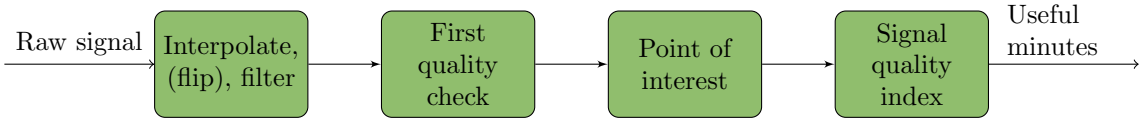


Figure 3.1: Flowchart of the PPG preprocessing steps.

Interpolate, (Flip), Filter. OSAsense measures the PPG data with a variable sampling frequency. For a sample frequency of 100 Hz the range was between 98.6-100 Hz, for 50 Hz it was between 48.2-50 Hz. Therefore, the PPG data was first linearly interpolated to a fixed sample frequency of 50 Hz. After that, the data was flipped by subtracting the data from a large number, in this study $1 * 10^6$ was chosen. This transformed the measured transmitted signal to an absorbed signal. This transformation was needed to compare the OSAsense data to the reference. The data from Philips was measured with an fs of 125 Hz and was not interpolated or flipped. The data from both OSAsense and Philips were then filtered using a 4th order Butterworth band-pass filter, with a frequency range of 0.8-20 Hz.

First Quality Check. After filtering, the first quality check was executed. For OSAsense the first check was to remove the minutes where the movement of the wrist was more than 0.02g from the median gravitational force for more than fifteen seconds. The first check for Philips consisted of checking whether each minute had at least 30 seconds of data. Time windows that did not fulfill this criterion were removed.

Point of Interest. Before the extensive quality check with a SQI could be performed, first the points of interest of each pulse needed to be found. The artifacts were removed from the signal using a threshold based on two moving averages with five second and 60 second windows of the squared signal. Then, for each 20-second window, all peaks were selected; this included the systolic peaks and the peaks of the diastolic phases. To select solely the systolic peaks, only the peaks with

amplitude higher than the standard deviation of the peaks were saved. The onsets were determined by finding the depression before the systolic peaks. The location of the diastolic peak was defined as the first depression of the second derivative between the systolic peak and the following onset. For the dicrotic notch, the locations where the second derivative between the systolic peak and diastolic peak crosses zero was used. The point of interest detection is visualized in Figure 3.2.

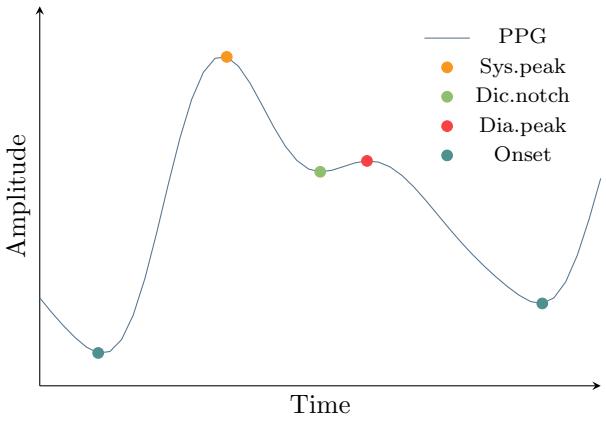


Figure 3.2: Point of interest detection of PPG signals.

Signal Quality Index. The used SQI method was adapted from Li and Clifford (2012).[63] It uses different templates and checks the correlation of each pulse with the templates to define the pulse as a good or bad pulse. The first template was made by averaging all pulses within one minute and the length of the template was set to the average length of the pulses. The pulses that had a correlation lower than 80% with the first template were discarded. If more than half of the pulses within the minute had a correlation less than 80%, the minute was regarded as not useful. The second template was the average of the remaining pulses. The correlation of each remaining pulse with the second template was determined in three different ways. The first method uses the length of the template as fixed length for the pulse. The second method resampled the pulse, so that the full pulse was matched with the template. In the third method, the pulses were resampled using the dynamic time warping method and the correlation was determined using this resampled pulse. A pulse was considered a good pulse if all three correlations were higher than 90%. If at least 50% of the pulses in one minute were good, the minute was considered a good and useful minute.

EMG

A summary of the preprocessing of the EMG data is shown in Figure 3.3. The preprocessing consisted of five steps: filtering, a first cardiac artifact removal, taking the moving average, a second cardiac removal, and resampling.

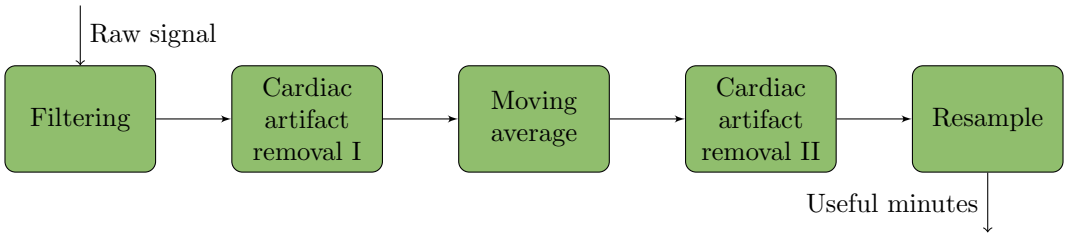


Figure 3.3: Flowchart of the EMG preprocessing steps.

Filtering. First, the onset, drift, and high-frequency noise was removed using a 2nd order Butterworth band-pass filter (20-150 Hz).

Cardiac Artifact Removal I. After the filtering, the cardiac artefacts were removed by QRS complex identification, using the Pan-Tompkins method.[64] This algorithm determines the QRS complexes only on the electrocardiography (ECG) activity, therefore a 2nd order Butterworth band-pass filter (5-15Hz) was used to reject muscle noise. The derivative of the ECG signal was taken and the signal was squared. Each 10 second window was checked for extreme artifacts, defined as an amplitude difference higher than 3000μV within the 10 second window. The whole 10 second window was discarded if it fulfilled the criterion. The start and end of a QRS complex were determined as the valley and peak of the moving-window integration (MWI) of the ECG signal, as shown in Figure 3.4a. The MWI was determined with a window length of 200 ms. The location of R-peak was defined as the minimal value of the ECG signal between the start and end of the QRS complex, see the blue dot in Figure 3.4a. The mid-points between two adjacent R-peaks were defined as the boundaries of an ECG beat.

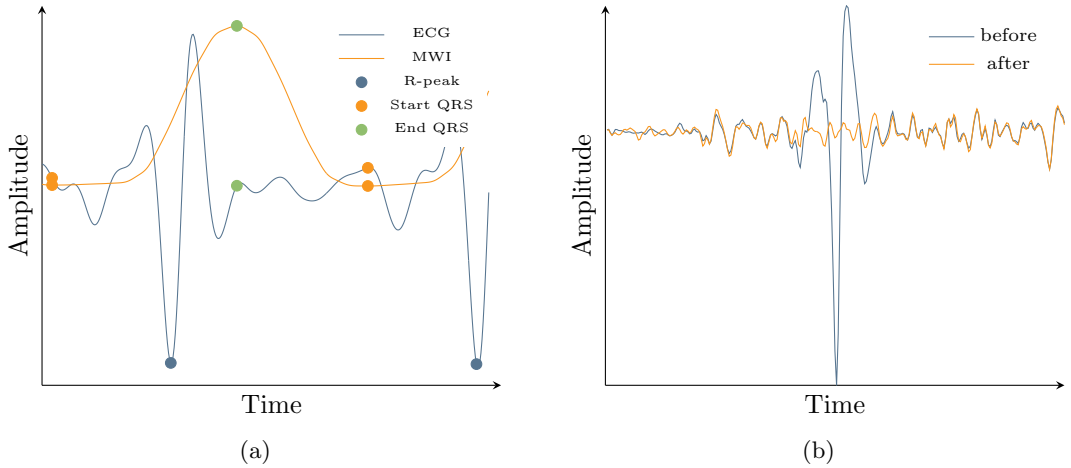


Figure 3.4: Cardiac artifact removal from EMG signal. (a) Point of interest detection of ECG signals. (b) EMG signal before and after cardiac artifact removal. MWI: moving-window integration.

Next, the ECG subtraction template was created for each individual ECG beat based on the template subtraction (TS) method of Petersen et al. (2020).[65] Petersen describes two template subtraction methods: basic TS and adaptive TS. Although Petersen gets the best results with adaptive TS, in this research the adaptive TS showed minimal improvements and the computational time was quadrupled in comparison to the basic TS. Therefore, the basic template subtraction was used in this analysis. The template for basic TS was constructed by averaging over 21 ECG beats: the current ECG beat, ten beats before and ten beats after the current ECG beat. For the first ten and last ten beats, all beat before, respectively, after the current beat were used, meaning that less than 21 ECG beats were averaged. The beats were aligned on the R-peaks and the window length of the template corresponded with the length of the current beat. The template and the current ECG beat were aligned by maximizing the cross-correlation. The offset and amplitude of the template were adjusted using linear regression. The aligned and adjusted template was then subtracted from the EMG signal. The result of the cardiac artifact removal is shown in Figure 3.4b.

Moving Average. The third step of the EMG preprocessing was taking the moving average of the EMG data. The moving average was determined by taking the mean of a moving window with a window size of 0.1 seconds.

Cardiac Artifact Removal II. The basic TS did not remove the cardiac artifacts completely, therefore a second cardiac artifacts removal was used. This second cardiac artifacts removal method

was also based on the basic TS, but with two templates. For each artifact the first template was constructed by taking the average of 21 artifacts: the current artifact, ten artifacts before and ten artifacts after the current artifact. The window length of the first templates was set to 0.14 seconds (0.07 seconds before and after the R-peak), as the lengths of the artifacts were equal to the window length of the moving window in the previous step. The correlation of each artifact with the first template was determined, only the artifacts with a correlation higher than 0.5 were used in the second template. The offset and amplitude of the second template were adjusted using linear regression. The adjusted template was then subtracted from the moving average.

Resample. Finally, the moving average was resampled from 500 Hz to 50 Hz. Only the moving average and the timestamps were saved and used in further analysis.

3.1.4 Data analysis

After the preprocessing steps, the quality and quantity of the OSAsense and the Sencure data were determined and the validation of the signals was done by comparison with the reference.

PPG

Quality and Quantity. The quality of the OSAsense was previously determined using the SQI. With the useful minutes, the quantity of the OSAsense data determined. The desired yield was that at least 60% of the minutes of a measurement needed to be useful and per hour at least 20 minutes needed to be useful.

Validation. The validation of the OSAsense data was done by comparing the PPG signals with the Philips PPG signals. The validation was performed in two ways, comparison of the heart rate (HR) and the relative amplitude (RA). The HR comparison will validate the time aspect of the signal and the RA will validate the amplitude aspect of the PPG signal. Only the good minutes of Philips and OSAsense that had an offset of maximal 30 seconds of each other were compared. For each waveform with a good SQI, the HR was determined based on the length of the waveform. For the RA, the amplitude of the systolic peak minus the amplitude of the onset was divided by the amplitude of the systolic peak. The mean HR and RA of the good minutes were determined and compared. For both features, the correlation was determined using Pearson's r and its corresponding p-value. A linear correlation was proven with $r > 0.9$ and p-value < 0.05. A Blant-Altman plot was used to determine the agreement between the Philips and the OSAsense data.

EMG

Quality. The first quality check of the EMG signal consisted of checking if each minute had at least 30 seconds of data, no data was removed with the artifact removal, and no Cheyne-Stokes breathing was recorded within the minute. The minutes that did not fulfill these requirements were discarded. Cheyne-Stokes breathing was excluded from the study, because making a point-of-interest detection algorithm for Cheyne-Stokes breathing would have cost too much time to develop within limited time of this research. After the first quality check, the points of interest were determined per minute, shown in Figure 3.5. For each breath, the start and end of the muscle activity, the maximal muscle activity and the start and end of the breath were determined. The start or end of the breath was defined as the midpoint between, respectively, the end of the muscle activity of the previous breath and the start of the muscle activity of the current breath or the end of the muscle activity of the current breath and the start of the muscle activity of the next breath. A second quality check checked whether at least half of the waves in the minute were useful breaths. Waves with a peak amplitude of more than 1.5 or less than 0.5 times the mean peak amplitude of the minute or waves of which the start or end of the breath were located at the same point as the maximal muscle activity, were defined as not useful waves, as the points were not correctly determined.

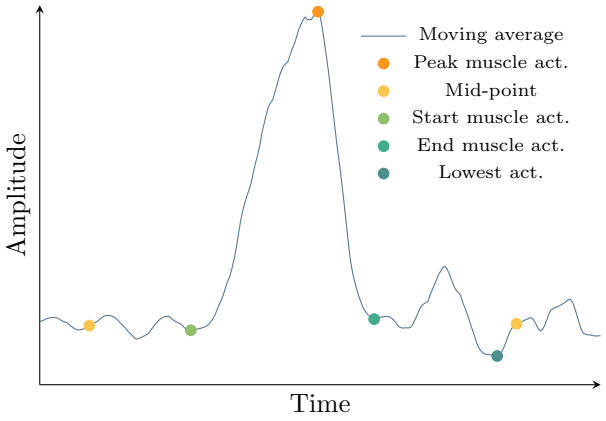


Figure 3.5: Point of interest detection of EMG signals. Act. = activity.

For EMG signal, the signal-to-noise ratio (SNR) is a widely used quantitative measure of the quality.[66–68] The SNR is, in this research, defined as the ratio between the amplitude of the maximal muscle activity and the mean amplitude of between muscle activities. The SNR needs to be at least larger than one and ideally five of higher. Due to the second cardiac artifact removal, the moving averages sometimes became negative. This is physiologically impossible and the negative parts of the moving average were therefore redefined as zero. These zero values caused the SNR for those minutes to approach infinity. The SNR values higher than 15 were therefore discarded from the average SNR calculation.

Quantity. As with the PPG signals, the quantity of the EMG signals were determined based on the useful minutes. The required yield was that at least 60% of the minutes of a measurement needed to be useful and per hour at least 20 minutes needed to be useful.

Validation. The validation of the EMG signals was done by comparing the respiratory rate (RR) measured with the Sencure with the RR nurses had registered in the electronic health record (EHR). The RR measured with the Sencure was determined in two different ways: based on the peak-to-peak distance and based on the power spectral density. The peak muscle activity peaks were used to determine the RR based on peak-to-peak distance. For the frequency based method, the frequency with the highest power was defined as the respiratory frequency, with a minimal frequency of 0.16 Hz (9.5 bpm). The RR method with the higher correlation with the reference will be used in the analysis of the long-term measurements. The RR registered by the nurses was manually extracted from the EHR. The RR from the EHR was compared to the mean RR of Sencure of five minutes before and after the registered time. For both methods of RR determination, the correlation with the EHR was determined using Pearson's r and it corresponding p-value. A linear correlation was proven with a $r > 0.9$ and p-value < 0.05. A Blant-Altman plot was used to determine the agreement between the Philips and the OSAsense data.

3.1.5 Health Technology Assessment

A part of the feasibility study was a HTA of the two wearable devices, performed by medicine students. The main objective of the HTA was to assess the applicability through the experiences of patients, nurses and research assistants. For each group a personalized questionnaire was made, which can be found in Appendix A.

The questionnaire for the patients consisted of 14 statements with 0-10 scores, where zero meant totally disagree and ten meant totally agree. The questionnaire was based on the Comfort Rating Scale and consisted of six domains: emotion, attachment, harm, perceived change, movement, and anxiety. The patients were asked to fill in the questionnaire after each measurement, so the

difference in experience after the first and second measurement could be examined.

The questionnaire of the nurses consisted three domains (knowledge, user experience, and patient experience) and had a total of nine statements. Every nurse that cared for a patient with a wearable device was asked to fill in a questionnaire.

For the research assistants, the questionnaire was mainly focused on the usage of the user manual of the wearables and consisted of ten questions. The research assistants were only asked to fill in the questionnaire after their first usage of the manual.

3.2 Results

3.2.1 Population

In total, 27 subjects were included in the feasibility study. The characteristics of these subjects are shown in Table 3.1.

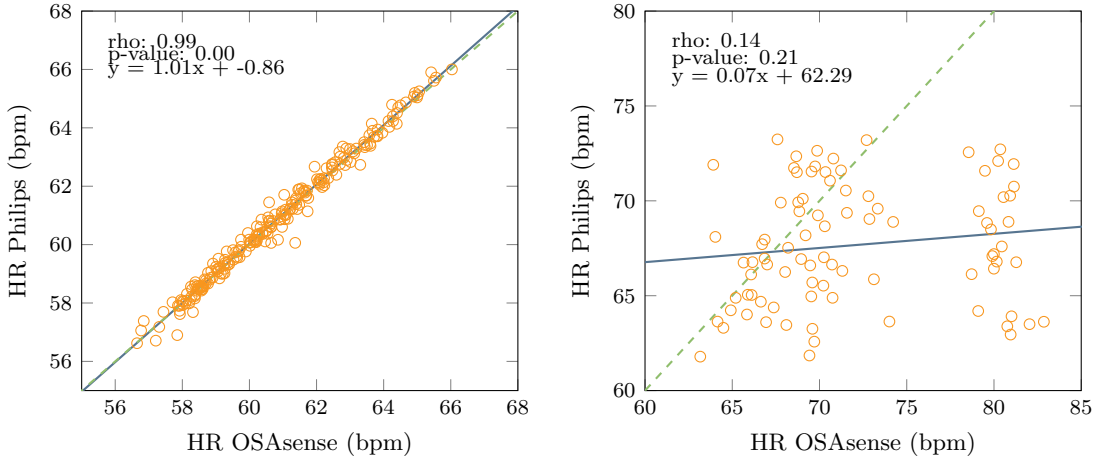
Table 3.1: Baseline characteristics of the subjects.

Characteristic	Subjects (N=27) *no. (%)*
Age group	
<60	4 (14.8)
60-69	8 (29.6)
70-79	12 (44.4)
>80	3 (11.1)
Sex	
Female	9 (33.3)
Male	18 (66.7)
Infection type	
Urinary tract infection	14 (51.9)
Pulmonary tract infection	13 (48.1)
Measurement type	
Feasibility	12 (44.4)
Long-term	15 (55.6)
No. measurement per devices	
OSAsense	26 (96.3)
Sencure	11 (40.7)
Philips	16 (59.3)
HTA Questionnaire	7 (25.9)

3.2.2 PPG

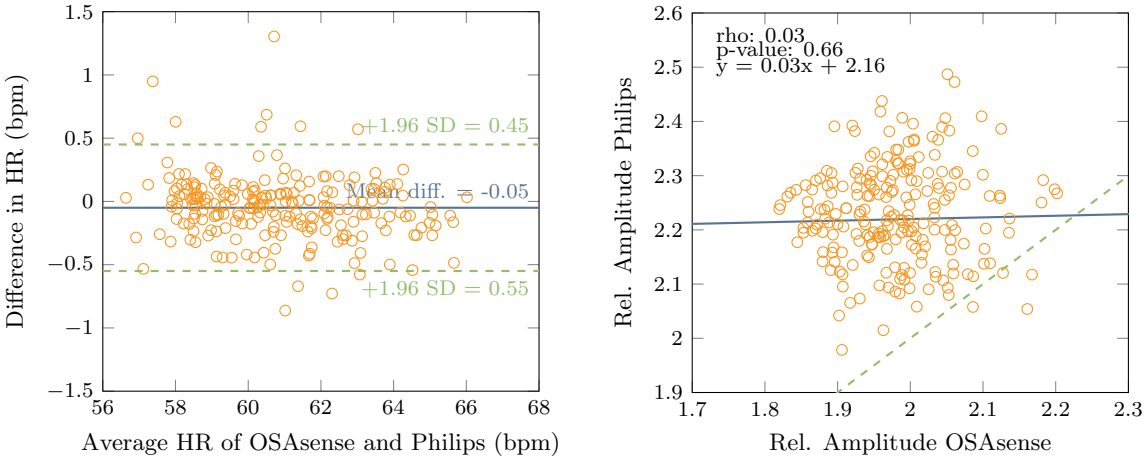
For both the OSAsense and the Philips device the quantity of the data was determined. OSAsense had an overall yield of 60.6±18.3% (mean±SD) and a total of 32.7±13.4 (mean±SD) minutes per hour was determined to be useful. Philips scored a little higher on both analyses, with an overall yield of 70.2±16.4% (mean±SD) and 34.8±14.3 (mean±SD) useful minutes per hour. The requirements for the quantity were an overall yield of 60% and 20 useful minutes per hour, meaning that both devices met these requirements.

To validate the PPG signals measured with the OSAsense, the correlation and agreement of the HR and RA were determined for the overlapping useful minutes. Twelve patients had overlapping minutes in the PPG data and there were large differences in the amount of overlapping minutes



(a) (b)

Figure 3.6: Two examples of heart rate correlation scatterplots. (a) Good correlation. (b) Bad correlation. Dashed green line: perfect correlation. Solid blue line: linear fit of data.



(a) (b)

Figure 3.7: (a) Bland-Altman plot of the heart rate of a measurement with good correlation, solid blue line: mean difference, dashed green lines: +1.96 standard deviation. (b) Scatterplot of the relative amplitudes of OSAsense and Philips in a measurement with a good HR correlation, dashed green line: perfect correlation, solid blue line: linear fit of data.

per patient. The average number of overlapping minutes was 64.9±54.7 (mean±SD) minutes. However, there were six patients with less than 30 minutes overlap.

The comparison of HR gave varying results. Two examples are shown in Figure 3.6. Three subjects gave a good correlation (r>0.9 and p-value <0.05), all the other measurements did not give a good correlation. The overall average correlation was 0.365±0.377 (mean±SD) and the p-value varied between 0.000 and 0.893. The three measurements with a good correlation had an average r of 0.977±0.011 (mean±SD) and a p-value smaller than 0.001. Two measurements with a bad correlation, r=0.85 and r=0.28, had a p-value smaller than 0.001. All other measurements did not have a significant correlation. Only for the measurements with a good correlation the agreement was determined with a Bland-Altman plot, shown in Figure 3.7a. The average agreement was -0.001 bpm (from -0.75 bpm to 0.75 bpm), meaning that overall Philips measured a slightly lower HR than OSAsense.

No correlation was found when comparing the relative amplitudes of the measurements. An example is shown in Figure 3.7b. The average r was 0.193±0.320 (mean±SD). Six subjects had a p-value smaller than 0.05. In all other subjects, the correlation was not significant.

3.2.3 EMG

The measurements with the Sencure had an average yield of 72.5±21.4% (mean±SD) and 41.0±15.7 (mean±SD) minutes per hour were useful. Both values are above the required amount. Combining the first and second quality checks, there were four reasons why a minute could be labeled as not useful. Most of these minutes were not useful (47.4%), because the minute did not contain enough signal. The other reasons were: too much artifacts (34.1%), Cheyne-Stokes breathing (16.2%), and not sufficient waveform quality (2.3%).

The quality of the EMG data was quantified by determining the SNR of the data. The average SNR was 2.522±0.673 (mean±SD). None of the measurements met the ideal SNR of 5.

The validation of the Sencure was done by comparing the RR of the Sencure with the RR reported in the EHR, an example is shown in Figure 3.8. Only for six subjects the data could be compared. All other patients had zero overlap or only one overlapping RR and a correlation could not be determined. For the six subjects with overlapping RRs, the average number of overlap was 6±3.33 (mean±SD) RRs. The RR of Sencure was determined using two methods. For the peak-to-peak method, the average r was 0.638±0.226 (mean±SD) with a p-value of 0.390 and for

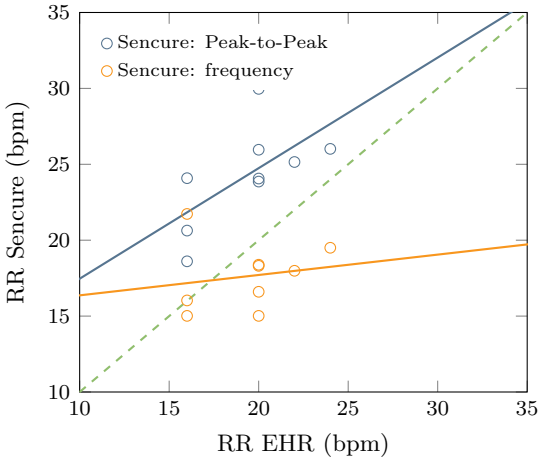
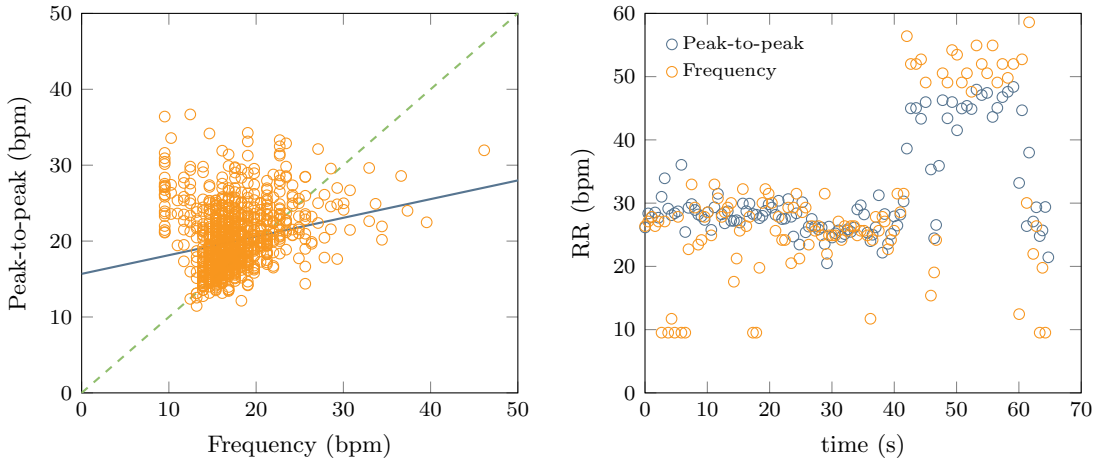


Figure 3.8: Example of respiratory rate correlation scatterplot of one subject. bpm: breaths per minute, EHR: Electronic health record, RR: respiratory rate, dashed green line: perfect correlation, solid blue line: linear fit of peak-to-peak data, solid orange line: linear fit of frequency data.



(a) (b)

Figure 3.9: Respiratory rate method comparison for Sencure data. (a) Correlation plot for the peak-to-peak and frequency methods, dashed green line: perfect correlation, solid blue line: linear fit of data. (b) Example of RR difference in time.

the frequency method, it was -0.015±0.562 (mean±SD) and 0.500, respectively. Meaning that both methods did not met the required r of 0.9 or higher. A more elaborated comparison between the two methods is shown in Figure 3.9. Both figures show that the peak-to-peak method has less variation in RR than the frequency based method. This in combination with the higher r and lower p-value, makes the peak-to-peak method a more reliable method for RR determination and will therefore be used in the long term study.

3.2.4 Health Technology Assessment

Seven patients of the long-term measurements were also included in the HTA. Six of those patients had filled in both questionnaires, meaning that thirteen patient questionnaires were analyzed. Ten nurses and eleven research assistants had filled in their questionnaire.

In Table 3.2, the results of the patient questionnaire per domain are shown. The domain 'Harm' has the highest score, meaning that the patients experienced the most problems in that domain. All other domains have a score below one and no major problems were experienced in those domains. The most important reason for the higher score in the 'Harm' domain was the red light of the OSAsense sensor, which caused sleeping problems in several patients.

Table 3.2: Results health technology assessment - patient questionnaire.

Domain	Mean (SD)
Emotion	0.72 (0.91)
Attachment	0.83 (0.79)
Harm	2.15 (2.73)
Perceived change	0.12 (0.22)
Movement	0.39 (0.96)
Anxiety	0.21 (0.57)

The nurses gave a perfect score for user experience and patient experience, meaning that they experienced no hindrance due to the wearable devices and that they did not get the impression that the devices caused any discomfort to the patients. In the domain 'Knowledge', 55.6% of the

nurses indicated that they did not know how technical aspects of the wearables work. However, 78% indicated that they have sufficient knowledge to use the wearable.

90.9% of the research assistants indicated that the manual was easy to use. However, 54.5% did not feel confident using the manual. The two main reasons for this are the workload of the research assistants and that the research assistants were still unfamiliar with the wearables. A decrease in workload and more experience with the wearables were suggested as solutions by the research assistants.

3.3 Discussion

In this research the performance of two wearable devices to continuously measure RR and HR were studied. The results show that these sensors have the required yield of data, however the accuracy for both HR and RR was not within the predefined acceptable range for several cases. The OSAsense has big differences in the feasibility. Three of the measurements showed high precision and accuracy while the nine other measurements had a poor performance. The relative amplitude of the OSAsense signals did not have any correlation with the relative amplitude of the Philips signals. For the Sencure, the RR was compared with the EHR recorded RR and these measurements also did not have any correlation. The HTA showed that implementation of the devices will not cause major discomfort for the patients or give hindrance to the nurses.

To the best of my knowledge, no articles have been published about the feasibility of the Sencure or OSAsense devices. Until recently, most feasibility studies to other wearable devices that measure HR or RR were obtained under laboratory conditions.[69,70] A few studies conducted the validation in a clinical setting. Weenk et al. researched the feasibility of the ViSi mobile and HealthPatch, two wearable devices that measure vital signs, at the general ward.[17,71] They found that both systems had a high correlation for HR and large difference in the RR when compared to the nurses measurements. In another research, Breteler et al. investigated for three wearable systems whether they could reliably measure HR and RR and found that all sensors were highly accurate for HR and the RR accuracy was reasonably accurate or out of limits.[19] Garnholm et al. stated that 'a concerning lack of agreement was found between a wireless monitoring system and the standardized clinical approach' when researching the agreement for RR between three different approaches.[72] The accuracy of HR in this study is far below the level of accuracy described by other researchers. The lack of agreement for RR in other devices is comparable with our results.

A strength of this research is that the measurements took place in a clinical setting instead of testing with healthy participants in a controlled setting. The results are therefore a more accurate representation of the feasibility of these wearables for clinical usage.

There were two main limitations with the RR comparison. First, the sample size of RR pairs was too small to determine a significant correlation, with an average of only six RR pairs per patient that could be compared. Secondly, the reference method may have some deficiencies. Different studies have shown that counting of chest movement by nurses is associated with inaccurate measurements, because of large inter- and intra-observer variation.[73–75] Furthermore, due to limited time per patient, most nurses only count the chest movements for 15 seconds instead of the advised 60 seconds. With these limitations in mind, it could be argued that an average correlation of 0.638 for the peak-to-peak method is a good result. In the future, an alternative reference method, such as a chest band, could improve the validation of the method.

A striking result in this study is the big difference in HR correlation, with three measurements that had a high correlation and agreement with the reference, while all other measurements had a poor correlation and agreement. Different explanations have been explored. A different method for determining the time stamps of the OSAsense was tried, however this did not change the outcomes. To check whether the Philips or OSAsense had the true HR, the HR was compared with the ECG recordings in the EHR. This HR always matched the Philips HR, this suggests that the Philips HR was indeed a true and correct reference and the peak detection method of the PPG signal was not

the reason for the unexpected results. To substantiate this conclusion about the peak detection, the peak selection was manually checked by viewing randomly selected parts of the Philips and OSAsense signals and this did not show any major deviations. For the measurements of OSAsense, two devices were used in the recording. To check whether it could be a hardware problem with one of the two devices, the results of the devices were compared and the three good measurements were all recorded with one of the devices. However, two measurements with that device did not have the good correlation. It is suspected that the sampling frequency of OSAsense is not constant over time, which could result in small differences in time between two samples. Over a short recording, these differences may be too little to influence the HR. However, in long recordings these small deviations may give large differences in sampling times. By averaging the sampling times over the whole measurement, these deviations will cause major HR deviations. However, this suspicion could not be confirmed within the time of this research.

Another unexpected result is the lack of correlation in the relative amplitudes of the PPG signals. The amount of blood flowing through the fingertips should be approximately equal and therefore the hypothesis was that the relative amplitudes of the PPG signals would show some kind of correlation. A possible explanation for this lack of correlation may be the auto-gain used in one or both devices. Auto-gain is the adjustment of light intensity and/or the modification of the amplification by the electronics and it is used to keep the baseline amplitude of the waveform constant.[76] OSAsense uses auto-gain to maintain a constant baseline amplitude and if Philips also uses auto-gain, it is highly possible that the amount of auto-gain is not equal in both devices. This would make a comparison of relative amplitude quite difficult and could explain the lack of correlation.

An important clinical implication of this research are the results of the HTA study. These results show that the user experience of these wearables are good and that patients and nurses have a positive view on the use of wearables, which supports the findings described by Leenen at al.[77] The only problems that were raised during the HTA are easy to solve. For example, the disturbing red light of OSAsense could be taped to reduce the brightness and an additional training could be given to the research assistants who felt unfamiliar with the devices.

Furthermore, these wearables are able to measure continuous signals with the required yield for twelve hours. However, the average battery life and storage space of such wearable devices ranges from 3 to 7 days, which is a lot longer than the Sencure and OSAsense can measure.[77] Before using these two devices in a hospital setting, it is advised to improve the battery and storage, so that the devices are able to measure for longer periods of time.

3.4 Conclusion

In this study, the feasibility of two wearable devices was investigated for patients with a severe infection at the ED and the general ward. Both devices have met the required yield. The accuracy and precision of the OSAsense still left some room for improvement, due to the possible hardware problems with the sample times. Due to the limitation in the reference method, the accuracy and precision of Sencure could not be fully investigated. The HTA showed that the implementation of both devices will not cause any major problems for the patients, nurses or research assistants.

Chapter 4

Long-term study

4.1 Methods

4.1.1 Design

The objective of the long-term study was to investigate which features from continuous diaphragm EMG and PPG are early signs of deterioration in patients with a severe infection. The primary goal of this study was to find out which parameters are able to predict a deteriorating MEWS, hours before the MEWS is determined and the secondary goal was to investigate if it is possible to predict the overall clinical outcome based on measurements of the first 36 hours after hospital admission.

To investigate these questions, the following measurement set-up was used. Because both devices could only measure for 12 consecutive hours, each patient was measured twice. The first measurement was started within 6 hours after admission to the ED, with the aim to start the measurement as soon as possible. The measurement continued during the admission to the general ward and lasted for 12 hours. The second measurement started 24 hours after the first measurement started. If a subjects was discharged before the second measurement could start, only the first measurement was included in the analyses. In Figure 4.1 an example timeline of a measurement is shown.

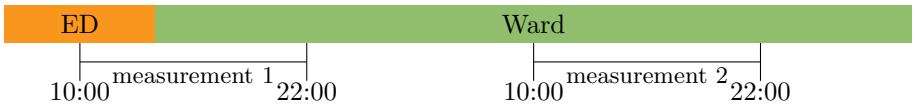


Figure 4.1: Example timeline of the long-term measurements.

4.1.2 Population

24 patients were included in the long-term measurements. All patients were admitted to the ED of the UMCG between 9:00 and 23:00 during six months (March 2021 till August 2021). The additional in- and exclusion criteria were formulated as follows:

- Inclusion criteria:
  - Adult ($\geq$ 18 years)
  - One of the following (early) sepsis criteria of Acutelines:
    - Clinical suspicion of sepsis by the physician or nurse

        - Two or more qSOFA-criteria
        - Two or more SIRS-criteria
        - Blood cultures taken in combination with red/orange triage-color or admission by ambulance and yellow triage-color.
        - Temperature $< 35°C$ or $> 38°C$ in combination with red/orange triage-color or admission by ambulance and yellow triage-color
    - Urinary tract infection or pulmonary tract infection as suspected focus of the (early) sepsis

- Exclusion criteria:
    - Known cardiac arrhythmias
    - Pacemakers, deep-brain stimulation, and other stimulation devices implanted under the skin in the thoracic or abdominal area
    - Comorbidities with known signal disturbance, such as pneumothorax and ascites
    - No admission to the nursing ward at the UMCG

Most exclusion criteria were chosen to reduce the amount of artifacts or noise in the measurements. A proven or suspected COVID-19 infection was not an exclusion criterion for this research, as these patients are part of the desired population with pulmonary infections. These patients were included following the Acutelines protocol for patients in isolation.

4.1.3 Data analysis

The data preprocessing steps used in the long-term study are the same as in the feasibility study. Thirteen hemodynamic features were determined with the PPG features and six respiratory features were determined with the EMG signals. All features will be described below.

PPG features

The PPG features are divided into four categories: amplitude dependent features, time dependent features, indexes and ratios, and second derivative features, also known as acceleration plethysmography (APG) features. Most of the features are visualized in Figure 4.2.

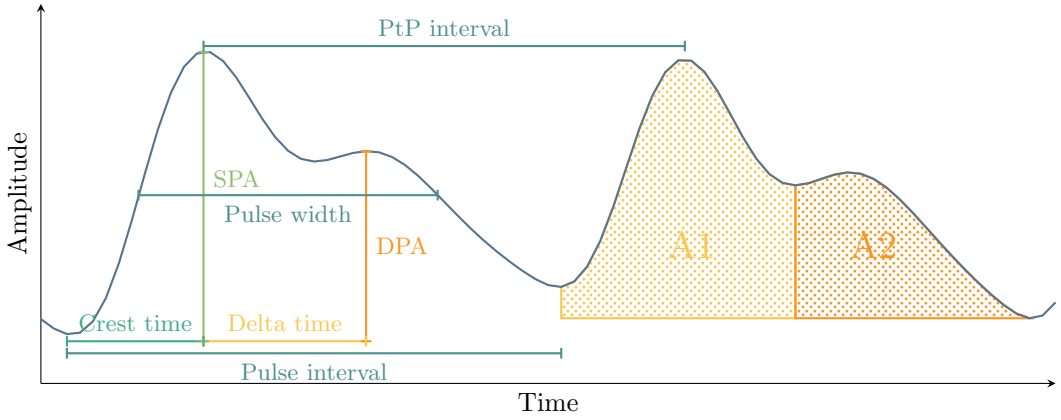


Figure 4.2: Overview of PPG features.

Amplitude Dependent. There are three amplitude dependent features. One of the most used features of PPG is the systolic peak amplitude (SPA). The SPA is defined as the height of

the first peak in a single PPG waveform.[55,78] It represents the pulsatile changes in blood volume in the finger as a result of the systolic contraction of the heart. The SPA has been related to the stroke volume.[57] The second amplitude feature is the diastolic peak amplitude (DPA). This is the height of the second peak of the PPG waveform. The DPA is sometimes referred to as the late systolic peak amplitude, because the component arises mainly from the reflected systolic wave from the lower body.[55] The last amplitude dependent feature is the relative amplitude (RA), which is determined in the same matter as in the feasibility study, by dividing SPA by the true value of the systolic peak.

Time Dependent. In this study six time-dependent features were determined with the PPG signals. The peak-to-peak (PtP) interval is the time between two consecutive systolic peaks and is highly correlated with the heart rate.[79] The PtP interval is widely used to determine the heart rate in PPG signals.[55] The time between the onset and the end of a PPG waveform is defined as the pulse interval.[55] The pulse interval could also be used as an alternative heart rate variation (HRV) measurement, instead of the ECG HRV.[80] The third time dependent feature, the pulse width, is determined at half the height of the systolic peak.[55] Awad et al. found that the systemic vascular resistance has a better correlation with the pulse width than with the amplitude of finger tip PPG signals.[81] The crest time is the time from the base of the PPG waveform to its peak and is a classifier for pulse wave velocity, which is a predictor of cardiovascular diseases.[55,78,82] Delta time is defined as the time between the systolic peak and diastolic peak. Since the diastolic peak is a reflection of the systolic peak propagating from the lower body, this time is related with the time it takes for the systolic pressure wave to propagate from the heart to the periphery and back.[78] The last time dependent feature is the heart rate (HR), which is one of the most used features of PPG signals. In this study the HR is determined based on the pulse interval, because the pulse interval showed to be a more reliable feature than the PtP interval in the feasibility study.

Indexes and Ratios. The ratio between the DPA and SPA is called the reflection index (RI), because it is the ratio between the original wave and the reflected wave.[55,78] The augmentation index (AI) is a normalized version of the reflection index. It is specified as the SPA minus the DPA divided by the SPA.[78] The area under the curve (AUC) can be divided into two parts at the dicrotic notch, as visualized in Figure 4.2. The infliction point area (IPA) ratio is the ratio between two areas and is specified as the area under the diastolic peak (A2) divided by the area under the systolic peak (A1).[78]

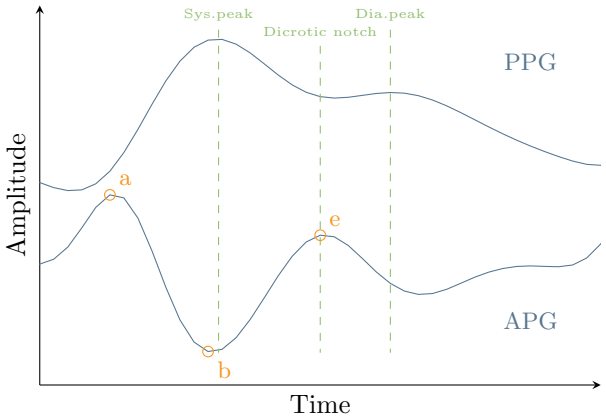


Figure 4.3: Acceleration Plethysmography and its points of interest.

Acceleration Plethysmography. The second derivative of the PPG is called the acceleration plethysmography (APG) because it represents the acceleration of blood volume in the arteries. The APG waveform is characterized by five peaks, four systolic peaks and one diastolic peak. Different ratios between these peaks can be determined and each ratio is associated with a different disease

or vascular characteristic. The (b-c-d-e)/a-ratio is a commonly used ratio, however most subjects of this study did not have c and d peaks and it was therefore not possible to determine the (b-c-d-e)/a-ratio for those subjects. An alternative for the (b-c-d-e)/a-ratio is the (b-e)/a-ratio and to determine a uniform feature for all subjects, only the (b-e)/a-ratio was used in this study.[83] The location of the e peak represents the dicrotic notch and is related to the closure of the aortic valve and the subsequent backwards blood flow and it may therefore be used to investigate the cardiac function.[55] In Figure 4.3, an example of an APG waveform is shown where the c and d peaks are not visible.

EMG features

From the EMG signals two amplitude dependent, three time dependent and one area under the curve feature were derived. In Figure 4.4, an overview of most features is shown.

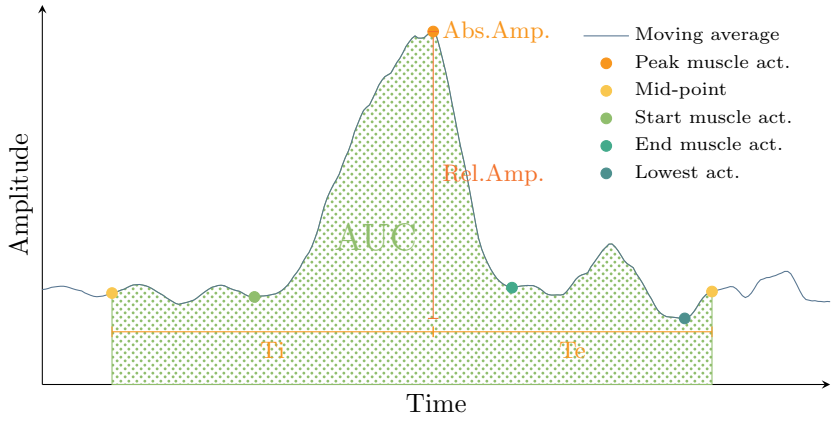


Figure 4.4: Overview of EMG features. Abs.Amp.: absolute peak amplitude, Act.: activity, AUC: area under the curve, Rel.Amp.: relative peak amplitude, Te: expiratory time, Ti: inspiratory time.

Amplitude Dependent. The two amplitude dependent features are: relative peak amplitude and absolute peak amplitude. The relative peak amplitude is the height of the EMG activity related to the lowest activity. It is determined by subtracting the absolute value of the lowest activity from the absolute value of the highest activity.[84] The absolute peak amplitude is the highest absolute value of the EMG waveform.

Time Dependent. The RR method was based on the results of the feasibility study, which showed that the peak-to-peak distance of the EMG waveforms was the most reliable RR method. The inspiratory time (Ti) is defined as the time from the beginning of the breath to the maximum of diaphragm activity.[84] The expiratory time (Te) is defined as the time from the maximum activity of the diaphragm to the end of the breath.[84]

Area under the curve. The area under the curve (AUC) is suspected to correlate with the work of breathing and is determined by taking the integral over the EMG waveform.[61,85]

4.1.4 Statistical analysis

As said before, the long-term study has two goals. The primary goal is to assess whether the novel parameters are able to predict a deteriorating MEWS before the MEWS is determined and the secondary goal is to investigate if it may be possible to predict the overall clinical outcome based on measurements in the first 30 hours of hospital admission. The statistical analysis of both goals will be described below.

Primary goal

In order to investigate whether the novel parameters are able to detect a deteriorating patient earlier than the MEWS determined by the nurses, the differences in the PPG and EMG features between the deteriorating MEWSs and non-deteriorating MEWSs were determined.

First, the MEWSs of all included patients were extracted from the EHR. MEWSs with a score of 4 or higher or with an increase of 2 within 6 hours were defined as deteriorating MEWSs.[86] All other MEWSs were defined as non-deteriorating. The features of seven moments in time were compared to the MEWS: at the moment of the check-up, when the MEWS was determined (t_0), and at all six hours prior to the check-up ($t_{-1}, ..., t_{-6}$). A timeline is shown in Figure 4.5. The PPG and EMG features were averaged over a window of 10 minutes for each moment in time. Values higher or lower than the mean plus ten times the standard deviation of a feature were defined as extreme outliers and therefore excluded from the analysis. The difference of features over time was also compared, in windows of four hours. Meaning that the difference between t_{-2} and t_{-6}, $t_{-1} - t_{-5}$, and $t_{-4} - t_0$ were compared to the deteriorating and non-deteriorating MEWSs.

The Mann-Whitney U test was used as statistical test. A p-value of 0.05 or lower was defined as a significant difference.

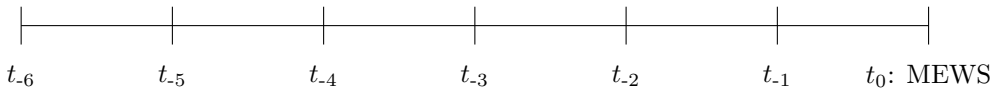


Figure 4.5: Timeline for the primary goal.

Secondary goal

The secondary goal of the long-term study was to investigate whether the PPG and EMG features are able to predict the clinical outcome based on measurements of the first 48 hours of hospital admission.

The clinical outcome of a subject was defined as deteriorating when at least one of the following statements was true within the hospital admission:

1. Increased use of interventions (increase of vasopressor medication and/or increase in oxygen admission)
2. ICU admission
3. In-hospital death

When none of the above was true, the subject was defined as not deteriorating. The features of the two groups were compared with each other for the first four hours of recording. There were also two trends analyzed to determine the differences between 24 hours. An overview of these moments is shown in Figure 4.6. Same as in the primary gaol, values higher or lower than the mean plus ten times the standard deviation of a feature were defined as extreme outliers and therefore excluded from the analysis. For the secondary goal, the statistical test was also the Mann-Whitney U test and a significant difference was defined as a p-value of 0.05 or lower.

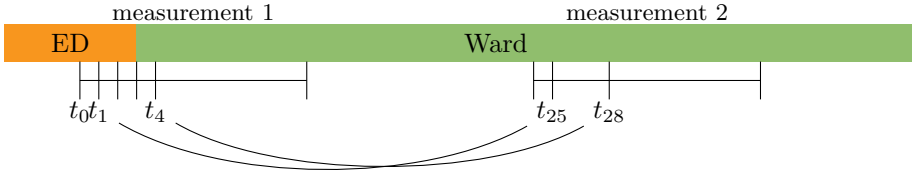


Figure 4.6: Timeline for the secondary goal.

4.2 Results

4.2.1 Population

In total, 24 subjects were included in the long-term study. Only five patients met the conditions of clinical deterioration, which meant that the deterioration group for the secondary outcomes was very small. The characteristics of all subjects are shown in Table 4.1.

Table 4.1: Baseline characteristics of the subjects.

Characteristic	Non-deteriorating (N=19) *no. (%)*	Deteriorating (N=5) *no. (%)*
Age group		
<60	5 (26.3)	0 (0.0)
60-69	5 (26.2)	2 (40.0)
70-79	8 (42.1)	2 (40.0)
>80	1 (5.3)	1 (20.0)
Sex		
Female	7 (36.8)	2 (40.0)
Male	12 (63.2)	3 (60.0)
Comorbidities		
Cardiovascular	8 (42.1)	2 (40.0)
Infection type		
Urinary tract infection	9 (47.4)	0 (0.0)
Pulmonary tract infection	10 (52.6)	5 (100)
Clinical deterioration		
Increased use of interventions	0 (0.0)	2 (40.0)
ICU admission	0 (0.0)	1 (20.0)
In-hospital death	0 (0.0)	2 (40.0)
No. measurement per device		
1 OSAsense measurement	4 (21.1)	2 (40.0)
2 OSAsense measurements	14 (73.7)	3 (60.0)
1 Sencure measurement	4 (21.1)	3 (60.0)
2 Sencure measurements	8 (42.1)	1 (20.0)

4.2.2 Primary outcome

Four of the 24 subjects had no overlap in MEWSs and the recorded signal. These patients were therefore excluded from the primary outcome. All twenty remaining subjects had at least one non-deteriorating MEWS and twelve subjects also had at least one deteriorating MEWS. In total, 102 non-deteriorating MEWSs and 40 deteriorating MEWSs were included. The average number of deteriorating and non-deteriorating MEWS per subject was, respectively, 1.67±2.22 and 4.25±2.80 (mean±SD).

Seventeen of the nineteen features gave a significant difference between the deteriorating MEWSs and non-deteriorating MEWSs. All PPG features and four of the six EMG features showed a significant difference between the two groups for at least one of the moment in time. All p-values for the primary outcome are shown in Appendix B.1.

PPG features

Amplitude features. In Figure 4.7, the boxplots of the amplitude features are shown. SPA has four moments in time with a significant difference between the deteriorating MEWSs and non-

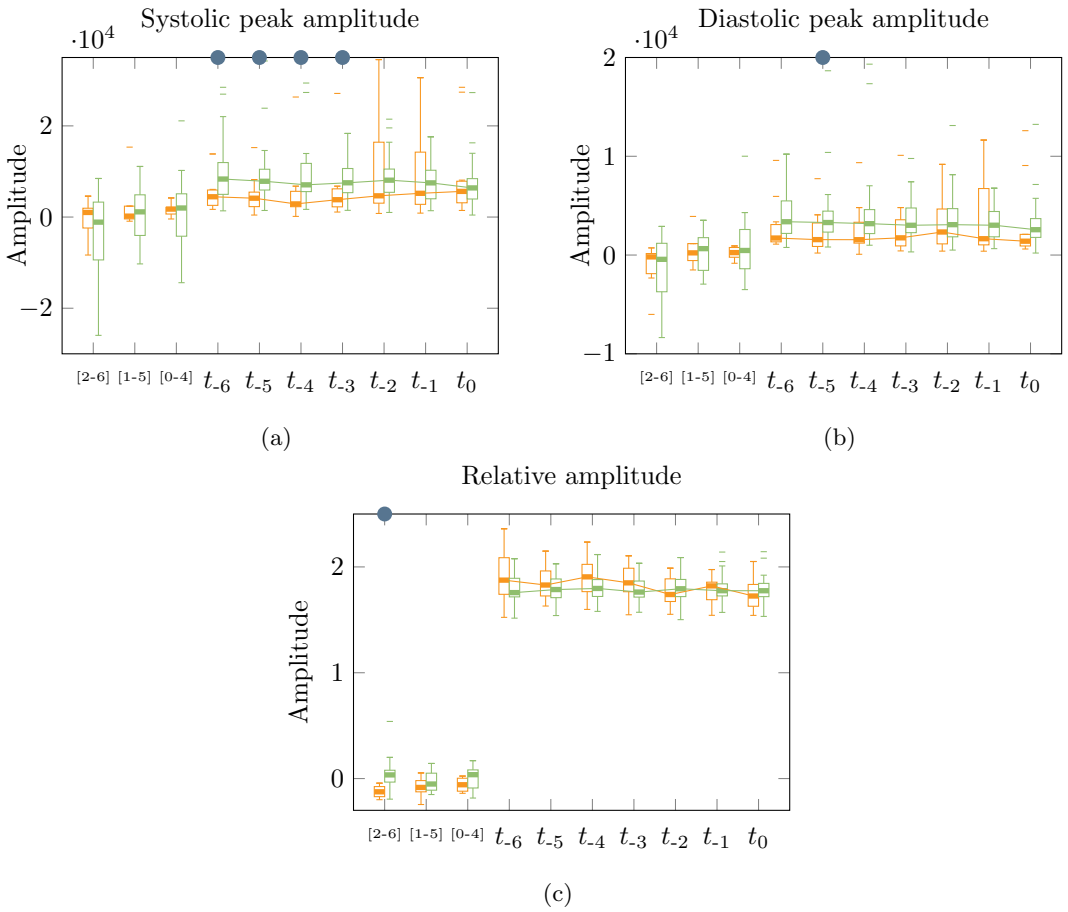


Figure 4.7: Long-term study primary outcome. PPG amplitude features: (a) systolic peak amplitude, (b) diastolic peak amplitude, and (c) relative amplitude. Orange: deteriorating MEWSs. Green: non-deteriorating MEWSs. Blue circles: significant difference between the two groups. [i-j]: difference between t_{-i} and t_{-j}.

deteriorating MEWSs. The earliest significant difference of SPA is six hours before the check-up. Only five hours before the check-up, there is a significant difference for DPA (p-value: 0.038). The amplitudes of the deterioration group are lower than of the non-deterioration group. The RA only gave a significant difference for the trend analysis of $t_{-2} - t_{-6}$.

Time features. The results of the time features are shown in Figure 4.8. HR has the most significant differences, with two differences in the trend analyses and at two moments in time. Delta time has the earliest detection of the time features, with significant differences at t_{-4} and t_{-3}. The crest time has three significant differences. Pulse width, PtP interval, and pulse interval are less promising than the others, because they only gave one or two significant differences.

Indexes and Ratios. Both indexes gave significant differences at the same moments in time, at t_{-4} and t_0 and at two trend analyses, as shown in Figure 4.9a to 4.9c. The IPA had five significant differences, with the earliest difference at t_{-6}.

Acceleration Plethysmography. The (b-e)/a ratio, determined with the APG, gave only one significant difference in the trend analysis of $t_{-2} - t_{-6}$ (p-value: 0.004), see Figure 4.9d.

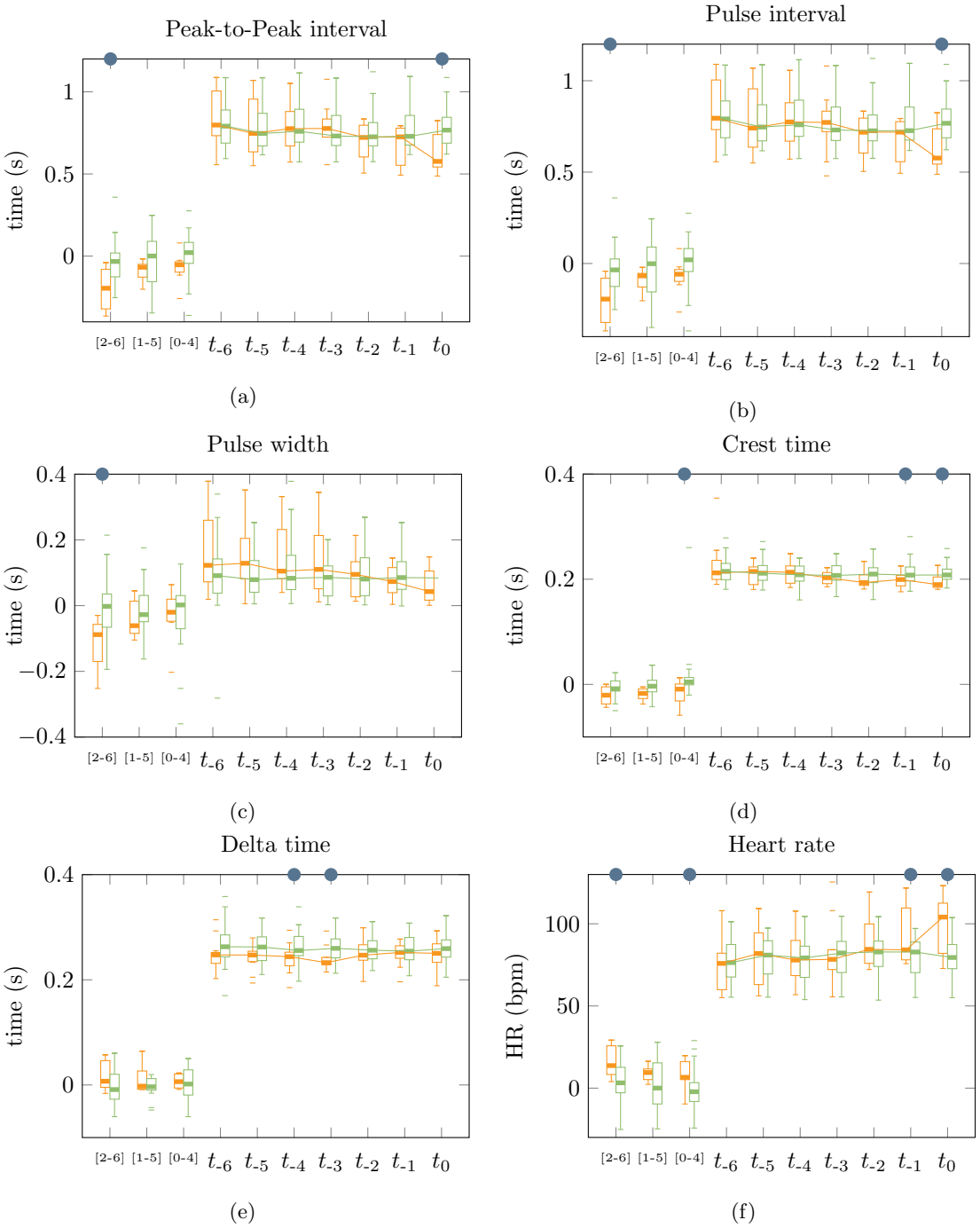


Figure 4.8: Long-term study primary outcome. PPG time features: (a) peak-to-peak interval, (b) pulse interval, (c) pulse width, (d) crest time, (e) delta time, and (f) heart rate. Orange: deteriorating MEWSs. Green: non-deteriorating MEWSs. Blue circles: significant difference between the two groups. [i-j]: difference between t_{-i} and t_{-j}.

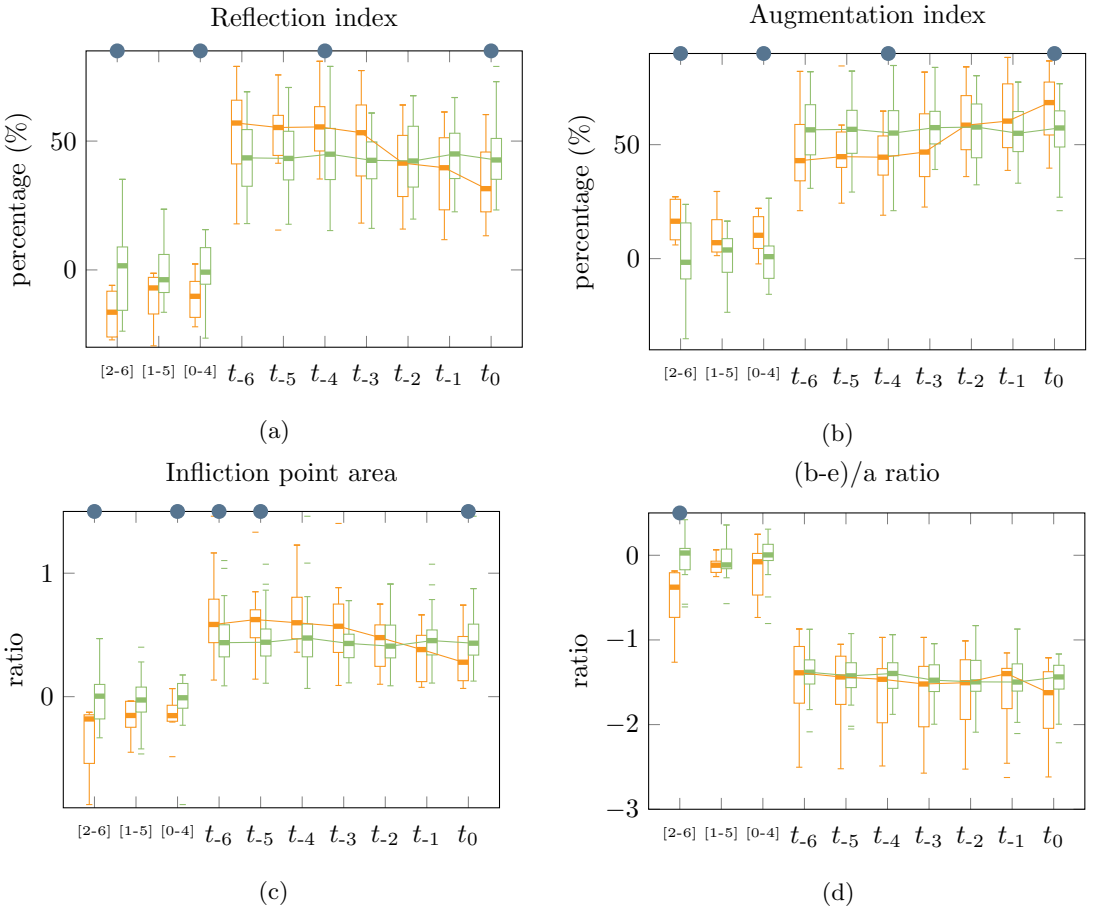


Figure 4.9: Long-term study primary outcome. PPG index and acceleration plethysmography features: (a) reflection index, (b) augmentation index, (c) infliction point area, and (d) (b-e)/a ratio. Orange: deteriorating MEWSs. Green: non-deteriorating MEWSs. Blue circles: significant difference between the two groups. [i-j]: difference between t_{-i} and t_{-j}.

EMG features

Amplitude features. In Figure 4.10a and 4.10b, the boxplots of the amplitude features are shown. Both features gave significant differences at the same moments in time. The earliest moment is six hours before the check-up. At the moments in time where no significant difference was found, the variation in amplitude was larger within the non-deterioration group.

Time features. The only two features that did not show a significant difference in the primary outcome are Ti and Te, as shown in Figure 4.10c to 4.10e. The RR gave a significant difference for the trend analysis of $t_0 - t_{-4}$ (p-value: 0.032) and at one hour before the nurses check-up (p-value: 0.045).

Area Under the Curve. The AUC showed significant differences at almost the same moments as the amplitude features of the EMG, see Figure 4.10f. Only at t_{-3}, the AUC did not show a significant difference, where the amplitude features did. The earliest significant difference was six hours before the check-up.

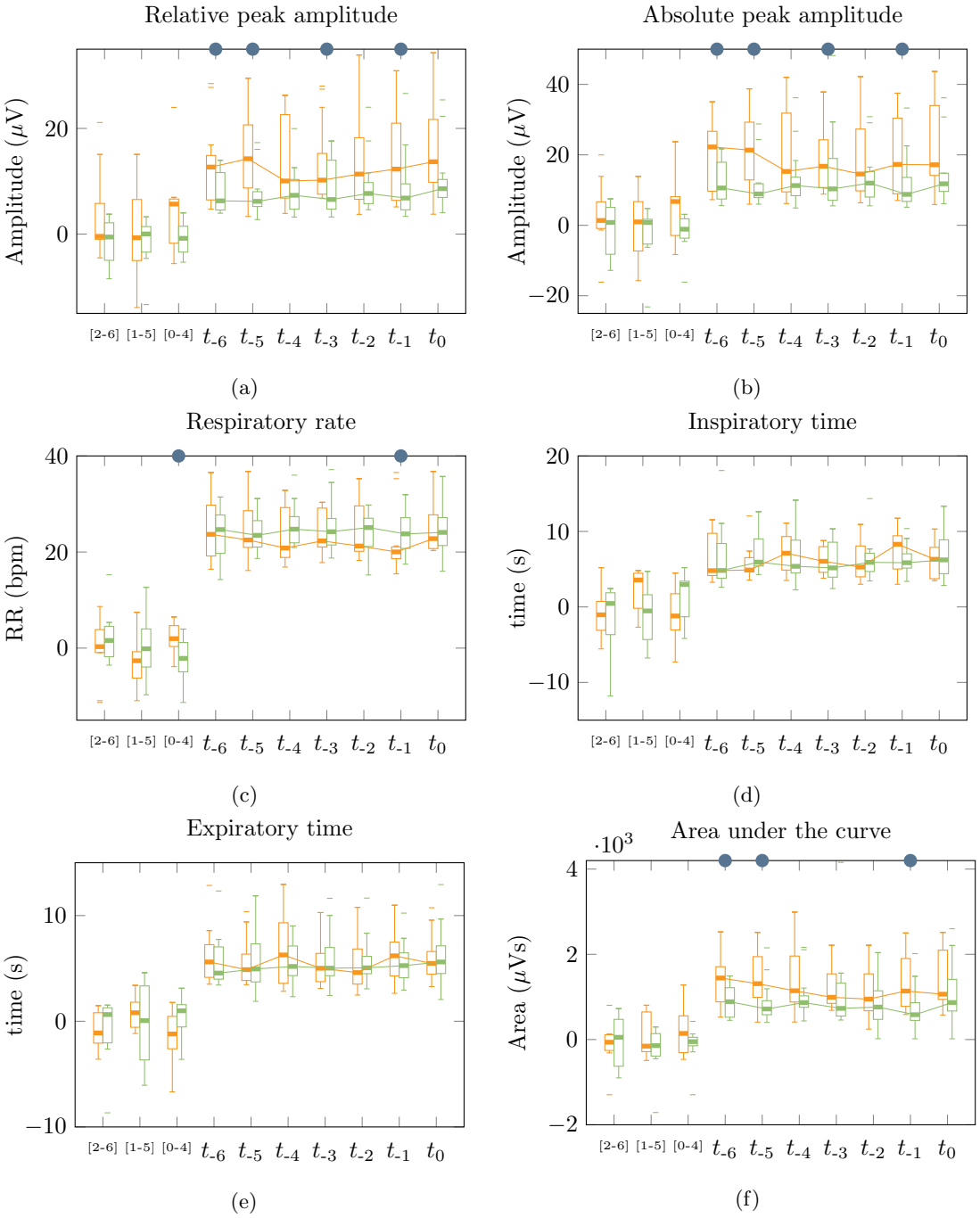


Figure 4.10: Long-term study primary outcome. EMG features: (a) relative peak amplitude, (b) absolute peak amplitude, (c) respiratory rate, (d) inspiratory time, (e) expiratory time, and (f) area under the curve. Orange: deteriorating MEWSs. Green: non-deteriorating MEWSs. Blue circles: significant difference between the two groups. [i-j]: difference between t_{-i} and t_{-j}.

4.2.3 Secondary outcome

One subject was excluded from the secondary outcome, due to insufficient data in the first four hours of the measurements. Of the other 23 subjects, only five were divided into the clinical deterioration group, as shown in Table 4.1. All eighteen subjects of the non-deterioration group had PPG data of the first four hours and only ten subjects (55.6%) also had PPG data after 24 hours. For EMG data of the non-deterioration group, this was much lower: five subjects (27.8%) had EMG data for the first four hours and four of them (22.2%) also had data after 24 hours. For the deterioration group, all five had PPG data at the first four hours and only two of them (40%) also had PPG data after 24 hours. The EMG data of the deterioration group also had a lower yield, three subjects (60%) at the first four hours and only one subject (20%) after 24 hours.

The secondary outcome had less significant features than the primary outcome. Seven of the nineteen features showed a significant difference between the two groups. This was the reason for the performance of an additional ad hoc analysis to search for promising features. Promising features had a p-value between 0.05 and 0.1. Six additional features were defined as promising. The most interesting promising features are presented in this section. The p-values of all features for the secondary outcome are shown in Appendix B.2. The boxplots of the features not presented in this result section are shown in Appendix C.

Significant features

All seven significant features were PPG features: PtP interval, pulse interval, pulse width, crest time, HR, relative amplitude, and the APG feature, as shown in Figure 4.11 and 4.12. In the first four hours, only significant differences were found at t_0 and t_1. Although only two subjects of the deterioration group had PPG recordings after 24 hours, five features showed significant differences in the trend analyses. The most interesting feature is the crest time, with three significant differences.

Promising features

Three PPG and three EMG features showed promising differences. The most interesting of these are the EMG features, shown in Figure 4.13. Relative peak amplitude seems the most promising feature, with promising differences at t_0, t_1 and t_4. Absolute peak amplitude and AUC both have one promising moment. The promising PPG features are shown in Appendix C.

4.3 Discussion

In this discussion, first the key findings of this study will be mentioned, subsequently interpretation of the features will be elaborated. Afterwards, the strengths and limitations of this study and the future perspective will be discussed.

4.3.1 Key findings

The aim of the long-term study was to investigate which features from continuous PPG and diaphragm EMG are early signs of deterioration. Nineteen features were investigated and seventeen of those features showed significant differences between deteriorating MEWSs and non-deteriorating MEWSs. Five features were already significantly different six hours before the check-up of the nurses. This suggests that it would be possible to predict which patient will deteriorate six hours before a nurse notices a deteriorating patient.

Especially, the EMG amplitude and AUC features seems very promising in the distinction between the two groups. All these features had significant differences five and six hours before the check-up. In the secondary outcome, these features showed clear visual differences, however due to the small sample size of the deterioration group, only promising differences were found.

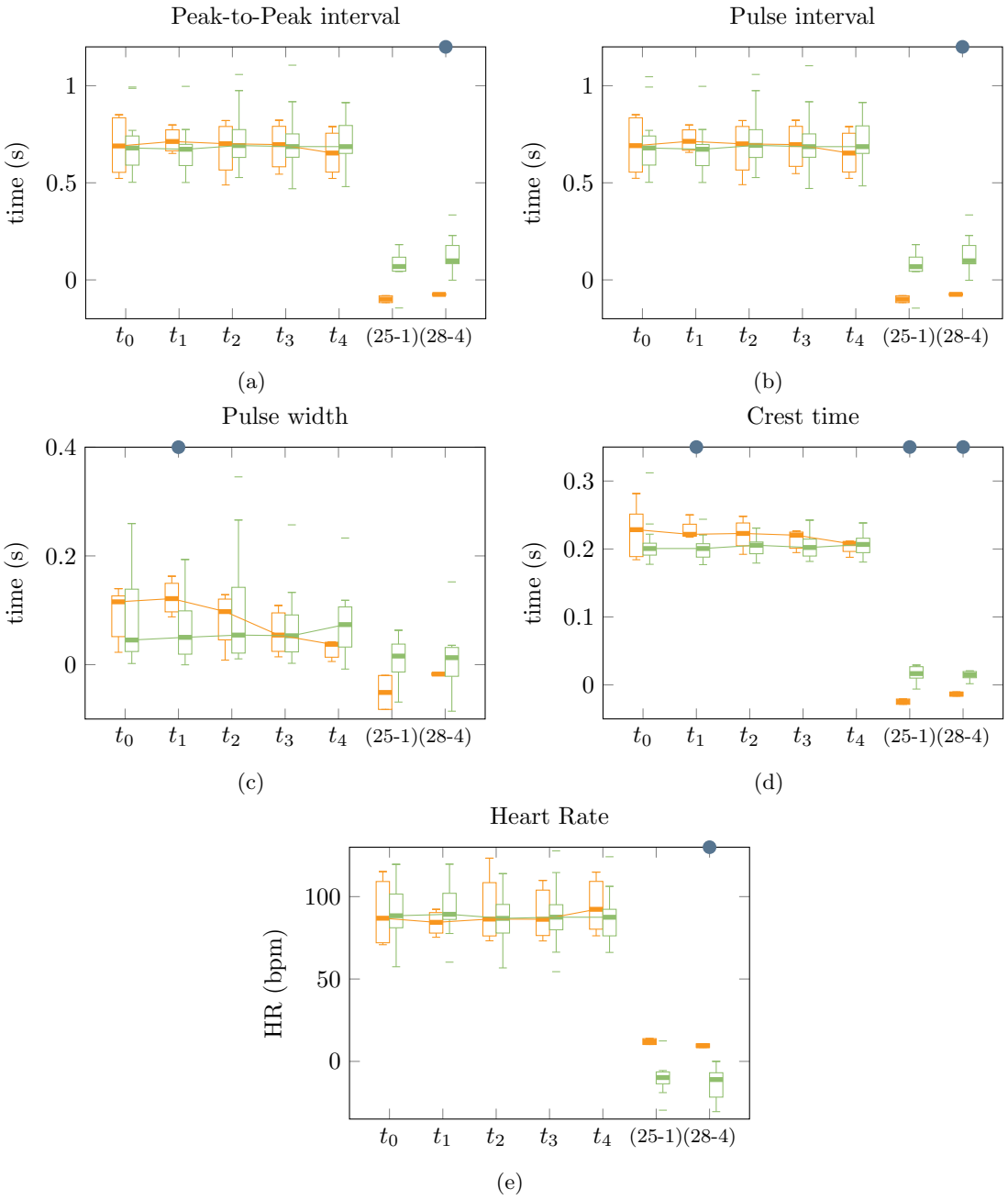


Figure 4.11: Long-term study secondary outcome. Significant time features. (a) Peak-to-peak interval, (b) pulse interval, (c) pulse width, (d) crest time, and (e) heart rate. Orange: deteriorating subjects. Green: non-deteriorating subjects. Blue circles: significant difference between the two groups. (i-j): difference between t_i and t_j.

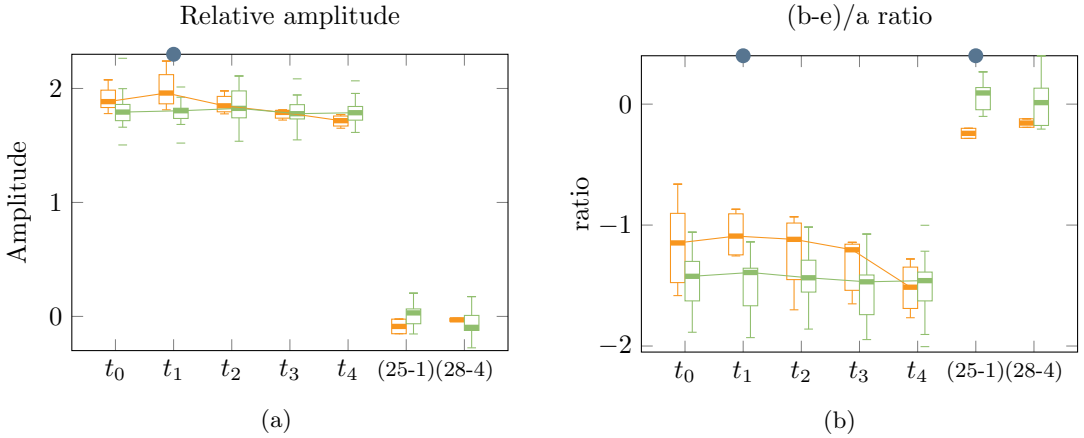


Figure 4.12: Long-term study secondary outcome. Significant PPG amplitude and APG features. (a) Relative amplitude and (b) (b-e)/a. Orange: deteriorating subjects. Green: non-deteriorating subjects. Blue circles: significant difference between the two groups. (i-j): difference between t_i and t_j.

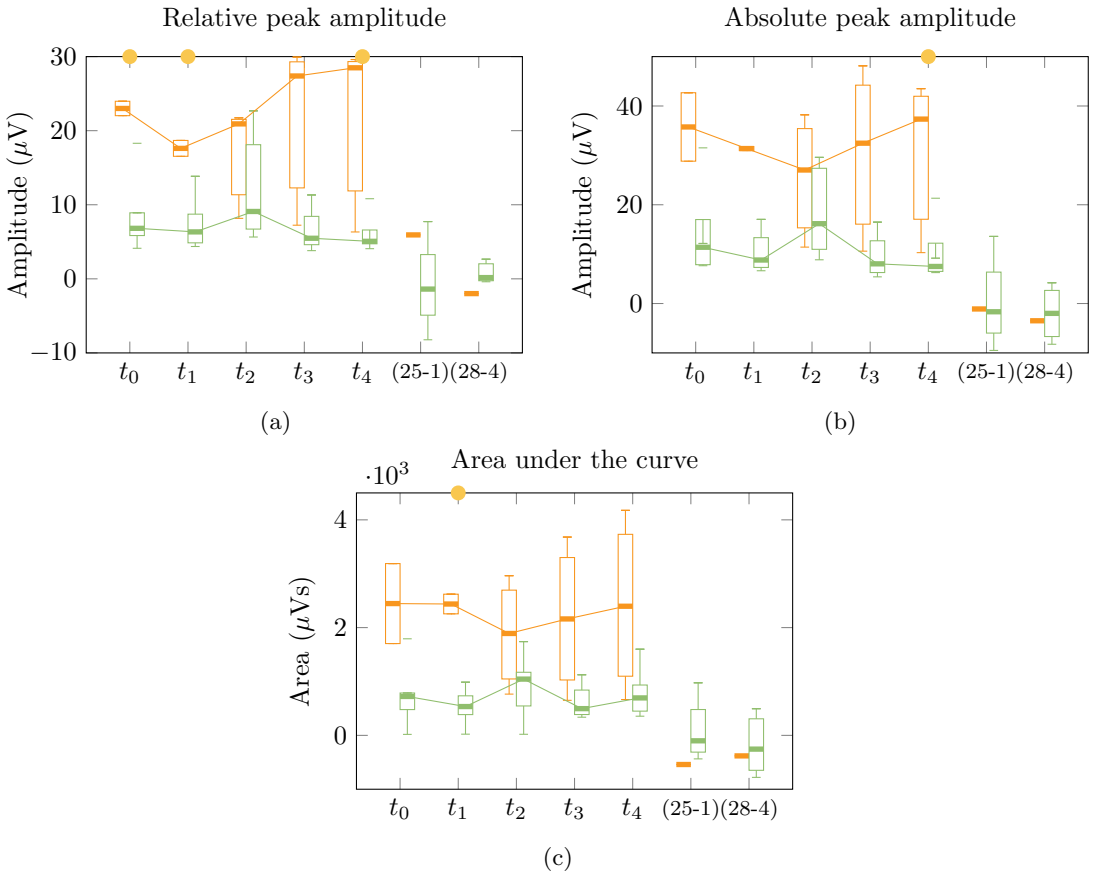


Figure 4.13: Long-term study secondary outcome. Promising EMG amplitude and AUC features. (a) Relative peak amplitude, (b) absolute peak amplitude, and (c) area under the curve. Orange: deteriorating subjects. Green: non-deteriorating subjects. Yellow circles: Promising difference between the two groups. (i-j): difference between t_i and t_j.

The IPA had the most significant differences of the primary outcome and was one of the five features with a significant difference at t_{-6}. This feature is therefore one of the promising features of the PPG waveform. Another promising PPG feature is the crest time. This feature had the most significant differences when combining the results of the primary and secondary outcome.

4.3.2 PPG feature interpretation

Amplitude features. The amplitude of the PPG waveform is related to the blood volume pulsations in the peripheral arteries at the measuring site. Stroke volume and vascular distensibility are known to influence these blood volume pulsations.[57, 87] An increase in distensibility or vasodilation will result in larger pulsations, which will give an increase in waveform amplitude.[88]

Vasodilation is one of the physiological abnormalities in the response to sepsis.[89] The hypothesis was that deteriorating patients will have the similar physiological characteristics as septic patients. It was therefore expected that deteriorating patients would have higher PPG amplitudes than non-deteriorating patients. However, the results of the primary outcome showed the opposite. The deterioration group had significant lower amplitudes than the non-deterioration group. In the secondary outcome, only the RA was higher in the deterioration group for the first two hours.

Lower amplitudes can be a result of lower stroke volume or increased peripheral resistance. Given the pathophysiology of infections and sepsis, an increased peripheral resistance is less likely. Vieillard and Cecconi describe that in the early phase of septic shock, before sufficient resuscitation, patients have a lower stroke volume related to hypovolemia.[90] It is possible that the MEWSs of the deterioration group are at this early phase and that the low amplitudes are a result of lower stroke volume, however the definition of this early phase is not described in the article and it is therefore not possible to confirm this hypothesis in this research. Additional research is needed to investigate the correlation between stroke volume and PPG amplitude.

Time features. The crest time had overall the most significant differences in the primary and secondary outcome. In the preliminary results, the crest time of deteriorating MEWSs was clearly lower than the non-deteriorating MEWSs. In the final results, presented in this thesis, this difference was less clearly visible. There are multiple possible explanations for the decrease in crest time in deteriorating patients. It is possible that an increase in HR causes the whole waveform to shorten, including the crest time. The preliminary results showed that the HR does indeed increase in the deteriorating MEWSs, however the HR was only significantly different in t_{-1} and t_0 and the crest time was significantly different from t_{-3}. Another explanation could be that a decreased vascular resistance accelerates the propagation of the crest of the blood volume pulsation and this will decrease the crest time.[91] As said before, vasodilation, or a decreased vascular resistance, is one of the physiological abnormalities in the response to sepsis and may already be seen in patients with severe infections.[89] Furthermore, as the steepness of the systolic peak can be used as an indicator of force of ventricular contraction, an increased force of ventricular contraction could be a possible explanation.[57] The final results showed that in the secondary outcome the crest time was higher in the deteriorating subjects than in the non-deteriorating subjects. As the HR was similar in these two groups the explanation that the crest time is dependent on ventricular contraction seems more plausible than the relationship with the HR.

The large number of significant features may be biased, because three of the PPG time features have similar physiological meaning. The PtP interval, pulse interval, and HR are all changing to due the HR and shown therefore significant differences at the same moments in time. The HR determination used in this study is based on the pulse interval and which make it not surprising that these features have the same significant differences. For future research it is advised to only use one of these features to reduce the biases in the results and as HR has the most significant differences and is the most commonly used feature in other research, this would be the advised feature.

A conclusion of the feasibility study was that there may be problems with the sample times of OSAsense. It is possible that these problems may have resulted in incorrectly determined time

features. Because there are still significant differences found in the primary and secondary outcome of the time features, it may seem that these sample time problems of OSAsense do not affect the time features in a great manner. However, it is not known what the results would have been if the time features were determined correctly. Resolving the sample times problem of OSAsense should give more reliable results.

Indexes and ratios. IPA in deteriorating MEWSs was higher in six to two hours before the check-up. Three hours before the check-up, the IPA of deteriorating patients decreases, meaning that the area of the diastolic phase decreases relative to the area of the systolic phase when a patient is deteriorating. As the diastolic component mainly arises from the reflected systolic wave from the lower body, a decrease in diastolic component would mean that the wave from the lower body is less reflected to the fingertip.[55] A possible explanation would be that due to the increased HR a new wave arrives relatively faster than the reflected wave, which would leave less time for the reflected wave to fully appear at the measuring site. Another explanation could be that total peripheral resistance (TPR) changes in these subjects. A reduction of TPR is a known symptom of sepsis and Wang et al. (2009) had found that the IPA is a very good indicator of the TPR when it changes.[92,93]

Same as with the time features, the RI and AI have similar physiological meaning and it is not surprising that these features had the same significant differences. Having multiple features with similar physiological meaning may result in a bias in the amount of significant features. In the future it is advised to use only one of these features.

Acceleration plethysmography. In the literature, the (b-e)/a feature is related to the vascular age, as the age increases the ratio also increases.[55,83] It was expected that deteriorating patients would show similar vascular characteristics as elderly people. The secondary outcome did indeed show that the (b-e)/a ratio is higher in deteriorating patients than in non-deteriorating patients.

he (b-e)/a ratio was chosen in this study, because most subjects did not had the c and d peaks. However, a few of the subjects did have these peaks and the detection algorithm was not based on these waveforms. It is therefore possible that not the correct peak was selected as e-peak, which would be of influence on this feature. A possible improvement would be to use the b/a ratio instead of the (b-e)/a ratio, because the a-peak and b-peak are easier to determine correctly.

4.3.3 EMG feature interpretation

Amplitude features. The amplitude of EMG signals are correlated with the muscle activity and an increase in amplitude means an increase in muscle activity.[61] When looking at the diaphragm activity, an increase in muscle activity would mean an increased work of breathing.[94] The results of this study showed that deteriorating patients had a higher EMG amplitude than non-deteriorating patients. This endorses our hypothesis that deteriorating patients have an increased work of breathing. It is striking that in both the primary and secondary results the deteriorating patients have a higher EMG amplitude at all moments in time. This would suggest that the deteriorating patients overall have an increased work of breathing during the first two days of hospital admission. An additional study, where the diaphragmatic EMG is continuously measured during the first two days may prove this suggestion.

Similar as with some PPG features, the relative peak amplitude and absolute peak amplitude have the same underlying physiological meaning. In future research, it would be advised to only use one of the amplitude features, because the features are greatly correlated and using both could cause bias in the results. Relative peak amplitude has more promising moments in the secondary outcome and would therefore be advised as amplitude feature.

Time features. The EMG time features appear not to be useful in the distinction between deteriorating and non-deteriorating patients, which is striking considering that RR is one of the MEWS criteria. Even at t_0, the moment of the check-up, the RR was not significantly different. When looking at the RR of non-deteriorating MEWSs, the average RR was around 25 bpm, which

is higher than the 12-15 bpm in healthy people at rest. This suggests that the breath detection algorithm used in this study is not correct. The Ti an Te will therefore also not be correctly calculated, because they are mostly based on the RR determination.

Area under the curve. The AUC of the EMG signals gave similar results as the amplitude features, which was not surprising as they are correlated with each other. The AUC consists of a time and an amplitude aspect and because the results of AUC had the most similarities with the amplitude features, it is suspected that in diaphragmatic EMG the amplitude aspect has the most influence in the AUC. However, the time features may not have been calculated correctly, which would have an influence on the AUC. When improving the time features, the AUC should also be improving.

4.3.4 Strengths and limitations

Strengths. The strength of this study is the use of novel continuous features for the recognition of early sepsis in ward patients. Most of the features have not been continuously measured in ward patients before and describe the hemodynamic and respiratory state of the patients in a different way. With these features a clear difference between deteriorating and non-deteriorating patients was found. Another strength is the number of MEWSs investigated, in total 142 MEWSs of 20 subjects were investigated. While there may be a bias in the results due to the multiple MEWSs per patient, this bias would be in both the deterioration and non-deterioration group, which would compensate the biases. Moreover, the measurement took place at a general ward, which is innovative for wearable diaphragm EMG measurements. Most literature found on diaphragm EMG was performed on ventilated ICU patients.[84,94–96] To the best of my knowledge, this study is first to measure the diaphragmatic activity in ward patients.

Limitations. Several limitations were present in this study. At first, the study data had some limitations. Only a few subjects had a complete data set with two measurements for both the Sencure and OSAsense devices, meaning that there was a lot of missing data. The most important reason for the missing data was the high workload of the research assistants performing the measurements, which made it difficult to start all measurements. Another important reason was that some patients indicated that they did not want to be measured with one of the devices. The high workload of the research assistants also resulted that not all patients that met the inclusion criteria were indeed included. It is not known which patients were not included, because some records were not correctly filled in and it is therefore also not known if there may be a bias in the patients that were included compared to the true study population. Furthermore, the deterioration group of the secondary outcome only consisted of five subjects, with only one subject with all four measurements. This resulted in the fact that the 24-hour analysis could only be determined for that subject. The statistical value of the 24-hour analysis of the secondary outcome is therefore very low. Including more subjects and focusing on gathering complete data sets, should improve the statistical power of the secondary outcome.

Besides the study data, the study method had some limitations as well. In the trend analyses only a fixed number of hours was used in each outcome, four hours in primary outcome and 24 hours in secondary outcome. It is however possible that longer or shorter periods of time would contain more interesting information than the periods used in this study. Especially for the secondary outcome may this be true, because only one large period was used in the trend analysis. The 24 hours of this research were chosen to eliminate the normal variation during a day from the trend analysis. However, the results show that only in 52% of the subjects a trend analysis of 24 hours is possible. To include more subjects in the trend analyses, it would be advised to investigate trends within one measurement. Furthermore, trend analyses of the first hours of ED admission could provide interesting information about the acute state of the subjects.

Another limitation of the secondary outcome method was the choice of t_0. t_0 was in this study defined as the start of the measurement, however the measurements were not started at a fixed moment after ED admission. The start of the measurements differed between one to six hours

after ED admission. To make a better comparison of the acute state of the subjects, t_0 should be a fixed moment related to the ED admission and not the start of the wearable device measurements. A logical t_0 choice would be to use the time of ED admission as t_0 in future research.

4.3.5 Clinical relevance

Sepsis is a severe disease with yearly over ten million deaths worldwide. Early recognition and timely treatment will decrease the mortality and long-term effects of this disease. In this study, novel early detection features are investigated, which could improve the early recognition of deteriorating infectious patients. The primary outcome showed that six hours before the nurses check-up a difference between the deteriorating and non-deteriorating patients is visible with these features. This suggests that implementation of these features in a clinical setting may improve the detection of deteriorating patients. Especially the EMG amplitude and AUC features showed promising results in differentiating between subject groups.

Furthermore, this study proves that diaphragm EMG can easily be measured in general ward patients. This could also be useful for other clinical application, besides detecting early sepsis. For example, the work of breathing could be continuously monitored at the pulmonary department to monitor the improvement or deterioration of different pulmonary diseases.

4.3.6 Future research

In future research, first some of the limitations should be solved, such as t_0 choice of the secondary outcome and the trend analyses. In addition, if the devices could measure more hours instead of twelve hours, the yield per subject would probably be higher. In order to facilitate this, the wearable devices should be improved by implementing better batteries or more memory capacity. Moreover, the respiratory rate detection method used in this study appeared to be incorrect. To improve this method, first a better validation method is necessary, for example a chest band or capnography. Another improvement could be to investigate the difference between the feature for more than six hours before the nurse's check-up. The primary outcome showed that four features had significant difference at six hours before the check-up. It is possible that these differences are visible even earlier than six hours before the check-up. Comparing the feature for more hours could improve the results and the early prediction of deterioration. Furthermore, more subjects need to be included to improve the secondary outcome. In this study only five subjects met the criteria for clinical deterioration and only one of these subjects had all measurements. Therefore, only the trend analysis of one deteriorating subject was possible. This population is too small to draw conclusions from.

Besides improving the study method and including more subjects, more fundamental research could be done to the study features. The SPA and DPA of the deteriorating MEWS were lower than the non-deteriorating MEWSs, which was an unexpected result and more fundamental research could provide an explanation for this result. It is possible that a decrease stroke volume in combination with vasodilation does give these results, however in this research nothing is known about the stroke volume and vasodilation. A study which compares the stroke volume of infectious patients with the SPA and DPA could provide an explanation for the results of this study. Furthermore, in the preliminary results, the crest time also showed some results that may be correlated with the stroke volume. Investigation of the relationship between stroke volume and PPG waveform could therefore be an interesting study. A non-invasive method to measure the stroke volume is the use of ultrasound.[97,98] It is preferable that the ultrasound is done by an experienced person and that the ultrasound measurements are frequently done to correlate changes in the PPG features with changes in stroke volume.

The next step for future research would be to investigate a prediction algorithm that could predict which patients with severe infections will deteriorate based on the features extracted from continuously measured PPG and diaphragm EMG. For both outcomes of this study a prediction

algorithm could be made. The first algorithm would be based on the primary outcome and would predict whether a patient will deteriorate at the general ward within a couple of hours. To fully implement this in a clinical setting, the measurements should be analyzed in real-time and the algorithm should be connected to the EHR to notify the nurses of a deteriorating patient. Furthermore, research should be done to determine the alarm thresholds to minimize false positive alarms while keeping a high sensitivity. The second prediction algorithm would be based on the secondary outcome and would predict the overall clinical outcome of a patient based on the measurements preformed at the ED. This algorithm does not need to be real-time, however fast calculation of the prediction is desirable. It would be ideal if the algorithm could distinguish between the different types of deterioration to make the prediction more useful for the physicians.

4.4 Conclusion

In this study, various features from continuous diaphragm EMG and PPG were extracted to investigate if they were early signs of deterioration in patients with severe infections. The primary outcome showed that up to six hours before the nurses check-up significant differences in the features can be found between the deteriorating MEWSs and non-deteriorating MEWSs. The most promising features were the EMG amplitude and AUC, as these features showed differences five and six hours before the check-up. In the secondary outcome, seven features showed significant differences. However, due to the small population, the statistical value of this outcome can be questioned. In future research, it is advised to include more subjects to improve the statistical power of the study.

Chapter 5

Conclusion

Early recognition of deterioration is key in order to improve the outcome of sepsis, however the vital signs where most of the predication methods are based on, may not indicate the start of deterioration. The aim of this research was to investigate the added value of novel parameters extracted from continuous PPG, measured by the OSAsense, and diaphragm EMG, measured by the Sencure, for the prediction of deterioration in patients with severe infections, by means of a feasibility study and long-term study.

The feasibility study showed that both devices had met the required yield of 60%. However, the accuracy and precision of Sencure could not be fully investigated. An improvement could be to use a chest-band or capnography as reference for the respiratory rate instead of the manually counted breaths by the nurses. For the OSAsense, the feasibility study showed a possible inconsistency in the sampling times, influencing the HR of the OSAsense measurements, but this did not seem to affect the results of the long-term study in a great manner. The HTA showed that the user experience of these wearables are good and that patients and nurses have a positive view on the use of wearables.

The long-term study showed that the novel parameters were able to detect a deteriorating patient earlier than the MEWS. Five of the features (SPA and IPA of the PPG signal and relative and absolute amplitude and AUC of the EMG signal) showed differences up to six hours before the nurse's check-up. These results indicate that continuously measured PPG and diaphragm EMG can indeed be of added value in the prediction of deterioration of ward patients. However, before these wearables can be implemented for clinical usage, first a prediction algorithm needs to be investigated to determine which combination of features and threshold values can indeed predict whether a patient will deteriorate.

The secondary outcome of the long-term study showed that four PPG features (pulse width, crest time, relative amplitude, and (b-e)/a ratio) showed significant differences at the first four hours of recording and that the amplitude and AUC features of the EMG are promising. However, in this research t_0 was defined as the start of the measurement instead of a fixed moment. In future research, it is advised to use a fixed moment, such as time of hospital admission, as t_0 to better interpret the results.

Although more research is needed before these devices can be fully implemented for clinical usage, this research showed the potential of PPG and diaphragm EMG in the prediction of clinical deterioration in patients with severe infections.

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Appendix A

Health Technology Assessment Questionnaires

A.1 Subjects

The questionnaire was divided into six domain with one to four statements. The statements were rated on a scale from 0 to 10, where 0 meant totally disagree and 10 meant totally agree. Every statement had an field for comments.

1. Emotie
   (a) Ik voel mij ongerust en beschaamd
   (b) Ik voel mij gespannen
   (c) Ik zou de wearable dragen als hij onzichtbaar was
2. Fysieke gevoel van de wearable
   (a) Ik voel de wearable op mijn lichaam zitten
   (b) Ik voel het apparaat bewegen
   (c) Ik was niet in staat om te bewegen zoals ik normaal beweeg
   (d) Het was lastig om het apparaat op en af te doen
3. Fysieke effect van de wearable
   (a) Het aangesloten apparaat gaf mij ongemak
4. Fysiek anders voelen
   (a) Ik voel mij omvangrijk/lijvig/groot met het apparaat op mijn lichaam
   (b) Ik voel dat mensen mij anders aankijken
5. Mobiliteit
   (a) Ik voel mij niet veilig met het apparaat
6. Gesteldheid betreft wearable
   (a) Ik voel dat mensen mij anders aankijken
   (b) Ik heb het gevoel dat het apparaat niet goed is aangesloten
   (c) Ik heb het gevoel dat het apparaat niet goed werkt

A.2 Nurses

All statements were true or false statements and had an individual field for comments.

1. Ik denk dat ik de wearable vaak wil gebruiken.
2. Ik vond de wearable onnodig complex.
3. Ik vond de wearable makkelijk in gebruik bij ADL.
4. Ik denk dat ik hulp nodig heb van een technisch persoon om de wearable uit te voeren.
5. Ik vond de wearable mooi geïntegreerd.
6. Ik vond de wearable te inconsistend.
7. Ik denk dat de meeste mensen de wearable makkelijk begrijpen.
8. Ik vond de wearable erg omslachtig om te gebruiken.
9. Ik voelde me zelfverzekerd om de wearable te gebruiken.
10. Ik moest veel dingen leren voordat ik de wearable kon gaan gebruiken.
11. Ik begrijp hoe de wearable werkt.
12. Ik heb het idee dat de patiënt ongemak ervaart doordat hij/zij een wearable draagt.

A.3 Research Assistents

All statements were true or false statements and had an individual field for comments.

1. Ik denk dat ik het protocol vaak ga gebruiken.
2. Ik vond het protocol onnodig complex.
3. Ik vond het protocol makkelijk te gebruiken.
4. Ik denk dat ik hulp nodig heb van een technisch persoon om het protocol uit te voeren.
5. Ik vond het protocol mooi geïntegreerd.
6. Ik vond het protocol te inconsistend.
7. Ik denk dat de meeste mensen het protocol makkelijk begrijpen.
8. Ik vond het protocol erg omslachtig om te gebruiken.
9. Ik voelde me zelfverzekerd om het protocol te gebruiken.
10. Ik moest veel dingen leren voordat ik het protocol kon gaan gebruiken.

Appendix B

P-values long-term study

B.1 Primary outcome

In the table below, the p-values of the primary outcome are shown. The green highlighted p-values are significant (≤ 0.05) and the yellow highlighted p-values are promising (≤ 0.10).

	[2-6]	[1-5]	[0-4]	t_{-6}	t_{-5}	t_{-4}	t_{-3}	t_{-2}	t_{-1}	t_0
PPG features										
Systolic peak amplitude	0.561	0.714	0.944	0.017	0.007	0.003	0.011	0.359	0.565	0.582
Diastolic peak amplitude	0.934	0.816	0.870	0.098	0.038	0.055	0.139	0.359	0.255	0.072
Relative amplitude	0.024	0.479	0.187	0.103	0.323	0.163	0.124	0.544	0.973	0.204
Peak-to-peak time	0.010	0.146	0.079	0.497	0.878	0.811	0.741	0.385	0.068	0.002
Pulse interval	0.010	0.146	0.071	0.528	0.900	0.792	0.897	0.359	0.052	0.001
Pulse width	0.009	0.351	0.656	0.194	0.109	0.286	0.201	0.991	0.563	0.144
Crest time	0.083	0.057	0.037	0.851	0.878	0.870	0.321	0.065	0.038	0.001
Delta time	0.094	0.434	0.678	0.065	0.098	0.032	0.024	0.625	0.324	0.293
Heart rate	0.022	0.192	0.046	0.528	0.856	0.792	0.943	0.323	0.050	0.001
Reflection index	0.012	0.192	0.020	0.089	0.077	0.049	0.111	0.497	0.143	0.021
Augmentation index	0.012	0.192	0.020	0.089	0.077	0.049	0.111	0.497	0.143	0.021
Infliction point area	0.016	0.192	0.023	0.044	0.044	0.065	0.087	0.934	0.192	0.033
(b-e)/a	0.004	0.526	0.214	0.934	0.813	0.274	0.556	0.560	0.563	0.079
EMG features										
Relative peak amplitude	0.408	0.879	0.073	0.037	0.013	0.100	0.019	0.167	0.025	0.082
Absolute peak amplitude	0.762	0.595	0.053	0.020	0.025	0.181	0.046	0.167	0.017	0.060
Respiratory rate	0.897	0.224	0.032	0.728	0.979	0.056	0.776	0.889	0.045	0.694
Inspiratory time	0.897	0.068	0.113	0.877	0.117	0.392	0.747	0.459	0.167	0.722
Expiratory time	0.408	0.704	0.084	0.438	0.979	0.346	0.864	0.535	0.546	0.955
Area under the curve	0.717	0.649	0.218	0.032	0.019	0.130	0.055	0.247	0.003	0.139

B.2 Secondary outcome

In the table below, the p-values of the secondary outcome are shown. The green highlighted p-values are significant (≤ 0.05) and the yellow highlighted p-values are promising (≤ 0.10).

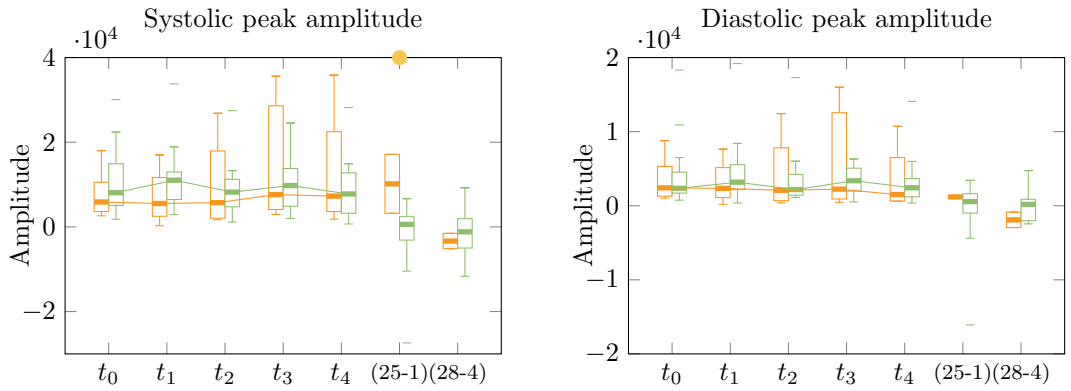
	t_0	t_1	t_2	t_3	t_4	$25-1$	$28-4$
PPG features							
Systolic peak amplitude	0.302	0.263	0.741	0.960	0.893	0.073	0.485
Diastolic peak amplitude	0.967	0.395	0.603	0.802	0.687	0.582	0.182
Relative amplitude	0.091	0.044	0.665	0.880	0.165	0.436	0.606
Peak-to-peak time	0.901	0.227	0.885	1.000	0.397	0.145	0.030
Pulse interval	0.901	0.227	0.885	1.000	0.459	0.145	0.030
Pulse width	0.536	0.044	0.961	1.000	0.397	0.145	0.485
Crest time	0.433	0.011	0.152	0.209	0.964	0.036	0.030
Delta time	0.076	0.964	0.469	0.340	0.964	0.218	0.485
Heart rate	0.901	0.227	0.885	1.000	0.459	0.073	0.030
Reflection index	0.386	0.139	1.000	0.451	0.117	0.145	0.485
Augmentation index	0.386	0.139	1.000	0.451	0.117	0.145	0.485
Infliction point area	0.710	0.263	0.736	0.291	0.090	0.436	0.273
(b-e)/a	0.127	0.008	0.221	0.175	0.893	0.036	0.273
EMG features							
Relative peak amplitude	0.071	0.095	0.548	0.114	0.071	0.800	0.500
Absolute peak amplitude	0.190	0.133	0.571	0.114	0.071	1.000	1.000
Respiratory rate	0.643	0.190	0.714	1.000	1.000	0.400	0.500
Inspiratory time	1.000	0.190	0.262	0.629	1.000	0.800	0.500
Expiratory time	0.857	0.190	0.548	0.857	0.400	0.800	0.500
Area under the curve	0.143	0.095	0.262	0.114	0.250	0.400	1.000

* No values were determined for the deterioration group. A statistical test was therefore not possible.

Appendix C

Additional results long-term study

Only the graphs of features that are not already shown in the thesis are shown here.



(a) (b)

Figure C.1: Long-term study secondary outcome. PPG amplitude features. (a) systolic peak amplitude and (b) diastolic peak amplitude. Orange: deteriorating subjects. Green: non-deteriorating subjects. Yellow circles: promising difference between the two groups. (i-j): difference between t_i and t_j.

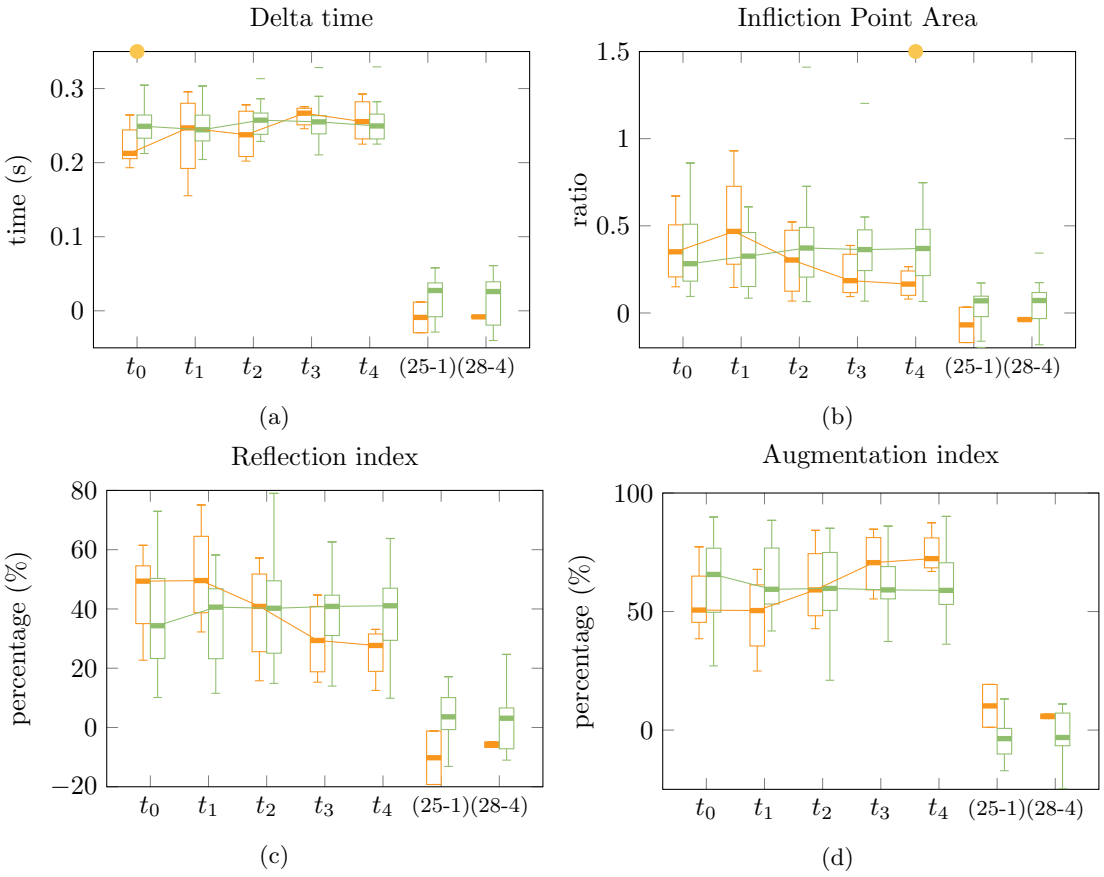


Figure C.2: Long-term study secondary outcome. PPG time features and indexes and ratios. (a) delta time, (b) infliction point area, (c) reflection index, and (d) augmentation index. Orange: deteriorating subjects. Green: non-deteriorating subjects. Yellow circles: promising difference between the two groups. (i-j): difference between t_i and t_j.

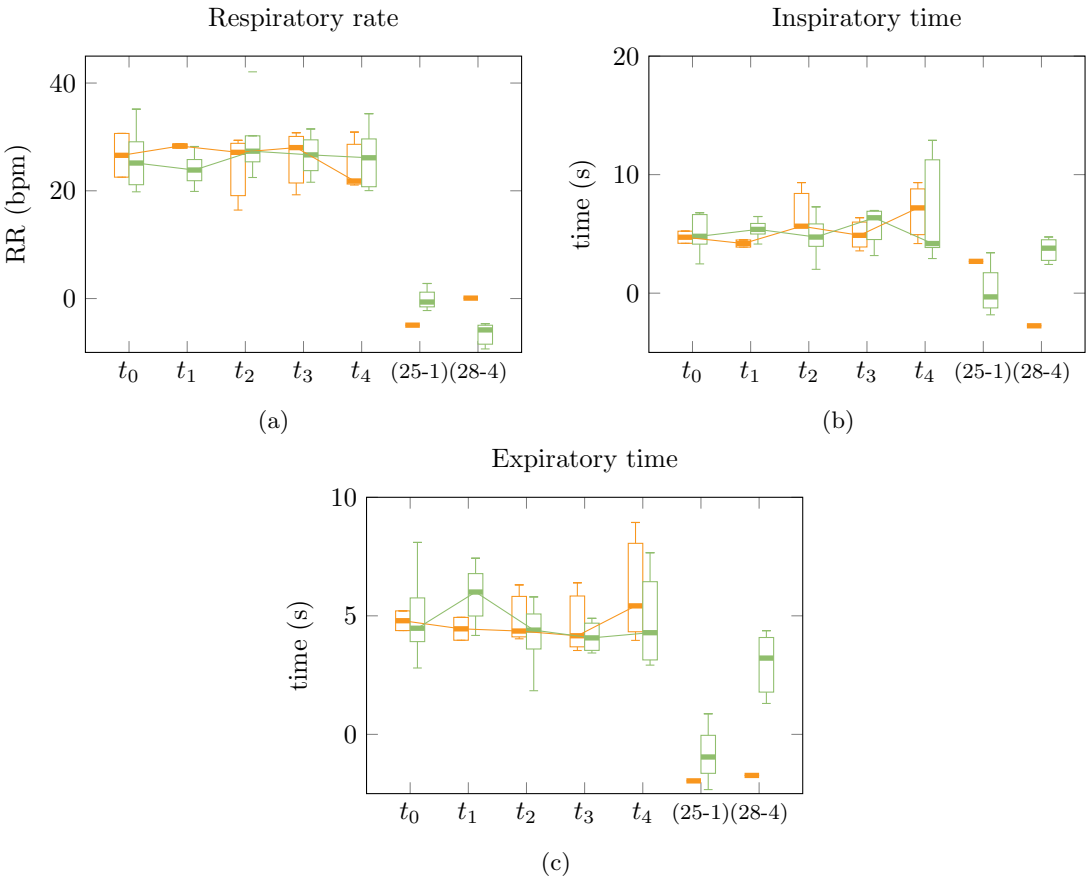


Figure C.3: Long-term study secondary outcome. EMG time features. (a) respiratory rate, (b) inspiratory time, and (c) expiratory time. Orange: deteriorating subjects. Green: non-deteriorating subjects. Yellow circles: promising difference between the two groups. (i-j): difference between t_i and t_j.

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