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PhD thesis by Mikkel Elvekjær

Wireless assessment of respiratory and circulatory distress in chronic obstructive pulmonary disease

with special emphasis on physiological abnormalities, validation and patient outcomes in acute exacerbation

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Abbreviations

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

BP: blood pressure

bpm: beats per minute

brpm: breaths per minute

COPD: chronic obstructive pulmonary disease

DO: direct observation

ECG: electrocardiogram

EWS: early warning score

HR: heart rate

ICD: implantable cardioverter defibrillator

ICU: intensive care unit

LoA: limits of agreement

MET: medical emergency team

NEWS: national early warning score

PACU: post anesthesia care unit

PR: pulse rate

RR: respiratory rate

RRS: rapid response system

SAE: serious adverse event

SD: standard deviation

SpO_2: peripheral oxygen saturation

WARD: wireless assessment of respiratory and circulatory distress

Original Paper/Manuscripts

The thesis is based on the following studies, which can be found at the end of the thesis:

Study 1

Elvekjaer M, Aasvang EK, Olsen RM, Sørensen HBD, Porsbjerg CM, Jensen JU, Haahr-Raunkjær C, Meyhoff CS. Physiological abnormalities in patients admitted with acute exacerbation of COPD: an observational study with continuous monitoring. *Journal of Clinical Monitoring and Computing* 2020;34**,**1051–1060.

Study 2

Elvekjaer M, Carlsson CJ, Rasmussen SM, Porsbjerg CM, Grønbæk KK, Haahr-Raunkjær C, Sørensen HBD*, Aasvang EK*, Meyhoff CS*. Agreement between wireless and standard measurements of vital signs in acute exacerbation of chronic obstructive pulmonary disease: a clinical validation study. *Submitted, January 2021.*

*Shared last authorship

Study 3

Elvekjaer M, Rasmussen SM, Grønbæk KK, Porsbjerg CM, Jensen JU, Haahr-Raunkjær C, Mølgaard J, Søgaard M, Sørensen HBD, Aasvang EK†, Meyhoff CS†. Clinical impact of vital sign abnormalities in patients admitted with acute exacerbation of chronic obstructive pulmonary disease – an observational study using continuous wireless monitoring. *Submitted, January 2021.*

†Contributed equally

Summary in Danish (dansk resumé)

Akut syge indlagte patienter stoler på at hospitalet er et sikkert sted. Hvis deres tilstand skulle forværres yderligere, forventes det at personalet hurtigt vil opdage det og reagere. Der er dog data der tyder på at dette ikke altid er tilfældet. Fysiologiske afvigelser kan efterfølges af alvorlige komplikationer og tidlig opdagelse af tegn på klinisk forværring er derfor essentielt. Nuværende standardmonitorering på sengeafdelinger er imidlertid baseret på intermitterende manuelle observationer, og der er bekymring for, at dette system fungerer suboptimalt, herunder særligt hos patienter med kronisk obstruktiv lungesygdom. Patienter indlagt med akut exacerbation af kronisk obstruktiv lungesygdom (AECOPD) er i høj risiko for pludselig forværring i tilstanden. Trådløse monitoreringssystemer kan måle vitalparametre kontinuerligt, og det kan potentielt forbedre behandlingen ved at sikre, at fysiologisk forværring opdages tidligere. Formålet med denne ph.d.-afhandling var at undersøge afvigelser af vitalparametre hos AECOPD-patienter (Studie 1) samt at undersøge nøjagtigheden af trådløse monitoreringsapparater hos denne patientgruppe (Studie 2). Derudover var formålet at undersøge sammenhængen mellem episoder med afvigelser af vitalparametre og alvorlige komplikationer (*serious adverse events* = SAE) (Studie 3).

Vi foretog kontinuerlig monitorering af perifer iltmætning, hjerte- og respirationsfrekvens samt højfrekvente automatiske målinger af blodtrykket. I Studie 1 og 3 blev patienter kontinuerligt monitoreret i løbet af de første 4 dage efter indlæggelse med AECOPD, mens vi i Studie 2 foretog parrede målinger af vitalparametre med forskellige apparater i en periode på to timer.

I Studie 1 sammenlignede vi 30 patienters abnorme vitalparametre påvist med standardmonitorering i forhold til målinger via kontinuerlig monitorering. Vi fandt episoder med moderat nedsat iltmætning hos 90% af patienterne, og disse hændelser blev kun opdaget med standardmonitorering hos 13% af patienterne ($p < 0.0001$). Episoder med alvorligt lav perifer iltmætning blev påvist hos 63% af patienterne med kontinuerlig overvågning, og der blev ikke registreret sådanne hændelser med standardmonitorering. I Studie 2 sammenlignede vi vitalparameterværdier målt med trådløse og vanligt anvendte apparater hos 20 AECOPD patienter. Overensstemmelsen mellem trådløse og standardmålinger var acceptabel for hjertefrekvens og puls. Målinger af perifer iltmætning var med acceptabel nøjagtighed, mens præcisionen var lige omkring grænsen i forhold til vores prædefinerede acceptable afvigelse. Præcisionen af trådløse målinger af respirationsfrekvens og blodtryk var ikke tilstrækkelig. I Studie 3 undersøgte vi episoder med afvigelse af vitalparametre i forhold til udvikling af SAE som forekom hos 41% af de inkluderede 200 patienter. Patienter med SAE under samtidig kontinuerlig monitorering, havde en gennemsnitlig kumulativ varighed af

enhver fysiologisk afvigelse på 455 minutter (standardafvigelse 413) pr. 24 timer, mens patienter uden SAE havde et gennemsnit på 292 minutter (standardafvigelse 246) pr. 24 timer, $p = 0.08$, svarende til en gennemsnitlig forskel på 163 minutter [95% konfidensinterval 61 - 265]. Der var ikke signifikant længere kumulativ varighed af de fleste undergrupper af vitalparameter-afvigelser hos patienter med SAE sammenlignet med patienter uden SAE.

Vi konkluderer at fysiologiske afvigelser er almindelige i de første dage efter indlæggelse for AECOPD, og at sådanne episoder oftest ikke opdages med standardmonitorering. Patienter indlagt med AECOPD har en høj risiko for at udvikle SAE, men betydningen af absolutte værdier af forudgående fysiologiske afvigelser er ikke endeligt fastlagt.

Ovenstående fund bør overvejes i forbindelse med udviklingen af fremtidige kontinuerlige monitoreringssystemer baseret på trådløse sensorer.

Summary

Patients who are hospitalized trust they are entering a safe place. They believe they are in the optimal place for prompt action, should their condition deteriorate further. However, there are data suggesting that this is often not the case. Unrecognized physiological instability can progress to severe complications, making it essential that impending deterioration is detected early. Current standard monitoring relies on intermittent observations and concern exists that these systems do not perform as well as expected, in particular in patients with chronic obstructive pulmonary disease (COPD). Patients admitted with acute exacerbation of COPD (AECOPD) have high mortality rates and may deteriorate suddenly. Wireless monitoring systems can measure vital signs continuously and this may improve patient care by permitting physiological abnormalities to be detected earlier. This thesis aimed to investigate vital sign abnormalities in the AECOPD setting (Study 1) and to evaluate the accuracy of wireless devices (Study 2). We also aimed to investigate the association between frequency and duration of vital sign abnormalities and subsequent serious adverse events (SAEs) (Study 3).

We continuously monitored peripheral oxygen saturation, heart rate and respiratory rate and performed high-frequency automatic measurements of non-invasive blood pressure. In Studies 1 and 3, patients were monitored during the first 4 days after admission with AECOPD while paired measurements of vital signs were recorded during a two-hour period in Study 2.

In Study 1, we assessed the frequency of vital sign abnormalities in 30 patients detected with standard monitoring (early warning score (EWS)) compared with continuous monitoring. We found episodes of moderate desaturation in 90% of patients, and these events were detected with standard monitoring in only 13% of patients ($p < 0.0001$). Severe desaturation episodes were detected in 63% of patients using continuous monitoring and no event was recorded with standard monitoring.

In Study 2 we evaluated the agreement between wireless and standard monitor recordings in 20 patients. The agreement between wireless and standard measurements was acceptable for heart rate and pulse rate. For measurements of peripheral oxygen saturation, we found acceptable accuracy while the precision was borderline acceptable. The precision of wireless measurements of respiratory rate and blood pressure was outside the acceptable limits.

In study 3, we compared events of physiological abnormalities with the occurrence of SAEs in 200 patients. SAE(s) occurred in 41% of included patients. In patients with SAEs during ongoing continuous monitoring, the average cumulative duration of any physiological abnormality was

455 minutes (standard deviation 413) per 24 hours, while patients without SAEs had an average of 292 minutes (standard deviation 246) per 24 hours, $p = 0.08$, mean difference 163 minutes [95% CI 61 – 265]. Episodes of most vital sign abnormalities were not of significantly longer cumulative duration in patients with an SAE when compared with patients without SAEs.

In conclusion, events of physiological abnormalities are common during the first days after hospitalization for AECOPD and such episodes are most often not detected with EWS. Patients admitted with AECOPD have a high risk of SAEs; however, the importance of absolute values of preceding vital sign abnormalities is unclear.

These findings should be considered in the development of future continuous monitoring systems based on wireless sensors, and the value of machine learning-based algorithms with trend analysis should be investigated.

Introduction

The word "monitoring" originates from the Latin verb *monēre* ("to warn"). Monitoring historically started as experiments on physiological measurement. In 1625 Santorio and Galileo presented methods of measuring the pulse rate (PR) with a pendulum and body temperature with an air thermometer [1]. A great number of experiments have been conducted since and during recent years several companies have introduced devices capable of wireless monitoring of vital signs (heart rate, respiratory rate, blood pressure, body temperature and oxygen saturation) in a hospital setting [2]. Currently, the standard method of vital sign measurement outside high-dependency units, such as intensive care units (ICU), emergency departments and postanesthetic care units (PACU), is manual, intermittent and has several limitations, including, physical restraints, large out-of-observation periods and substantial use of staffing resources. Wireless technology may therefore dramatically change the way hospitalized patients, including patients with acute respiratory disease, are monitored in the future. Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that causes long-term breathing problems due to obstructed airflow from the lungs. Patients hospitalized with COPD-related symptoms may have chronically disturbed physiology that challenges current systems for patient observation. Moreover, a knowledge gap currently exists regarding wireless monitoring of vital signs including the relation between physiological abnormalities and clinical complications. Additionally, the accuracy of new monitoring devices needs to be evaluated before widespread implementation.

Background

Historical perspective on vital sign measurements

Physicians of the antique period noticed and speculated about the association between fever and increased heart rate (HR); however, vital sign measurements as part of routine medical practice have been used only since the mid-nineteenth century. The first plotted episode of fever in a patient was published by Ludwig Taube in 1852 and he also reported measurement of the respiratory rate (RR) [3]. In 1866 Edward Seguin and William Draper reported three cases of pneumonia that included a chart of "vital signs" with daily recordings of temperature, pulse-beats and respirations at the bedside [4]. Railways had

increased the demand for accurate timing of arrivals and departures of trains and affordable pocket watches therefore became widely available, allowing every physician, to accurately record the PR. Measuring the blood pressure (BP) as a vital sign was adopted much more recently. The cuff-based mercury sphygmomanometer was developed by Scipione Riva Rocci in Italy, who was visited by recognized American neurosurgeon Harvey Cushing in 1901. Cushing made drawings of the sphygmomanometer and made a similar device in the US, which was successfully used during neurosurgical procedures. Cushing promoted the sphygmomanometer and also introduced the anesthetic chart with perioperative monitoring of pulse, respiration and temperature during ether anesthesia [5]. Technological advances by electronics companies in the 1960s and 1970s meant that patient monitoring devices were improving almost every year. Takuo Aoyagi developed the first pulse oximeter in 1972 [6], and peripheral oxygen saturation (SpO_2) was later considered a "fifth vital sign", improving clinicians' ability to detect arterial hypoxemia and related events [7]. Continuous or high-frequency monitoring of vital signs has now been the standard of care in operating rooms, PACU and ICU settings for many years, but this is not the case for general hospital wards, where vital sign parameters are still primarily monitored intermittently and manually. During recent years, several manufacturers have developed wearable sensors with different technology and capabilities, but with the overall aim of enabling continuous patient monitoring in general ward or home settings. Recent studies have also shown the ability to detect atrial fibrillation and myocardial ischemia using commercially available smartwatches [8, 9].

The current practice of in-hospital patient monitoring

Treatment of hospitalized patients is becoming more demanding due to increasing patient age, multiple comorbidities and extended treatment options. Unrecognized physiological changes in hospitalized patients can progress to major complications, such as respiratory failure, septic shock or cardiac arrest. However, most patients are hospitalized in a general ward (non-ICU) setting with limited resources for monitoring. Clinical deterioration has been defined as "movement from one clinical state to a worse clinical state which increases the individual risk of morbidity or death" [10]. For patients suffering unexpected deterioration, untimely or suboptimal medical intervention is associated with increased morbidity and mortality [11–13]. In 51–80 % of in-hospital cardiac arrests, one or more abnormal vital sign was recorded up to 24 hours before the event [14–16]. Rapid response systems (RRS) are widely used in hospitals to detect and treat acutely deteriorating patients on general wards before the condition

progresses beyond the point of no return where severe complications are inevitable. Key components of RRS are track-and-trigger systems designed to ensure early *detection* of impending deterioration, the afferent or "sensing" limb, and adequate *response* to the situation, the efferent or "acting" limb [17]. An important part of the efferent limb can be the alert of a medical emergency team (MET) consisting of experts in critical care, for clinical assistance at the bedside. Many different systems exist with variations according to the number of parameters analyzed as well as monitoring frequencies, trigger thresholds and the clinical response algorithm. The focus in this thesis is on the afferent limb; however, the performance of RRS also depends highly on the efferent part of the system, i.e., the alerting of staff and quality of interventions to stabilize physiology and ultimately improve patient outcome.

An example of a widely implemented track-and-trigger system is early warning score (EWS) systems used in many hospitals with vital signs recorded manually at regular intervals, usually starting at 12 hour-intervals and decreasing in the case of abnormal measurements. Each variable generates points according to the degree of physiological deviation from normal, and measurements are aggregated to a single score that reflects the severity of deterioration. This system was introduced after the concept of RRS had matured, beginning in the early 1990s when physicians became more aware of the fact that critical illness on general wards rarely developed suddenly; rather it was suddenly recognized [18]. The National EWS (NEWS) endorsed by the Royal College of Physicians was introduced in the United Kingdom in 2012 and updated in 2017 with NEWS2 [19, 20]. A similar system was implemented in the Capital Region of Denmark in 2013. Several observational studies have investigated the use of EWS systems, but only a few randomized controlled trials have been completed [21, 22]. A systematic review from 2014 concluded that a high aggregated EWS predicted cardiac arrest and death within 48 hours; however, the effect of the system on health outcomes and resource utilization was still uncertain [23] and fewer cardiac arrests may be attributed to more patients having 'Do-Not-Resuscitate' orders deployed when a high EWS is measured. Another systematic review concluded that EWS systems in clinical use have methodological weaknesses and therefore might not perform as well as expected [24]. Clinical deterioration may also occur between intermittent EWS recordings, potentially leading to critical delay in diagnostics and interventions and vital sign data from manual observations may be of low quality [25, 26]. Despite its limitations, EWS monitoring with manual sampling of vital signs is the current standard of care for general ward patients. At our institution, patients presenting with obviously unstable physiology can either be transferred urgently to the intensive/intermediate care unit or (depending on the clinical situation)

they may be monitored continuously at the general ward using wired pulse oximetry and electrocardiogram (ECG) leads to bedside monitors. However, nurses must be present at the bedside to react to simple monitor threshold alarms, of which the majority are often irrelevant due to artifacts or because they are self-limiting. Accordingly, monitoring is time consuming and such high-acuity care is possible for only a very limited number of hospitalized patients. Moreover, deterioration can also occur in seemingly stable patients and wired monitoring equipment limits patient mobility and comfort.

Monitoring patients hospitalized with acute exacerbations of COPD

COPD is the third leading cause of death globally [27] despite efforts to advance medical therapy, and patients may suffer acute exacerbation of COPD (AECOPD), causing a major health care burden. Most exacerbations are triggered by viral or bacterial respiratory tract infections, and these events negatively affect lung function, health-related quality of life, and prognosis [28]. Severe exacerbations can be defined as those resulting in hospitalization [29]. These patients carry a mortality rate of 4–11% during the hospital stay, and 21–43% within the first following year [30–33]. Re-admission is related to significantly increased mortality risk [34]. AECOPD patients are at risk of respiratory failure due to increased airway resistance, causing air-trapping and increased work of breathing. Patients usually have tachycardia and tachypnea, but bradypnea and respiratory acidosis may develop as respiratory compromise advances. Standard treatment of AECOPD comprises bronchodilation with β-agonists and anti-muscarinic agents combined with supplemental intravenous drugs and oxygen treatment titrated to a SpO_2 of 88–92% [35]. Non-invasive ventilation or intubation with mechanical ventilation is required for the most severe cases. The clinical condition may rapidly change, requiring escalation of care, i.e., ICU admission and mechanical ventilation, occurring in 10% and 6% of patients, respectively [30]. Patients may also suffer from different serious adverse events (SAE) which can be defined according to the International Conference on Harmonisation guidelines for Good Clinical Practice [36], and includes all untoward medical events that are fatal, life threatening or prolongs hospitalization. COPD patients often have chronic deviations from the normal range on several physiological parameters including hypoxemia with need for supplemental oxygen, resulting in high EWS for most patients. When these values are measured, inappropriate alarms may be generated placing a substantial burden on health care staff. This may cause increased attention to clinically stable patients, leading to alarm fatigue with possible non-adherence to the EWS escalation protocol [37]. This lack of specificity of EWS systems in

the COPD population has resulted in debate about its use in this setting due to the high number of false alerts [38–40], and modified scoring systems have been proposed [41–44]. In the Capital Region of Denmark, individual acceptable chronic value thresholds for EWS variables can be specified by the attending physician. This automatically adjusts aggregated EWS scores recorded during the following 24 hours or until the patient is discharged. However, assigning different thresholds for scoring may result in missed opportunities for early intervention if patients are categorized in a too low risk group.

The complexity of patients with AECOPD is also attributed to the fact that these patients often have other comorbidities, including a higher risk of cardiovascular disease, making them more susceptible to cardiovascular events with dyspnea symptoms, which are indistinguishable from symptoms of AECOPD.

Wireless monitoring systems on general wards

Remote monitoring systems utilize wireless non-invasive technology with wearable sensors that continuously track a patient´s physiological variables with the primary aim of detecting clinical deterioration earlier. Such systems are expected to play an important part in future hospital organizations to ensure patient safety [45, 46]. Other potential effects of automated wireless monitoring are reduced workload and improved patient comfort (e.g., due to less disturbance at night). Sensor data can be transferred to a central receiver and used for warning the clinical ward staff or intervention teams if vital signs deviate to allow for rapid response when needed. An important factor of continuous monitoring systems for ambulating general ward patients is that sensors should be unobtrusive and wearable so that patients do not feel physically restricted. HR and ECG monitoring can be obtained from various chest patches [45] and patch devices can also measure peripheral skin temperature or even estimate central body temperature from the axilla [47]. Some patch devices can also monitor RR through analysis of the r-r interval (ECG signal), which is the most common method of RR estimation in continuous monitoring systems [48]. The RR might also be derived from pulse oximeters [49] or sensors of chest movement, including patches containing an accelerometer, or a piezoelectric sensor [50]. Available wireless monitors also includes textile-based smart shirts or harnesses as well as sensors for placement under the mattress [48]. Pulse oximetry can provide the pulse rate as well as SpO_2 which is an estimation of arterial oxygen-hemoglobin saturation. Low SpO_2-levels (i.e., desaturation) is considered a marker of arterial hypoxemia. However, it requires an arterial blood gas analysis to obtain the precise level of oxygen saturation, and tissue oxygen delivery also depends on the hemoglobin

concentration and cardiac output. Further, pulse oximetry has several limitations and potential sources of error [51]. Automated high-frequency measurements of BP can be obtained from wireless devices using the standard brachial cuff-based oscillometric method, and the finger cuff pulse-decomposition method enables continuous monitoring of BP with wireless transfer of data [52].

Continuous physiological monitoring generates huge amounts of data and alarm systems based on simple vital sign thresholds for individual parameters may therefore generate an excessive number of false and irrelevant alarms. However, an inherent advantage of continuous monitoring is the insight into vital sign trends and patterns, which may be considerably more informative and predictive than deviating values from intermittent measurements [53, 54]. For example, an increasing HR and RR with decreasing SpO_2 and BP may suggest circulatory shock, perhaps even before any of the individual values exceed a simple alarm threshold. Therefore, real-time analysis of data derived from multiple monitors can be an essential part of remote monitoring systems.

Objectives

Before this PhD was initiated, the use of wireless monitoring for AECOPD patients was not evaluated specifically and the accuracy and precision of wireless monitoring systems were rarely investigated in clinical settings. Furthermore, the association between continuous measurements of physiological abnormalities and SAEs had not been assessed in AECOPD patients. Since 2016, the WARD (Wireless Assessment of Respiratory and circulatory Distress, https://ward247.org) research project has striven to combine medical knowledge of complications and recovery with innovative technology and machine-learning-based algorithms to develop a continuous and wireless monitoring system for high-risk patients, including patients admitted with AECOPD. WARD is a collaboration between the Technical University of Denmark, Rigshospitalet and Bispebjerg Hospital.
The WARD-COPD project started in 2017 with a pilot study investigating vital sign abnormalities in the AECOPD setting (Study 1), followed by a study investigating aspects of accuracy (Study 2) and a large clinical outcome study in patients with AECOPD (Study 3).

The aim of Study 1 was to assess the frequency and duration of abnormal physiological parameters as assessed by continuous monitoring and by standard monitoring. We hypothesized that continuous monitoring would detect abnormalities in vital signs more frequently than would standard EWS monitoring.
The aim of Study 2 was to evaluate the accuracy and precision of vital sign measurements derived from a wireless patient monitoring system when compared with standard wired monitoring. We hypothesized that agreement between wireless and standard device measurements would be within clinically acceptable limits.
The aim of Study 3 was to assess the association between frequency and duration of preceding vital sign abnormalities and SAEs. We hypothesized that the cumulative duration of abnormal vital signs would be longer in patients during the time before an SAE than in patients without an SAE.

General methodology

Setting

All studies were conducted at Bispebjerg Hospital, which is a 500-bed hospital with a catchment area of approximately 460,000 people in the center of Copenhagen. Patients are admitted to hospital wards either directly from the general practitioner or the emergency department or from outpatient clinics or other departments/hospitals. Bispebjerg Hospital was one of the first hospitals in Denmark to use an EWS system [55]. Patients were included in the medical acute care ward and the pulmonary ward at Bispebjerg Hospital. Additionally, a subset of patients in Study 3 was included at the pulmonary ward at Gentofte Hospital, a hospital in the suburbs of Copenhagen.

EWS with a protocol for escalation of care based on NEWS is used for standard ward monitoring in the Capital Region of Denmark [56]. The escalation protocol defines the clinical response and competency of the provider according to the aggregated EWS. A MET is available 24/7 with a specially trained intensive care nurse and an anesthesiologist from the ICU. MET can be activated if general ward staff are concerned, regardless of EWS or any existing limitations of treatment (e.g., "do not resuscitate"). Patients with EWS 7–8 should be considered for MET and patients with EWS ≥ 9 must be evaluated immediately by a senior doctor and the MET team. Most patients are monitored with intermittent recordings of vital signs according to the EWS algorithm only. However, some ward units also have dedicated beds for patients needing high-frequency ward staff evaluations.

Description of the wireless monitoring system

All three studies were conducted using the WARD project's body-sensor network, including Lifetouch patch (Isansys Lifecare, Oxfordshire, UK), Nonin WristOx$_2$ Model 3150 (Nonin Medical Inc., Minnesota, USA) and Meditech BlueBP-05 (Meditech Ltd., Budapest, Hungary), with data relayed and displayed via the Isansys Patient Gateway (Fig. 1). Isansys Lifetouch is a wireless patch for placement on the left side of the chest with two ECG electrodes. It continuously collects a single lead ECG with 1000 samples per second and derives HR data from R-peak intervals (heartbeats). The RR is derived from the ECG signal using calculations of changes in the QRS complex amplitude during the respiratory cycle due to changes in the

Fig. 1. Wireless monitoring setup in the WARD project with patch sensor on the chest (1: Lifetouch Patch), pulse oximeter with probe on the finger (2: Nonin WristOx$_2$), automated blood pressure device (3: Meditech BlueBP-05), and a bedside gateway (4: Isansys Patient Gateway). Photo obtained after consent from patient.

impedance of the thoracic cavity. The HR and RR were sampled at one per minute and automatically transmitted via Bluetooth to the bedside gateway and monitor (Isansys Patient Gateway). Nonin WristOx$_2$ 3150 is a wearable fingertip pulse oximeter with a wrist unit (worn like a wristwatch) connected to a soft finger sensor. It measures SpO_2 and PR sampled at 1 Hz and averaged at 4 beats and transmits data via Bluetooth to the gateway. The Meditech BlueBP-05 is a compact device with an upper arm cuff for intermittent non-invasive oscillometric BP measurements. It can be programed for automatic measurements with predefined intervals and it stores data for later wireless transfer to the gateway via Bluetooth and to the server through wi-fi. Data were sent in real-time from the bedside gateway via a secured hospital wi-fi connection to a hospital server. Investigators were able to track recordings; however, due to the observational design of the studies the clinical staff were blinded to vital sign data from the bedside monitor.

Table 1: Overview of the studies

	Study 1	Study 2	Study 3
Study type	Observational pilot study	Observational method-comparison study	Observational study
Sample size	n = 30	n = 20	n = 200
Inclusion criteria	Adults admitted with AECOPD as admission diagnosis		
Exclusion criteria	- Expected admittance < 24h - Inclusion not possible within 24h from admission - Inability to consent or not cooperative - Active therapy withheld - Allergies to plastic, plaster or silicone - ICD/Pacemaker	- Isolation bed requirement - Inability to consent or not cooperative - Active therapy withheld - Allergies to plastic, plaster or silicone - ICD/Pacemaker	- Expected admittance < 24h - Inclusion not possible within 24h from admission - Inability to consent or not cooperative - Active therapy withheld - Allergies to plastic, plaster or silicone - ICD/Pacemaker
Primary analysis	Frequency of patients with abnormal vital signs detected with EWS vs. continuous monitoring	Bias and 95% limits of agreement of measured vital signs	Cumulative duration of abnormal vital signs in patients with SAE during monitoring vs. patients without SAE

Data from Isansys Lifetouch and Meditech BlueBP-05 were automatically stored on the devices when a patient was out of Bluetooth range from the bedside Gateway, allowing the transfer of data when the Bluetooth-connection was later re-established. In contrast, data from the Nonin WristOx$_2$ 3150 was not stored when patients were outside Bluetooth range.

Statistical analysis

In Study 1, Fisher's exact test and Wilcoxon rank sum test were used to analyze associations between categorical and continuous data, respectively.

In Study 2, limits of agreement (LoA) were calculated summing the between subjects and within subjects variances to account for repeated measurements of the same subject as suggested by Bland and Altman [57] and confidence interval estimation for LoA was calculated with the method of variance estimates recovery [58].

In Study 3, descriptive statistics of vital sign abnormalities were presented for patients with and without SAEs. The cumulative duration of physiological abnormalities occurring during the 24 hours preceding the first SAE was analyzed. For patients with the first SAE occurring after the monitoring period had ended and for patients without SAEs, we analyzed the total monitoring period for vital sign abnormalities. Duration and frequency of vital sign abnormalities *per 24 hours* were calculated to adjust for different exposure times. Mean differences between vital sign abnormalities in patients with an SAE during monitoring and patients without SAEs were calculated and the Wilcoxon rank sum test was used to test for associations.
Bland-Altman plots in Study 2 were performed with statistical software R (v.3.6.2). All other analyses in Studies 1, 2 and 3 were completed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value below 0.05 was considered statistically significant.

Ethical considerations, approvals and registration of studies

Informed consent was obtained from patients in all three studies before inclusion. They were informed that participation was completely voluntary, and that consent could be withdrawn at any time. Approval was sought but waived by the regional ethics committee for Studies 1 and 2 since approval from the ethics committee is not required for observational studies and patients received treatments and diagnostics according to department standards (protocol number H-18010815 and H-19023948). Study 3 was approved by the regional ethics committee (protocol number H-18026653). Study 2 was approved by the hospital board of directors as a quality improvement study. The studies were collectively approved by the Danish Data Protection Agency (2012-58-0004). All three studies were registered at ClinicalTrials.gov (NCT03467815, NCT04248842 and NCT03660501).

Study 1

Physiological abnormalities in patients admitted with acute exacerbation of COPD: an observational study with continuous monitoring

Methods:

In this pilot study assessing the occurrence of physiological abnormalities detected either by the WARD-continuous monitoring or standard interval-based monitoring (EWS), the study period started after informed consent, and monitoring continued for 96 hours (if the patient was still hospitalized). Continuous monitoring was performed using the WARD project's sensor network providing high-frequency vital sign data (sampling frequency of one per minute for HR, RR and SpO_2). The BP device was programed at inclusion to start measurements every 15 minutes during daytime and every 30 minutes during the night. If patients expressed discomfort due to the BP measurements, settings were changed to measure every 30 minutes during daytime and every hour during the night. Clinical staff and patients were blinded to data from the wireless monitoring equipment. Investigators attended to patients daily to confirm data quality and change device batteries when required. EWS measurements were performed with routine equipment on the medical wards using standard intervals, i.e., 12 hours with an escalation of monitoring frequency to 6, 4 and 1 hour(s) for aggregated EWS of 2, 3 and 7, respectively, and to every 30 min for scores ≥ 9 [56]. EWS measurements performed during the study period were collected from the electronic patient record.

Included patients:

Patients were assessed for eligibility according to in- and exclusion criteria (Table 1). Thirty patients were enrolled between February and June 2018 in the emergency department and pulmonary ward at Bispebjerg Hospital, Copenhagen, Denmark. Seventeen participants were male, the median age was 74 years and median body mass index was 26 kg/m^2.

Outcomes:

The EWS- and continuous data were compared using thresholds for abnormalities in vital signs similar to those defined in the EWS (Table 2), and vital signs had to be outside the threshold for at least 60 seconds to be included in the analysis.

The frequency of vital sign abnormalities detected with EWS and continuous monitoring was compared. We also evaluated the duration of desaturation events detected by EWS, which were analyzed based on a time-weighted average. Events detected by EWS below the SpO_2 thresholds were assumed to start and end halfway between the time of the normal and abnormal value.

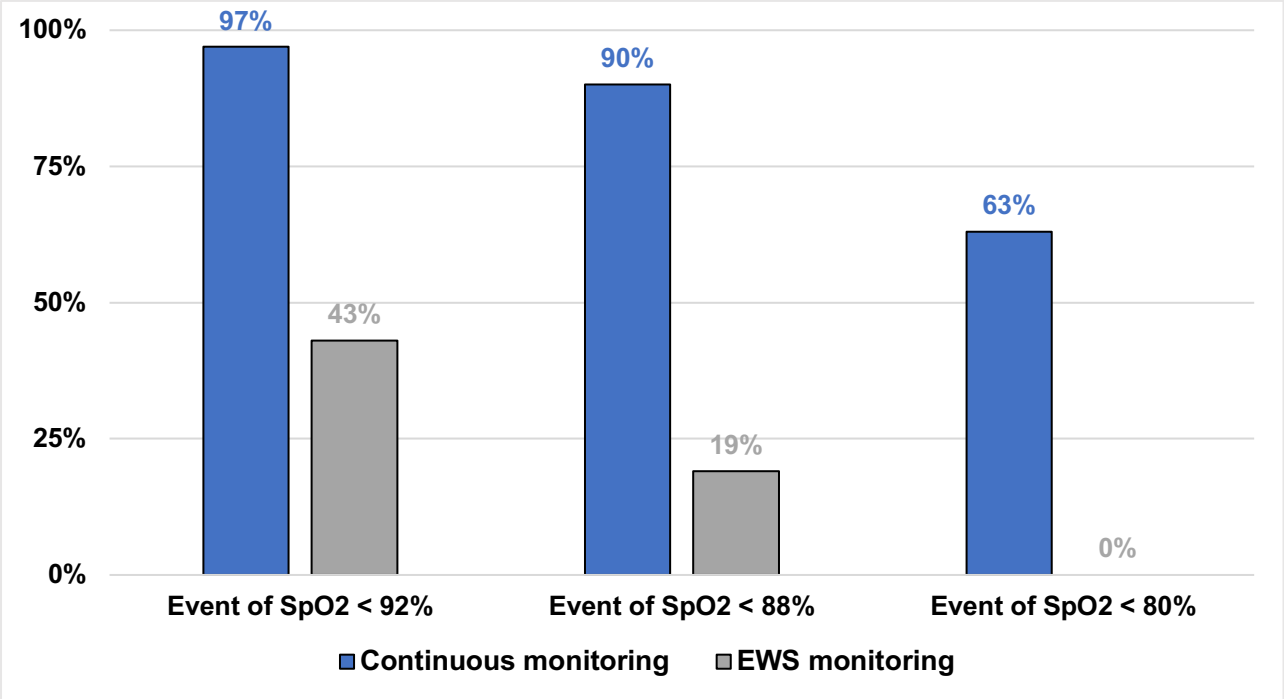

Fig. 2. Frequency of patients with desaturation micro events during admission for acute exacerbation of COPD detected with continuous monitoring (blue) and EWS monitoring (gray), p<0.0001 for all

Results:

A total of 2058 hours of patient monitoring (median of 71 hours) with at least one modality available was completed in 30 patients with the wireless monitoring equipment. After artifact removal, SpO_2 data were available for 55% of the time, whereas HR and RR were available during 71% of the time. BP data derived from wireless automatic monitoring with at least one measurement per hour were available for 49% of the total monitoring time. A total of 328 complete EWS recordings were collected from the electronic patient record resulting in an average EWS-measurement interval of 6 hours and 16 minutes.

Continuous monitoring detected events of $SpO_2 < 92\%$ in 29 of 30 patients (97%) compared with 13 of 30 patients (43%) detected by conventional EWS ($p < 0.0001$, Fig. 2). Events of moderate desaturation ($SpO_2 < 88\%$) were detected in 90% of patients with continuous monitoring compared with 13% recorded with EWS ($p < 0.0001$). Sixty-three percent of patients had severe hypoxemic events ($SpO_2 < 80\%$) detected with continuous monitoring and in 17%, the events

lasted longer than 10 minutes. No severe hypoxemic events of $SpO_2 < 80\%$ were recorded with EWS. Tachycardia, tachypnoea, and bradypnea were also more frequently detected with continuous monitoring ($p < 0.02$ for all, Table 2). There were no statistical differences in hypo- and hypertension events detected with wireless and automatic BP monitoring vs EWS ($p = 0.15$ and 0.49, respectively). No events of bradycardia were detected.

Table 2. Cardiopulmonary micro events during admission for acute exacerbation of COPD

	Continuous monitoring, n=30	EWS monitoring, n=30	p-value	Mean diff. (95% CI)
Desaturation micro events				
SpO_2 <92%				
Number of patients	29 (97%)	13 (43%)	<0.0001	
Duration, minutes	996 [101-3123]	0 [0-2066]	<0.0001	950 (475-1425)
Number of patients with at least one event lasting more than 60 minutes	24 (80%)	13 (43%)	0.01	
SpO_2 <88%				
Number of patients	27 (90%)	4 (13%)	<0.0001	
Duration, minutes	156 [0-1237]	0 [0-165]	<0.0001	359 (199-519)
Number of patients with at least one event lasting more than 60 minutes	11 (37%)	2 (7%)	0.01	
SpO_2 <80%				
Number of patients	19 (63%)	0	<0.0001	
Duration, minutes	3 [0-79]	0	<0.0001	13 (4-22)
Number of patients with at least one event lasting more than 10 minutes	5 (17%)	0	0.05	
Other cardiopulmonary micro events				
Heart rate >130/min	15 (50%)	4 (13%)	0.005	
Heart rate <41/min	0	0		
Respiratory rate >24/min	17 (57%)	7 (23%)	0.02	
Respiratory rate <9/min	16 (53%)	0	<0.0001	
Systolic Blood Pressure < 90 mmHg	7 (23%)	2 (7%)	0.15	
Systolic Blood Pressure > 219 mmHg	2 (7%)	0	0.49	

Values are number (percentage), median [5%-95% range] or mean difference (95% CI). Duration of desaturation is calculated as the median of the cumulative duration among all included patients.

Conclusions:

Moderate and severe events of desaturation and other cardiopulmonary abnormalities are common during hospitalization for AECOPD and most often these events are not detected with the usual standard of care (EWS monitoring).

Study 2

Agreement between wireless and standard measurements of vital signs in acute exacerbation of chronic obstructive pulmonary disease: a clinical validation study

Methods:

Paired measurements of vital signs (SpO_2, HR, PR, RR and BP) were recorded using both wireless and standard (wired) monitors with 15-minute intervals for two hours.

Wireless monitoring was performed using the WARD project's sensor network, whereas the system for comparison was a wired monitor (IntelliVue X2 connected to MP30 as host monitor, Philips, Amsterdam, The Netherlands) currently in use as clinical standard at Bispebjerg Hospital. The system uses ECG leads to measure HR and RR and a standard oscillometric device with cuff to measure BP; further, a fingertip pulse oximetry sensor was connected for measuring SpO_2 and PR. Measurements were performed with a study investigator at the bedside inspecting the signal quality from recordings throughout the monitoring period. For RR measurements, values from the wireless and standard devices were also compared with manual count by direct observation (DO) with respirations counted by investigators for one minute.

Patients with a confirmed admission diagnosis of AECOPD were assessed for eligibility according to in- and exclusion criteria (Table 1) and 20 patients were enrolled with 10 included in the emergency department and 10 in the pulmonary ward. The sample size was 20 patients by convenience each with nine measurements per modality corresponding to two monitoring-hours with recordings every 15 minutes, for a total of 180 sample-pairs for each parameter.

The primary analysis was bias and 95% LoA between wireless and standard devices. We also calculated root mean square deviation and percentage error.

We considered HR and PR to be clinically acceptable if measurements were within ±5 beats per minute (bpm), whereas recordings of SpO_2, RR and systolic/diastolic BP were acceptable if within ±3%-points, ±3 breaths per minute (brpm) and ±10 mmHg, respectively.

Results:

The principal findings of agreement between standard and wireless devices in 20 patients with AECOPD are presented in Table 3. Overall, 98% of HR measurements and 99% of PR measurements were within ±5 bpm (acceptable limit) when comparing values from the two devices. The bias of HR measurements was 0.03 bpm with LoA of -3.2 to 3.3 bpm (Fig. 3a) and

the bias of PR measurements was -0.1 bpm with LoA of -3.1 to 3.0 (Fig. 3b). For SpO_2 measurements, 98% of recordings were within the 3%-point acceptable limit when comparing values from the two devices. The bias of SpO_2 measurements was 1.4% with LoA of -0.7 to 3.6% (Fig. 3c). When comparing RR values from wireless and standard devices, 77% of measurements were within the acceptable limit of ±3 brpm. The bias between standard and wireless RR measurements was 0.75 brpm (LoA -6.1 to 7.5, Fig. 3d), whereas the bias between DO and wireless RR measurements was 1.02 brpm (LoA -5.0 to 7.0, Fig. 3e). The bias between standard and wireless measurements of systolic BP was -7.8 mmHg (LoA -22.3 to 6.8 mmHg, Fig. 3g), whereas the bias of diastolic BP measurements was -6.2 mmHg (LoA -16.8 to 4.5 mmHg, Fig. 3h).

Table 3. Summary of agreement between standard and wireless devices

	Heart rate (bpm)	Pulse rate (bpm)	Respiratory rate (breaths per min)			SpO_2 (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
	Standard vs Wireless	Standard vs Wireless	Standard vs Wireless	DO vs Standard	DO vs Wireless	Standard vs Wireless	Standard vs Wireless	Standard vs Wireless
Range of recordings	62 - 145	41 - 132	12 - 33	12 - 33	12 - 31	82 - 98	97 - 207	47 - 111
Bias (standard deviation)	0.03 (0.4)	-0.1 (0.5)	0.75 (2.7)	0.28 (1.2)	1.02 (2.6)	1.4 (0.6)	-7.8 (3.7)	-6.2 (2.9)
Lower LoA (95% CI)	-3.2 (-3.7 to -2.9)	-3.1 (-2.7 to -3.5)	-6.1 (-7.9 to -4.2)	-4.0 (-4.7 to -3.3)	-5.0 (-6.8 to -3.1)	-0.7 (-1.2 to -0.4)	-22.3 (-25.1 to -20.2)	-16.8 (-18.6 to -15.0)
Upper LoA (95% CI)	3.3 (2.9 to 3.7)	3.0 (2.6 to 3.4)	7.5 (6.0 to 9.9)	4.5 (3.8 to 5.3)	7.0 (5.4 to 9.4)	3.6 (3.2 to 4.1)	6.8 (4.7 to 9.6)	4.5 (2.7 to 6.3)
Percentage error	1%	1%	24%	11%	23%	1%	5%	8%
Root mean square deviation	1.7	1.6	3.5	2.2	3.2	1.8	10.7	8.2

Negative numbers indicate that the wireless monitor overestimates measurement values when compared with the standard monitor.

Bpm, beats per minute; DO, direct observation; LoA, limits of agreement; SpO_2, peripheral oxygen saturation.

Conclusions:

Measurements of HR was accurate and precise in patients with AECOPD when comparing wireless with wired standard devices. Agreement between recordings of SpO_2 was borderline acceptable, and measurements of RR and BP should be interpreted with caution in this clinical setting.

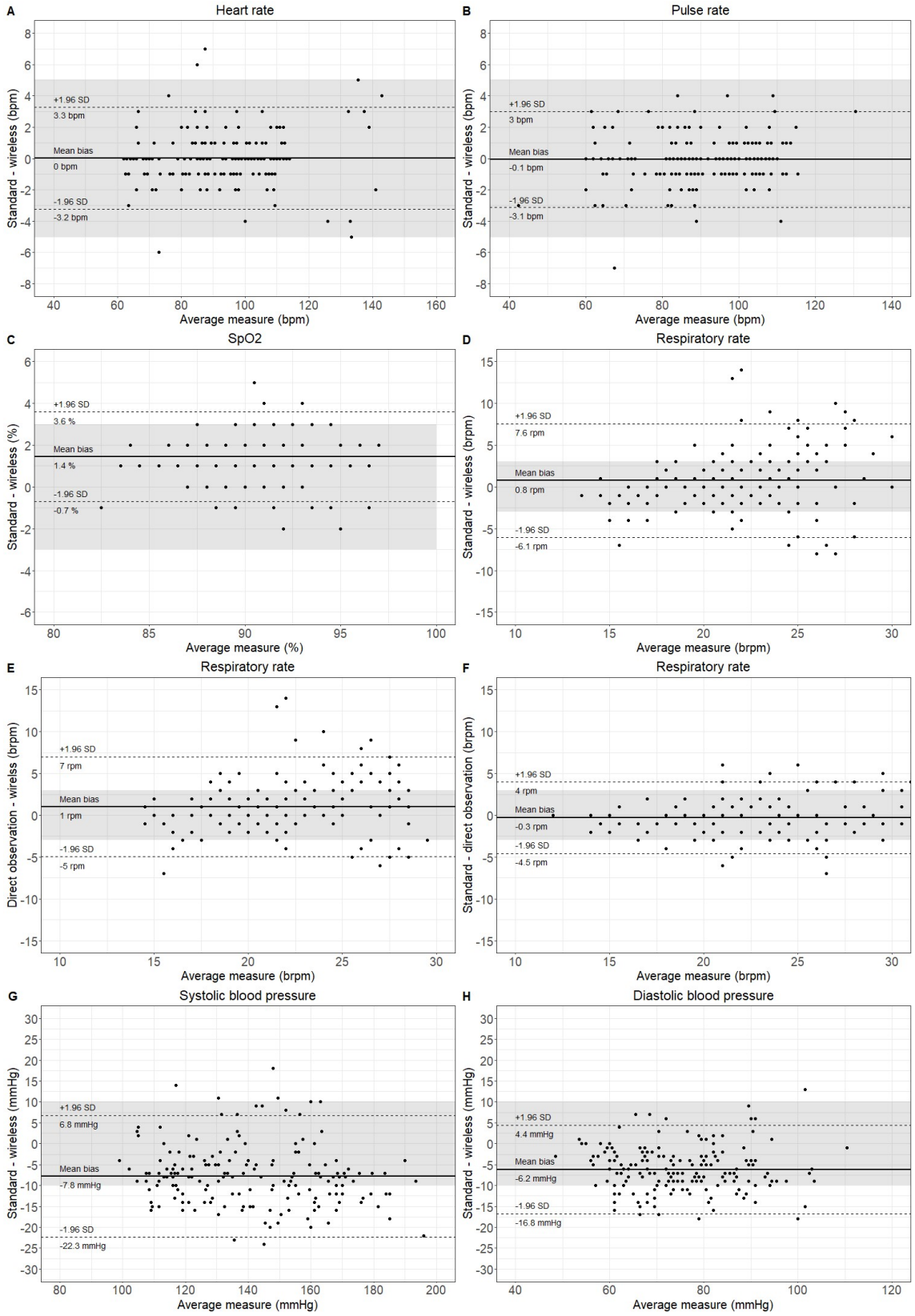

Fig. 3. Bland-Altman plots of agreement between measurements of heart rate (Fig. 3a), pulse rate (Fig. 3b), peripheral oxygen saturation (Fig. 3c), respiratory rate (Fig. 3d-f), systolic blood pressure (Fig. 3g) and diastolic blood pressure (Fig. 3h). Solid line = bias; dotted lines = upper and lower 95% limits of agreement (LoA). The shaded area shows the predefined clinically acceptable LoA. Wireless measurements were performed with Isansys Lifetouch (heart rate, respiratory rate), Nonin WristOx$_2$ 3150 (pulse rate, SpO_2) and Meditech BlueBP-05 (blood pressure). Standard (wired) measurements were performed with the Phillips IntelliVue X2 system. bpm, beats per minute; brpm, breaths per minute; SpO_2, peripheral oxygen saturation.

Study 3

Methods:

In this observational study, vital signs (SpO_2, HR, RR) were wirelessly and continuously monitored in AECOPD patients using the WARD project's sensor network during the first 4 days after admission. Non-invasive BP was automatically measured with the wireless device every 30 minutes during daytime and every hour during night-time. The clinical staff, as well as patients, were blinded to data from the wireless monitoring devices; therefore, standard observation was completed with vital sign recordings according to the usual standard of care (i.e., EWS [56]). Patients were attended daily by study investigators to check data quality and change device batteries if required.

Patients admitted to the medical acute care ward or pulmonary wards (Bispebjerg Hospital and Gentofte Hospital in Copenhagen, Denmark) with AECOPD as admission diagnosis were assessed for eligibility according to the in- and exclusion criteria (Table 1).

Outcomes and data analysis:

The primary outcome was SAEs at 30 days after inclusion. Exploratory outcomes included predefined SAE categories (neurological, respiratory, cardiovascular, infectious, and other SAEs). Vital sign data were analyzed for abnormalities of respiratory and circulatory vital signs occurring in patients with and without SAEs. Data for patients with an SAE occurring during ongoing monitoring were analyzed in the 24h period preceding the SAE. Data for patients with an SAE occurring after monitoring and patients without SAE were analyzed for abnormalities in the complete monitoring period (up to 4 in-hospital days). To adjust for different exposure times, results are presented as descriptive statistics of frequency and duration of vital sign abnormalities per 24 hours. Mean differences between vital sign abnormalities in patients with SAEs during monitoring and patients without SAEs are presented and the Wilcoxon rank sum test was used to test for associations.

Results:

Two hundred patients were included, resulting in 13,263 patient monitoring hours with at least one sensor modality providing data (median of 72 hours per patient). After artifact removal, SpO_2 data were available for 57% of the time, while HR and RR were available during 83% of the total time.

The 30-day follow-up outcome assessment identified 81 (41%) patients with at least one SAE, including 7 patients (4%) who were admitted to the ICU; 14 patients (7%) died and 47 (24%) were readmitted after initially being discharged within 30 days of inclusion.

The mean cumulative duration of any vital sign abnormality was 455 minutes (standard deviation (SD) 413) per 24 hours for patients with SAEs during the continuous monitoring period compared with 292 minutes (SD 246) for patients without SAEs, p = 0.08, mean difference of 163 minutes [95% CI 61 – 265] (Table 4). The mean cumulative duration of bradypnea (RR < 11) was 48 minutes (SD 173) per 24 hours for patients with SAEs occurring during continuous monitoring compared with 30 minutes (SD 84) for patients without SAEs, p = 0.01. The number of severe hypoxemic events (SpO_2 < 80% for at least one minute) per 24 hours was 7 (SD 12) for patients with SAEs during monitoring compared with 5 (SD 5) for patients without SAEs, p = 0.07. The duration and frequency of other vital sign abnormalities were not significantly different in patients with and without SAEs (Table 5).

Table 4. Summary of the association between preceding cardiopulmonary abnormalities duration and serious adverse events within 30 days in 200 patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	Patients with SAE		Patients without SAE	Mean difference*	P-value*
	SAE during monitoring (n=50)	SAE after monitoring (n=31)	(n=119)	[95% CI]	
Any vital sign abnormality					
Mean cumulative duration per 24 h	455 (413)	289 (264)	292 (246)	163 [61 to 265]	0.08
Median cumulative duration per 24 h	318 [12 – 710]	235 [54 – 451]	191 [110 – 425]		
Any respiratory abnormality					
Mean cumulative duration per 24 h of respiratory abnormalities	333 (367)	199 (226)	214 (186)	118 [34 to 203]	0.42
Median cumulative duration per 24 h of respiratory abnormalities	148 [0 – 535]	116 [35 – 298]	155 [77 – 324]		
Any circulatory abnormality					
Mean cumulative duration per 24 h of circulatory abnormalities	194 (326)	135 (212)	119 (216)	75 [-9 to 160]	0.69
Median cumulative duration per 24 h of circulatory abnormalities	35 [0 – 240]	60 [7 – 121]	29 [6 – 115]		

Values are mean (standard deviation) or median [interquartile range] cumulative duration in minutes. Data for patients with an SAE occurring during monitoring were analyzed for vital sign abnormalities in the 24h period preceding the SAE. Data for patients with an SAE occurring after monitoring and patients without SAE were analyzed for vital sign abnormalities in the complete monitoring period (up to 4 days). All values are presented as frequency and duration of vital sign abnormalities *per 24 hours* to adjust for different exposure times. *Mean differences and p-values are calculated for patients with an SAE during monitoring vs. patients without SAE.

Conclusion:

Continuous and wireless vital sign monitoring detected frequent physiological abnormalities of long cumulative duration in AECOPD patients, in particular preceding SAEs. However, the frequency and duration of physiological abnormalities were significantly different only for episodes of bradypnea.

Table 5. Association of preceding cardiopulmonary abnormality duration and frequency and serious adverse events within 30 days in 200 patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	Patients with SAE/death		Patients without SAE	Mean difference*	P-value*
	SAE during monitoring (n=50)	SAE after monitoring (n=31)	(n=119)	[95% CI]	
Respiratory abnormalities					
SpO_2 <88%					
Mean (SD) cumulative duration per 24 h	194 (282)	127 (132)	115 (150)	78 [11 to 146]	0.28
Median [IQR] cumulative duration per 24 h	79 [0 – 535]	60 [21 – 209]	71 [21 – 141]		
Mean (SD) number of events per 24 h (> 10 min)	6 (10)	4 (5)	4 (4)	2 [0 to 4]	0.50
SpO_2 <85%					
Mean (SD) cumulative duration per 24 h	78 (135)	61 (73)	41 (84)	37 [3 to 72]	0.97
Median [IQR] cumulative duration per 24 h	14 [0 – 71]	19 [5 – 100]	17 [4 – 43]		
Mean (SD) number of events per 24 h (> 5 min)	4 (9)	4 (4)	3 (3)	1 [-0.3 to 4]	0.17
SpO_2 <80%					
Mean (SD) cumulative duration per 24 h	17 (38)	14 (26)	9 (22)	8 [-1 to 18]	0.07
Median [IQR] cumulative duration per 24 h	0 [0 – 11]	3 [0.3 – 10]	2 [0.5 – 7]		
Mean (SD) number of events per 24 h (> 1 min)	7 (12)	7 (7)	5 (5)	2 [-0.9 to 4]	0.07
Tachypnea RR > 24					
Mean (SD) cumulative duration per 24 h	135 (275)	80 (172)	79 (124)	56 [-5 to 117]	0.46
Median [IQR] cumulative duration per 24 h	18 [0 – 87]	2 [0.1 – 22]	11 [0.9 – 99]		
Mean (SD) number of events per 24 h (> 5 min)	7 (15)	4 (8)	4 (7)	3 [-0.7 to 6]	0.64
Tachypnea RR > 30					
Mean (SD) cumulative duration per 24 h	9 (40)	15 (47)	4 (11)	5 [-3 to 13]	0.39
Median [IQR] cumulative duration per 24 h	0 [0 – 1]	0 [0 – 0.5]	0 [0 – 1]		
Mean (SD) number of events per 24 h (> 1 min)	8 (39)	7 (19)	3 (7)	5 [-2 to 12]	0.51
Bradypnea RR < 11					
Mean (SD) cumulative duration per 24 h	48 (173)	15 (39)	30 (84)	18 [-21 to 57]	0.01
Median [IQR] cumulative duration per 24 h	0 [0 – 7]	0.8 [0 – 4]	3 [0 – 11]		
Mean (SD) number of events per 24 h (> 5 min)	2 (8)	0.6 (2)	1 (4)	0.8 [-1 to 3]	0.01
Circulatory abnormalities					
Heart rate > 110/min					
Mean (SD) cumulative duration per 24 h	188 (328)	133 (213)	116 (217)	72 [-13 to 157]	0.55
Median [IQR] cumulative duration per 24 h	24 [0 – 219]	54 [5 – 120]	24 [4 – 109]		
Mean (SD) number of events per 24 h (> 60 min)	0.8 (2)	0.8 (2)	0.6 (1)	0.2 [-0.3 to 0.7]	0.34
Heart rate > 130/min					
Mean (SD) cumulative duration per 24 h	18 (48)	19 (76)	16 (56)	2 [-16 to 20]	0.27
Median [IQR] cumulative duration per 24 h	0 [0 – 7]	0.3 [0 – 7]	0.3 [0 – 4]		
Mean (SD) number of events per 24 h (> 30 min)	0.4 (2)	0.2 (0.5)	0.2 (0.5)	0.2 [-0.1 to 0.7]	0.53
Heart rate < 40/min					
Mean (SD) cumulative duration per 24 h	0.3 (1)	1 (4)	2 (11)	-1 [-5 to 2]	0.02
Median [IQR] cumulative duration per 24 h	0 [0 – 0]	0 [0 – 0.6]	0 [0 – 0.3]		
Mean (SD) number of events per 24 h (> 5 min)	0	0	0.1 (0.6)	0.1 [-0.2 to 0.1]	0.09
Systolic Blood Pressure < 90 mmHg					
Mean (SD) number of events per 24 h	4 (14)	0.3 (0.8)	0.3 (1)	4 [1 to 7]	0.22
Systolic Blood Pressure > 180 mmHg					
Mean (SD) number of events per 24 h	3 (9)	0.6 (1)	0.8 (3)	2 [-0.1 to 4]	0.06

Values are mean (standard deviation) or median [interquartile range] cumulative duration per 24 hours in minutes and mean (SD) number of events. Data for patients with an SAE occurring during monitoring were analyzed for vital sign abnormalities in the 24h period preceding the SAE. Data for patients with an SAE occurring after monitoring and patients without SAE were analyzed for vital sign abnormalities in the complete monitoring period (up to 4 days). All values are presented as frequency and duration of vital sign abnormalities per 24 hours to adjust for different exposure times. *Mean differences are calculated for patients with an SAE during monitoring vs patients without SAE.

Discussion

Main findings

The principal finding of Study 1 was that continuous vital sign monitoring detected physiological abnormalities (desaturation, tachycardia, tachypnea and bradypnea) in more patients than did standard intermittent EWS monitoring. Desaturation events of long duration occurred frequently, and these episodes were rarely reported with EWS.

In Study 2, the agreement between measurements using a wireless sensor system and a standard monitoring system was within predefined acceptable limits for HR and PR. The accuracy of wireless measurements of SpO_2 was acceptable, whereas the precision was borderline acceptable. Wireless measurements of RR and BP should be interpreted with caution.

In Study 3, one-quarter of patients with AECOPD had SAEs during ongoing continuous monitoring. The cumulated duration of abnormal vital sign episodes was long and there was a substantial mean difference between the duration of any vital sign abnormality occurring before SAEs as compared with patients without SAEs. The cumulative duration of bradypnea events was significantly longer in patients with an SAE during monitoring than in patients without SAEs, with a mean difference of 18 minutes.

Recent findings involving general ward monitoring

Clinical deterioration is frequently missed with routine intermittent vital sign monitoring. On this background, a consensus conference held in 2008 with international experts in safety, risk prediction, RRS, healthcare technology and education recommended (if practical and affordable) that all patients should be monitored continuously [59]. However, intermittent monitoring has continued to be the standard of care. Although it may be reasonable to anticipate that continuous monitoring methods can improve patient safety in general wards, the evidence to support this is currently sparse [45, 60]. Taenzer et al. continuously monitored HR and SpO_2 in postsurgical patients in orthopedic wards over 10 months [61]. They reported fewer rescue events and ICU transfers than in the period before the intervention. A recent study of 4.402 patients (total of control and intervention group) admitted at two general medical wards reported a decrease in cardiac arrest and hospital mortality rates after the implementation of a continuous monitoring system with pagers to alert nurses to patient deterioration [62]. Continuous monitoring of vital signs has also been recognized as a form of medical overuse in certain settings. A multicenter

cross-sectional study to evaluate the practice of continuous SpO_2 monitoring for children hospitalized with bronchiolitis reported frequent use of the monitoring in children not receiving supplemental oxygen [63]. The authors concluded that continuous monitoring in this population occurred despite the absence of an evidence-based indication and could contribute to prolonged length of stay, increased costs and potential for iatrogenic harm as well as alarm fatigue among nurses.

In the aforementioned studies, the monitoring devices were wired, thus limiting patient mobility. In contrast, wireless monitors may allow patients to move within their rooms and within the hospital while being monitored. Leenen et al. recently reviewed the literature on continuous vital sign monitoring with wearable wireless devices [64]. They included 27 studies evaluating 13 different devices and concluded that no high-quality studies are currently available that show a significant clinical impact or cost-effectiveness of wireless monitoring. Weenk et al. investigated barriers to and facilitators of wearable monitoring devices in a randomized control trial of 90 patients admitted to medical and surgical wards [65]. They randomly assigned patients to continuous monitoring with one of two monitoring devices (ViSi Mobile (Sotera Wireless, San Diego, CA, USA) and Healthpatch (VitalConnect, San Jose, CA, USA)) or a control group and interviewed both patients and clinicians to evaluate their experiences and expectations. Both monitoring systems were generally well received by patients and health care staff alike, and most favored the idea of continuous monitoring on general wards. Another interview study concluded that patients can see the benefit of continuous monitoring, particularly during the night [66]. However, the authors also reported that patients appreciate the face-to-face contact associated with manual vital sign measurements as it permits social interaction, reassurance and gives them an opportunity to ask questions.

Discussion of findings

Hospitalized patients may deteriorate with acute cardiorespiratory instability not being noticed, leading to SAEs that could potentially have been prevented with timely action. Markers of impending deterioration can be subtle vital sign changes, but several studies have reported that these physiological signs are often missed or misinterpreted with current intermittent recordings [25, 67]. Our findings in Study 1 confirm the results from other studies. In the postsurgical setting, our research group found similar results with a large proportion of patients having physiological abnormalities [68]. Severe desaturation events ($SpO_2 < 80\%$ for at least one minute) occurred in 56% of patients after major abdominal cancer surgery, and other cardiopulmonary abnormalities

were also frequent. Similarly, another study involving patients recovering from abdominal surgery reported frequent events of hypotension with 18% of patients having events of mean arterial pressure lower than 65 mmHg [69]. However, the clinical impact of such physiological abnormalities is not firmly established. A large Danish study from 1993 evaluated the effect of pulse oximetry in the perioperative setting on postoperative complications [7]. The study included 20,802 patients randomly assigned to monitoring with pulse oximetry or to the control group (without SpO_2-monitoring) in the operating room and PACU. Myocardial ischemia in the operating room was diagnosed in 12 patients in the pulse oximetry group vs. 26 patients in the control group ($p < 0.03$). The study also documented that pulse oximetry can improve the ability to detect hypoxemic events and it is now considered standard monitoring practice in the perioperative setting. Bowton et al. reported already in 1994 that hospitalized medical patients with desaturation events ($SpO_2 < 90\%$ for at least 5 minutes) during the first day after admission have reduced survival compared with patients without such events [70]. In a large database study using vital signs from 27,722 patients, an in-hospital mortality of 24% was reported for patients with three critical abnormal vital sign recordings, whereas patients with only one critical abnormal vital sign observation had a mortality of only 0.9% [71]. Similarly, an Australian study from 2004 reported that several signs of physiological deterioration in hospitalized patients (tachypnea, bradypnea, desaturation and hypotension as well as an affected level of consciousness) were independently associated with mortality [72]. However, such associations may be a result of the underlying condition, and thus with the degree of physiological deviation being a marker of disease severity.

In Study 3 we assessed vital sign abnormalities carefully with analyses accounting for variable exposure time. It was contrary to our hypothesis that most categories of vital sign abnormalities were not significantly associated with subsequent SAEs. Although we found longer point estimates of vital sign abnormalities in patients with SAE when compared with patients without SAEs, this was not statistically significant in this sample. Conversely, Breteler et al continuously measured vital signs (HR, RR and SpO_2) with wireless sensors in 31 high-risk surgical patients recovering at a step-down unit or traumatology/surgical ward and reported abnormalities in vital sign trends preceding adverse events [73]. Physiological abnormalities with episodes of tachycardia and tachypnea also occurred in patients without adverse events; however, these episodes were less frequent and often shorter. Interestingly, none of the patients without adverse events had concurrent abnormalities of HR, RR and SpO_2, apart from during periods with mobilization. Despite a small sample size (the study was designed for validation of wireless sensors), these findings give weight

to the fact that alarms should not be based on single parameter thresholds, but rather that vital sign data should be analyzed together to find patterns of abnormalities.

In Study 2 we found an acceptable accuracy with a relatively low bias for all parameters. However, the precision was challenged reflected in wide LoAs for measurements of RR and BP. Similar results have been reported in other studies. In particular, several studies investigating wireless sensors have reported difficulty in recording precise measurements of RR [74–78]. However, when evaluating the performance of wireless sensors, we also need to consider the current standard of care, which is usually manual recordings. Hence, numerous studies have shown poor quality of vital sign recordings from manual observations, including significant interobserver variability of up to 6 brpm for RR measurements [79–83]. The quality of manual vital sign data may also be limited by non-adherence to the monitoring protocol: a study from our institution evaluated the performance of EWS by review of all SAEs during a 6-month period [84]. The minimally required time interval between vital sign recordings was in only 19% of the cases performed according to the EWS protocol. And patients with higher aggregated EWS were less likely to be observed adequately. Another study from Copenhagen found that 10% of vital sign records had one or more missing value [85]. Digit preferences were also reported for numbers divisible by 4 and 10 (e.g. RR being 10, 12 or 16 bprm). HR values were also biased to values under 91 bpm, a value that generates less workload for health care staff according to the escalation protocol. Taenzer et al. compared intermittent manual SpO_2 data with automated continuous pulse oximetry monitoring and reported that manually documented SpO_2 measurements were 6.5% higher on average [86].

Notably, most of the RR data points in Study 2 that were outside confidence limits in the Bland-Altman plot (Fig. 3d-e) were in the upper range of mean RR. Such inconsistent variability in the data suggest a proportional bias, with the wireless RR measurements being less precise during tachypnea, which is commonly associated with AECOPD. Accordingly, absolute RR values from wireless monitoring should be interpreted with caution in this setting. However, a wireless warning system may alert clinicians in any situation with a high or increasing RR, and the absolute value may thus be of less value.

Strengths and limitations

The primary overall strength of Studies 1 and 3 is that we were able to monitor vital signs continuously for several days in high-risk patients in an acute care setting. We obtained prospective high-quality data (blinded to clinical staff) derived from wireless sensors with

artifacts removed, and the vital sign abnormalities observed should therefore be clinically representative. In Study 3, we were also able to evaluate the association between vital sign abnormalities and clinical outcomes. These outcome data were obtained through comprehensive review by physicians of the electronic medical record of all included patients. A primary strength of Study 2 is that measurements were conducted in a real clinical setting because studies with healthy volunteers may introduce a falsely high accuracy and precision. Moreover, the data collection was completed by investigators who inspected the signal quality from measurements.
The studies also have several important limitations that should be mentioned. Due to the observational design, we are not able to confirm or reject causality and when performing multiple testing in exploratory studies there is an increased risk of significant results occurring by chance. Thus, our findings must be considered hypothesis-generating. Several factors may limit the generalizability of the studies. Patients were mainly included from one study site and a large proportion of eligible patients were excluded or declined participation. Reasons for exclusion were primarily an inability to consent and uncooperative patients; these patients were typically severely distressed with acute symptoms including dyspnea and hypercapnia. Therefore, excluded patients may have had even more vital sign abnormalities than we reported, further supporting the potential to detect physiological deviations with continuous monitoring.
Data incompleteness was a challenge in Studies 1 and 3, and it is a common problem in studies with continuous vital sign monitoring in general wards. We achieved valid SpO_2 data for 55% and 57% of the time in Studies 1 and 3, respectively. Therefore, it is likely that desaturation (and other physiological abnormalities) had occurred during periods with missing data. Comparable challenges with missing or non-valid data have been reported in other studies with continuous vital sign monitoring [68, 87–89], whereas others have reported significantly less data loss [74]. Technical issues were the main challenges resulting in missing data. However, data incompleteness also occurred as a result of patients and clinical staff removing devices due to discomfort or physical examinations. In Study 3, we accounted for missing data by calculating the frequency and duration per 24 hours. However, different exposure times should be mentioned as a limitation as the average monitoring time with at least one modality providing data for patients with SAE was 77 hours compared with 59 hours for patients without SAE. The challenge of data incompleteness underlines the importance of future monitoring systems with integrated failure recognition and real-time alerts to staff in the case of missing data.
In Studies 1 and 3 we chose to focus on vital sign abnormalities in the first four days after admission with AECOPD for several reasons. First, the Lifetouch patch sensor battery life is

between 4 and 6 days. Second, the mean length of hospital stay in patients admitted with AECOPD was 3 days in a large cohort of 811 patients from our institution [90]. Third, the clinical staff are usually aware of the degree of clinical instability during the first phase/day of an acute admission. Therefore, the problem of "failure to rescue" may be more pronounced in patients who initially respond to treatment but then suffers subsequent deterioration; accordingly, we wanted to address this situation. Clinical complications occurring in the interval from admission to inclusion were adjudicated as present at baseline. Similarly, any SAE occurring as a result of initial diagnostic imaging (performed within 24 hours of admission) was not included in the outcome analysis.

In Study 2 we compared wireless and wired (standard) measurements of vital signs; however, the reference methods cannot be regarded as gold standard, and this should be considered in the interpretation of our findings. The most widely accepted method for evaluating the accuracy of pulse oximeter devices is by comparison of SpO_2 with arterial oxygen saturation, which was not performed in the study. Pulse oximetry has several limitations and devices are subject to both biological and sensor variability [91]; nevertheless, the devices compared in this study are both medically approved. The optimal reference method for the validation of RR measurements has not been defined [64]. Although capnography is often considered the gold standard, it has several disadvantages (for non-intubated patients in particular) and it is infrequently used for continuous monitoring in the general ward setting. Instead, the reference method was a standard impedance technique device with manual count of respirations as a second reference. For the validation of BP devices, a mercury sphygmomanometer or an invasive (intra-arterial) method is usually recommended as the reference [92]. However, this was not feasible because measurements were conducted in an acute-care setting. Although a strength of the study was that patients were monitored at rest during supervised (optimal) conditions, this may also be seen as a limitation, as we can make no conclusions on the performance of devices during motion, which is especially relevant when devices are used for ambulating patients on general wards, such as in our setup.

The wireless monitoring devices used for all three studies were chosen based on a medicotechnical evaluation of currently available systems for wireless patient monitoring. Our results might have been different if other devices had been used, in particular in the method-comparison (study 2). However, large discrepancies of reported physiological abnormalities are unlikely, since many similarities exist regarding the technical aspects of currently available monitors [48].

Considerations regarding monitoring of patients hospitalized with AECOPD

Physiological instability in patients hospitalized with AECOPD should trigger a more comprehensive clinical evaluation (including arterial blood gas analyses) to assess the situation and possible requirement for urgent intervention. The optimal RRS for patients with chronic respiratory disease has been debated due to lack of specificity of traditional systems in the COPD population, resulting in many false alerts [40]. Therefore, modified scoring systems have been developed, including the chronic respiratory EWS (CREWS) [41] and Salford-NEWS [42]. These systems may decrease the high number of alerts in COPD patients; however, this, in turn, may decrease the sensitivity, causing an increased risk of overlooking impending deterioration [93]. Concern has also been raised, that excessive oxygen administration is associated with poor outcome in AECOPD [35, 44, 94], but this risk has not been addressed in traditional EWS systems, which could encourage use of too high SpO_2 target levels to reach a lower EWS score. The recently updated NEWS2 includes different SpO_2 targets in patients with hypercapnic respiratory failure encouraging the delivery of oxygen to target SpO_2 of 88–92%, but the utility of this new score in clinical practice is subject of debate [95–97]. Some argue that it would be better to change the escalation-of-care protocol rather than modify the weighting system as proposed with NEWS2 [96, 98]. The evidence to support current recommendations of SpO_2 target levels in COPD patients is limited due to a lack of controlled studies investigating different oxygenation levels in this population. However, in the prehospital setting, an SpO_2 target of 88–92% reduced mortality by 78% in COPD patients when compared with a more liberal oxygen administration of 8–10 L/min [94]. Patients receiving titrated oxygen were also less likely to develop acute respiratory acidosis. A retrospective study of 680 patients hospitalized with AECOPD reported an increased risk of serious adverse outcome in patients admitted with an SpO_2 <88% as well as patients with SpO_2 >96% [99].

COPD patients generally have decreased physiologic reserve and a high cardiovascular risk profile. Studies suggest that more than half of patients admitted to hospital with AECOPD also have cardiovascular disease and about one-fifth of exacerbations might be caused by worsening of underlying cardiovascular disease [100]. Biochemical evidence of cardiac dysfunction (e.g. high concentrations of cardiac troponin or B-type natriuretic peptide) during exacerbation is common and this is an independent predictor of increased risk of all-cause mortality [101]. Moreover, angiographically confirmed ischemic heart disease requiring revascularization has been reported to occur in 39% of AECOPD patients with elevated cardiac troponin [102]. In Study 3, 12 patients (6%) had a myocardial infarction and 19 patients (10%) had new-onset heart

failure diagnosed within 30 days of inclusion. These data underline the importance of a high degree of clinical vigilance for monitoring of AECOPD patients, in particular when further deterioration occurs, despite relevant standard treatment. Notably, COPD patients may be hospitalized with other medical or surgical emergencies (apart from AECOPD) and this also warrants cautious clinical monitoring. Correspondingly, COPD patients undergoing major surgery are at increased risk of developing perioperative complications, including respiratory failure and postoperative chest infections [103]. COPD has been reported as an independent predictor of hypoxemic episodes requiring intubation within 3 days of noncardiac surgery [104].

How continuous monitoring may be used in the future

Identification of deteriorating patients and appropriate escalation of monitoring or interventions require every part of the system to be effective, but failure in managing deteriorating patients often originates in the afferent limb [105]. Continuous monitoring in non-ICU/PACU settings can potentially counter the challenges of health care systems arising from demographic changes in many countries with older and medically more complex patients. This could transform hospital monitoring and lead to important reductions in complications and to health economic benefits.

The recent COVID-19 crisis has brought to the public's attention that there is a limit to the number of health care workers and ICU beds in all health care systems around the world. COVID-19 and other outbreaks of respiratory viruses have increased awareness of the need to reduce bedside observations and interventions from healthcare staff in order to limit contamination [106, 107]. Continuous monitoring may improve patient care through earlier detection of deterioration, while limiting the labor-intensive workload associated with manual vital sign measurements. Furthermore, frequent manual nurse measurements may be distressing to patients (especially during night-time) and, therefore, wearables may also improve patient wellbeing. Although wireless sensors allow mobilization, patients may also feel restricted, if wireless sensors are not adequately comfortable for patients.

As previously mentioned, an important factor for future monitoring systems will almost certainly be the incorporation of advanced analytical methods for real-time interpretation of the enormous amount of wirelessly transferred data derived from wearable sensors. These algorithms will likely integrate trend analysis, which may be of particular interest in COPD patients with chronically deviating vital signs. It is also essential that monitoring systems minimize rates of false alarms to

limit alarm fatigue and that data incompleteness is considered. Further, multiparametric data must be analyzed together to find patterns of vital sign deviations instead of single values that are abnormal. Currently available continuous monitoring systems allow the clinician to take timely reactive actions to limit the duration of potentially harmful physiological abnormalities and can be considered a tremendous improvement on interval-based monitoring. However, future clinical support systems developed through machine learning techniques applied on large datasets may improve capabilities to predict impending clinical events [108, 109]. These datasets should include physiological parameters and clinical outcomes and may also integrate demographic information and paraclinical data (e.g., blood samples, diagnostic imaging) from electronic patient records. A recent study in the ICU setting showed that machine learning-based survival prediction from aggregation of previous medical history and acute physiological variables was possible [110]. However, although such algorithms have potential to provide good accuracy for detection or prediction, their clinical application may be limited due to difficulties with the data interpretation. In contrast, interpretable methods explain why a specific prediction was made for a patient and understanding what drives a prediction is pivotal for clinicians to trust predictions based on artificial intelligence and to determine optimal corrective actions in a clinical context [111]. Interestingly, a recent study described an explainable machine learning model with predictions for the prevention of hypoxemia during surgery and the system improved the performance of anesthesiologists [112]. Hopefully, future remote monitoring systems will provide clinicians with more meaningful and actionable information, and thus be better at predicting clinical deterioration than the current EWS-based systems. It should be stressed that even with a completely operational continuous monitoring system implemented, other indicators of physiological deterioration in general ward patients (e.g., changes in arterial pH levels, respiratory fatigue etc.) are essential and should be repeatedly assessed. Moreover, remote monitoring systems should increase rather than replace the time available for face-to-face contact between patients and healthcare staff.

This thesis has focused on the monitoring of classic vital signs (HR, RR, SpO_2 and BP), but other physiological bio-signals may be of interest for incorporation in future monitoring systems, including temperature, activity, skin conductance, body position and blood glucose. Further, heart rate variability index, photoplethysmogram analysis [113], and pulse-wave transit time techniques for advanced non-invasive BP estimations are also promising for tracking of circulatory changes. These different physiological signals can represent compensatory mechanisms that change earlier in the process of deterioration when compared with classic vital signs that may actually be interpreted as outcome variables [114]. Moreover, the ECG signal

from wearable patches could be used to detect arrhythmia and cardiac ischemia. It may be advantageous in patients admitted with AECOPD to continuously and non-invasively monitor CO_2 levels which is possible using transcutaneous sensors. This technique may reduce the requirement for repeated arterial punctures and thereby the risks and discomfort related to this procedure, in particular during ongoing non-invasive ventilation [115].

Table 6. Desirable characteristics of ward monitoring systems

Good agreement with gold standard monitoring	High accuracy and precision when compared to gold standard monitoring devices
Sensitive and specific	Low rate of artifacts and false alarms Reliably detects abnormal vital signs
Continuous	High sampling frequency
Multimodal	Allows several parameters to be monitored with few sensors
Wireless	Does not hinder patient mobility or impair comfort. Portable and wearable on an easily accesible body part. Secure transfer and storage of data
Incorporates trend analysis	Analysis of vital sign trends in realtime may be more important than changes in absolute numbers
Automated alarms	Alerts directed to various levels of care providers
Cost-effective, adaptable and upgradable	Preferably reusable and easy to clean devices. Ability to upgrade software/firmware remotely.
Integrates with existing systems	E.g. electronic medical record
Failure recognition	Detects and alerts when it is not working
Intuitive and adaptable display modes	Easy to use and adapts to different platforms (in room, mobile devices, workstation monitors, remote)
Smart algorithm	Self-learning system based on machine-learning and artificial intelligence

Adapted from DeVita MA, Smith GB, Adam SK, et al. Identifying the hospitalised patient in crisis´—a consensus conference on the afferent limb of rapid response systems. Resuscitation 2006;81:375-82.

Future monitoring systems will perhaps also integrate automatic medical interventions. An interesting example, in particular for AECOPD patients, that has already been developed is automated oxygen titration devices including O2matic (O2matic Ltd, Herlev, Denmark) and FreeO2 (OxyNov, Quebec, Canada). The control of administered supplemental oxygen to achieve an SpO_2 target level is time-consuming for the clinical staff; therefore, these systems use an automated closed-loop principle to improve control of oxygen administration, increase patient safety and reduce the nurses' workload. In a controlled study, time within the SpO_2 target interval was increased from 51% to 81% with the FreeO2 device compared with the use of standard (manual) control [116]. Similarly, the O2matic system was recently shown to effectively control SpO_2 for AECOPD patients and the system was superior in maintaining SpO_2 within the prescribed interval when compared with manual control by nurses [117].

Suggestions for future research

When designing the infrastructure of future remote monitoring solutions, all the desirable characteristics (Table 6) should be addressed and continuously evaluated. Although the future best-case scenario could be implementation of continuous wireless monitoring for all hospitalized patients, at this point, research should focus on high-risk patients, i.e., those most likely to suffer sudden cardiorespiratory deterioration. Emphasis should in particular be on monitoring methods being meticulously clinically validated and that other important factors, such as usability, health economics as well as the patient perspective, are investigated before new technologies are widely introduced. This PhD thesis has primarily focused on a monitoring system being continuous, multimodal, wireless, accurate and being able to reliably detect abnormal vital signs, i.e., the first five desirable characteristics of future ward monitoring systems outlined in Table 6. Studies 1-3 have contributed with several steps in the development of these characteristics. However, these factors should be addressed in further detail with comparison of different systems' performance, and it is essential that other desirable characteristics are also investigated in parallel. Additional studies are required to determine the accuracy and precision of currently available monitors in various patient populations, including extremes of vital signs and periods of mobilization. Perhaps more importantly, projects are also needed to determine which physiological parameters and thresholds and what duration of abnormalities are the most predictive of adverse outcome. Characteristics for the efferent limb (most important user-friendly design, smart algorithms and a secure IT-infrastructure) should be developed in close collaboration with users (e.g., ward nurses) and other health care specialists.

For patients discharged after hospitalization for AECOPD, readmission within 30 days has been reported to occur in 20% [118], which is comparable to our findings in Study 3. Continuous remote monitoring could be advantageous in patients' homes or rehabilitation units in this critical phase after hospital discharge and may thus represent an interesting area of future research. Similarly, investigations should include patients transferred from high-acuity settings to general wards with a considerably lower level of monitoring and nurse-to-patient ratio. These patients may be at increased risk of new episodes of deterioration, possibly necessitating ICU readmission.

Overall, wireless and continuous monitoring on general wards is largely unknown territory and although observational studies have inherent limitations, I firmly believe they are still needed to advance our understanding of the importance of signs of physiological instability in predicting clinical outcomes. Nevertheless, future large interventional trials of continuous vital sign monitoring in non-ICU settings are essential and should aim at substantiating the effect on early detection of SAEs in AECOPD patients as well as other high-risk patient populations.

Conclusions

Based on the pilot and large observational study, it can be concluded that moderate and severe episodes of desaturation and other physiological abnormalities of long duration are common during the first days after hospitalization for AECOPD. These episodes are most often not reported with EWS. Based on the validation study, commercially available and medically approved wireless sensors could accurately measure HR, PR and SpO_2 when compared with standard wired monitors. Nonetheless, wireless monitoring of RR and BP with these devices should be interpreted with caution because the precision needs to be improved.

Our results confirm that patients hospitalized with AECOPD have a high risk of clinical complications, with 41% suffering at least one SAE and a mortality rate of 7% within 30 days after inclusion. The mean cumulated duration of physiological abnormalities was longer in patients with SAEs; however, this was statistically significant only for events of bradypnea. These findings can aid in the development of future continuous monitoring systems based on wireless sensors and should be confirmed in larger intervention trials investigating the clinical impact of continuous monitoring.

Funding and conflicts of interests

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Role of the funding source

No funding source had any role in the study design; in the collection, analysis and interpretation of data; or in the writing and decision to submit the manuscripts and this thesis.

Conflicts of interest

Mikkel Elvekjær received departmental funding from Merck, Sharp & Dohme Corp outside the submitted work. Christian S. Meyhoff, Eske K. Aasvang and Helge B. Sørensen have founded a start-up company, WARD247 ApS, with the aim of pursuing the regulatory and commercial activities of the WARD-project. WARD247 ApS has finalized terms for license agreement for any WARD-project software and patents. There are currently no patents pending or filed. None of the funding entities has influence on the study design, conduct, analysis or reporting.
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References

[1] Bigotti F, Taylor D. The Pulsilogium of Santorio: New Light on Technology and Measurement in Early Modern Medicine. *Soc Polit* 2017; 11: 53–113.

[2] Michard F, Gan TJ, Kehlet H. Digital innovations and emerging technologies for enhanced recovery programmes. *BJA Br J Anaesth* 2017; 119: 31–39.

[3] Comisso I, Lucchini A, Bambi S, et al. *Nursing in Critical Care Setting: An Overview from Basic to Sensitive Outcomes*. 2018.

[4] Seguin E. The use of the thermometer in clinical medicine. *Chicago Med J* 1866; 23: 193–201.

[5] Molnár C, Nemes C, Szabó S, et al. Harvey Cushing, a pioneer of neuroanesthesia. *J Anesth* 2008; 22: 483–486.

[6] Severinghaus JW. Takuo Aoyagi: Discovery of Pulse Oximetry. *Anesth Analg* 2007; 105: S1–S4.

[7] Moller JT, Johannessen NW, Espersen K, et al. Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. *Anesthesiology* 1993; 78: 445–453.

[8] Indolfi C, Spaccarotella CAM, Polimeni A, et al. Multichannel Electrocardiograms Obtained by a Smartwatch for the Diagnosis of ST-Segment Changes. *JAMA Cardiol* 2020; 5: 1176–1180.

[9] Perez M V., Mahaffey KW, Hedlin H, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; 381: 1909–1917.

[10] Jones D, Mitchell I, Hillman K, et al. Defining clinical deterioration. *Resuscitation* 2013; 84: 1029–1034.

[11] Young MP, Gooder VJ, McBride K, et al. Inpatient transfers to the intensive care unit: Delays are associated with increased mortality and morbidity. *J Gen Intern Med* 2003; 18: 77–83.

[12] DeVita MA, Bellomo R, Hillman K, et al. Findings of the First Consensus Conference on Medical Emergency Teams. *Crit Care Med* 2006; 34: 2463–2478.

[13] Fuhrmann L, Lippert A, Perner A, et al. Incidence, staff awareness and mortality of patients at risk on general wards. *Resuscitation* 2008; 77: 325–330.

[14] Schein RMH, Hazday N, Pena M, et al. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest* 1990; 98: 1388–1392.

[15] Smith AF, Wood J. Can some in-hospital cardio-respiratory arrests be prevented? A prospective survey. *Resuscitation* 1998; 37: 133–137.

[16] Andersen LW, Kim WY, Chase M, et al. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation* 2016; 98: 112–117.

[17] Lyons PG, Edelson DP, Churpek MM. Rapid response systems. *Resuscitation* 2018; 128: 191–197.

[18] Morgan R, Williams F, Wright M. An early warning scoring system for detecting developing critical illness. *Clin Intensive Care* 1997; 8: 100.

[19] Royal College of Physicians. *National Early Warning Score (NEWS): Standardising the assessment of acute illness severity in the NHS. Report of a working party. London: RCP, 2012*.

[20] Royal College of Physicians. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP, 2017.*

[21] Haegdorens F, Van Bogaert P, Roelant E, et al. The introduction of a rapid response system in acute hospitals: A pragmatic stepped wedge cluster randomised controlled trial. *Resuscitation* 2018; 129: 127–134.

[22] Mestrom E, De Bie A, van de Steeg M, et al. Implementation of an automated early warning scoring system in a surgical ward: Practical use and effects on patient outcomes. *PLoS One* 2019; 14: e0213402.

[23] Smith MEB, Chiovaro JC, O'Neil M, et al. Early Warning System Scores for Clinical Deterioration in Hospitalized Patients: A Systematic Review. *Ann Am Thorac Soc* 2014; 11: 1454–1465.

[24] Gerry S, Bonnici T, Birks J, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. *BMJ* 2020; 369: m1501.

[25] Kellett J, Sebat F. Make vital signs great again – A call for action. *Eur J Intern Med* 2017; 45: 13–19.

[26] Clifton DA, Clifton L, Sandu DM, et al. 'Errors' and omissions in paper-based early warning scores: The association with changes in vital signs-a database analysis. *BMJ Open* 2015; 5: 1–7.

[27] *Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016.* Geneva, World Health Organization, 2018.

[28] Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786–796.

[29] Halpin DMG, Miravitlles M, Metzdorf N, et al. Impact and prevention of severe exacerbations of COPD: A review of the evidence. *Int J COPD* 2017; 12: 2891–2908.

[30] Groenewegen KH, Schols AM, Wouters EFM. Mortality and Mortality-Related Factors After Hospitalization for Acute Exacerbation of COPD. *Chest* 2003; 124: 459–467.

[31] Eriksen N, Vestbo J. Management and survival of patients admitted with an exacerbation of COPD: Comparison of two Danish patient cohorts. *Clin Respir J* 2010; 4: 208–214.

[32] Connors AF, Dawson N V, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; 154: 959–67.

[33] Almagro P, Calbo E, Ochoa De Echagüen A, et al. Mortality after hospitalization for COPD. *Chest* 2002; 121: 1441–1448.

[34] Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: Severe exacerbations and mortality. *Thorax* 2012; 67: 957–963.

[35] O'Driscoll BR, Howard LS, Earis J, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017; 72: i1-90.

[36] European Medicines Agency (EMA). *Guideline for good clinical practice E6(R2)*. 2018.

[37] Sendelbach S, Funk M. Alarm fatigue: A patient safety concern. *AACN Adv Crit Care* 2013; 24: 378–386.

[38] Kane B, Decalmer S, Murphy P, et al. S29 The Proposed National Early Warning System (NEWS) Could Be Hazardous For Patients Who Are at Risk of Hypercapnic Respiratory Failure. *Thorax* 2012; 67: A16-17.

[39] Smith GB, Prytherch DR, Schmidt PE, et al. Early warning scores and chronic respiratory disease. *Clinical Medicine, Journal of the Royal College of Physicians of London* 2012; 12: 395–396.

[40] O'Driscoll BR, Bakerly ND, Murphy P, et al. Concerns regarding the design of the bedside monitoring chart for use with the NEWS (National Early Warning System). *Clin Med* 2013; 13: 319–20.

[41] Eccles SR, Subbe C, Hancock D, et al. CREWS: Improving specificity whilst maintaining sensitivity of the National Early Warning Score in patients with chronic hypoxaemia. *Resuscitation* 2014; 85: 109–111.

[42] Hodgson LE, Dimitrov BD, Congleton J, et al. A validation of the National Early Warning Score to predict outcome in patients with COPD exacerbation. *Thorax* 2017; 72: 23–30.

[43] Lellouche F, L'her E. Usual and advanced monitoring in patients receiving oxygen therapy. *Respir Care* 2020; 65: 1591–1600.

[44] Echevarria C, Steer J, Bourke SC. Comparison of early warning scores in patients with COPD exacerbation: DECAF and NEWS score. *Thorax* 2019; 941–946.

[45] Michard F, Sessler DI. Ward monitoring 3.0. *Br J Anaesth* 2018; 121: 999–1001.

[46] Haahr-Raunkjær C, Meyhoff CS, Sørensen HBD, et al. Technological aided assessment of the acutely ill patient – The case of postoperative complications. *Eur J Intern Med* 2017; 45: 41–45.

[47] Pei L, Huang Y, Mao G, et al. Axillary temperature, as recorded by the iThermonitor WT701, well represents core temperature in adults having noncardiac surgery. *Anesth Analg* 2018; 126: 833–838.

[48] Joshi M, Ashrafian H, Aufegger L, et al. Wearable sensors to improve detection of patient deterioration. *Expert Rev Med Devices* 2019; 16: 145–154.

[49] Bergese SD, Mestek ML, Kelley SD, et al. Multicenter study validating accuracy of a continuous respiratory rate measurement derived from pulse oximetry: A comparison with capnography. *Anesth Analg* 2017; 124: 1153–1159.

[50] Ben-Ari J, Zimlichman E, Adi N, et al. Contactless respiratory and heart rate monitoring: Validation of an innovative tool. *J Med Eng Technol* 2010; 34: 393–398.

[51] Nitzan M, Romem A, Koppel R. Pulse oximetry: Fundamentals and technology update. *Med Devices Evid Res* 2014; 7: 231–239.

[52] Michard F, Sessler DI, Saugel B. Non-invasive arterial pressure monitoring revisited. *Intensive Care Med* 2018; 44: 2213–2215.

[53] Churpek MM, Adhikari R, Edelson DP. The value of vital sign trends for detecting clinical deterioration on the wards. *Resuscitation* 2016; 102: 1–5.

[54] Brekke IJ, Puntervoll LH, Pedersen PB, et al. The value of vital sign trends in predicting and monitoring clinical deterioration: A systematic review. *PLoS One* 2019; 14: e0210875.

[55] Christensen D, Jensen NM, Maaløe R, et al. Nurse-administered early warning score system can be used for emergency department triage. *Dan Med Bull* 2011; 58: A4221.

[56] Early Warning Score (EWS) - systematisk observation og risikovurdering af indlagte patienter samt dertil hørende handlingsalgoritme (Internal Standard Operating Procedure,

available upon request), http://vip.regionh.dk (accessed 16 November 2020).

[57] Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat* 2007; 17: 571–582.

[58] Zou GY. Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual. *Stat Methods Med Res* 2013; 22: 630–642.

[59] DeVita MA, Smith GB, Adam SK, et al. 'Identifying the hospitalised patient in crisis'-A consensus conference on the afferent limb of Rapid Response Systems. *Resuscitation* 2010; 81: 375–382.

[60] Cardona-Morrell M, Prgomet M, Turner RM, et al. Effectiveness of continuous or intermittent vital signs monitoring in preventing adverse events on general wards: a systematic review and meta-analysis. *Int J Clin Pract* 2016; 70: 806–824.

[61] Taenzer AH, Pyke JB, McGrath SP, et al. Impact of Pulse Oximetry Surveillance on Rescue Events and Intensive Care Unit Transfers. *Anesthesiology* 2010; 112: 282–287.

[62] Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Crit Care* 2017; 21: 1–9.

[63] Bonafide CP, Xiao R, Brady PW, et al. Prevalence of Continuous Pulse Oximetry Monitoring in Hospitalized Children with Bronchiolitis Not Requiring Supplemental Oxygen. *J Am Med Assoc* 2020; 323: 1467–1477.

[64] Leenen JPL, Leerentveld C, van Dijk JD, et al. Current evidence for continuous vital signs monitoring by wearable wireless devices in hospitalized adults: Systematic review. *J Med Internet Res* 2020; 22: e18636.

[65] Weenk M, Bredie SJ, Koeneman M, et al. Continuous monitoring of vital signs in the general ward using wearable devices: Randomized controlled trial. *J Med Internet Res* 2020; 22: e15471.

[66] Downey CL, Chapman S, Randell R, et al. The impact of continuous versus intermittent vital signs monitoring in hospitals: A systematic review and narrative synthesis. *International Journal of Nursing Studies* 2018; 84: 19–27.

[67] Calzavacca P, Licari E, Tee A, et al. A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. *Intensive Care Med* 2008; 34: 2112–6.

[68] Duus C, Aasvang E, Olsen R, et al. Continuous Vital Sign Monitoring after Major Abdominal Surgery—Quantification of Micro Events. *Acta Anaesthesiol Scand* 2018; 62: 1200–1208.

[69] Turan A, Chang C, Cohen B, et al. Incidence, Severity, and Detection of Blood Pressure Perturbations after Abdominal Surgery: A Prospective Blinded Observational Study. *Anesthesiology* 2019; 130: 550–559.

[70] Bowton DL, Scuderi PE, Haponik EF. The incidence and effect on outcome of hypoxemia in hospitalized medical patients. *Am J Med* 1994; 97: 38–46.

[71] Bleyer AJ, Vidya S, Russell GB, et al. Longitudinal analysis of one million vital signs in patients in an academic medical center. *Resuscitation* 2011; 82: 1387–1392.

[72] Buist M, Bernard S, Nguyen T V., et al. Association between clinically abnormal observations and subsequent in-hospital mortality: A prospective study. *Resuscitation* 2004; 62: 137–141.

[73] Breteler MJM, KleinJan E, Numan L, et al. Are current wireless monitoring systems capable of detecting adverse events in high-risk surgical patients? A descriptive study. *Injury* 2020; 51: S97–S105.

[74] Breteler MJM, Huizinga E, Van Loon K, et al. Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: A clinical validation study. *BMJ Open* 2018; 8: e020162.

[75] Weenk M, van Goor H, Frietman B, et al. Continuous Monitoring of Vital Signs Using Wearable Devices on the General Ward: Pilot Study. *JMIR mHealth uHealth* 2017; 5: e91.

[76] Hernandez-Silveira M, Wieczorkowski-Rettinger K, Ang S, et al. Preliminary assessment of the SensiumVitals®: A low-cost wireless solution for patient surveillance in the general wards. *Annu Int Conf IEEE Eng Med Biol Soc* 2015; 4931–4937.

[77] Breteler MJM, KleinJan EJ, Dohmen DAJ, et al. Vital signs monitoring with wearable sensors in high-risk surgical patients a clinical validation study. *Anesthesiology* 2020; 424–439.

[78] van Loon K, Peelen LM, van de Vlasakker EC, et al. Accuracy of remote continuous respiratory rate monitoring technologies intended for low care clinical settings: a prospective observational study. *Can J Anesth* 2018; 65: 1324–1332.

[79] Edmonds Z V., Mower WR, Lovato LM, et al. The reliability of vital sign measurements. *Ann Emerg Med* 2002; 39: 233–237.

[80] Lim WS, Carty SM, Macfarlane JT, et al. Respiratory rate measurement in adults - How reliable is it? *Respir Med* 2002; 96: 31–33.

[81] Liu LL, Gallaher MM, Davis RL, et al. Use of a Respiratory Clinical Score among Different Providers. *Pediatr Pulmonol* 2004; 37: 243–248.

[82] Brabrand M, Hallas P, Folkestad L, et al. Measurement of respiratory rate by multiple raters in a clinical setting is unreliable: A cross-sectional simulation study. *J Crit Care* 2018; 44: 404–406.

[83] Amirav I, Masumbuko CK, Hawkes MT. Poor agreement and imprecision of respiratory rate measurements in children in a low-income setting. *American Journal of Respiratory and Critical Care Medicine* 2018; 198: 1462–1463.

[84] Petersen JA, Mackel R, Antonsen K, et al. Serious adverse events in a hospital using early warning score - What went wrong? *Resuscitation* 2014; 85: 1699–1703.

[85] Pedersen NE, Rasmussen LS, Petersen JA, et al. A critical assessment of early warning score records in 168,000 patients. *J Clin Monit Comput* 2018; 32: 109–116.

[86] Taenzer AH, Pyke J, Herrick MD, et al. A comparison of oxygen saturation data in inpatients with low oxygen saturation using automated continuous monitoring and intermittent manual data charting. *Anesth Analg* 2014; 118: 326–331.

[87] Hernandez-Silveira M, Ahmed K, Ang S-S, et al. Assessment of the feasibility of an ultra-low power, wireless digital patch for the continuous ambulatory monitoring of vital signs. *BMJ Open* 2015; 5: e006606.

[88] Jeffs E, Vollam S, Young JD, et al. Wearable monitors for patients following discharge from an intensive care unit: practical lessons learnt from an observational study. *J Adv Nurs* 2016; 72: 1851–1862.

[89] Clifton L, Clifton DA, Pimentel MAF, et al. Predictive monitoring of mobile patients by combining clinical observations with data from wearable sensors. *IEEE J Biomed Heal informatics* 2014; 18: 722–30.

[90] Jabarkhil A, Moberg M, Janner J, et al. Elevated blood eosinophils in acute COPD exacerbations: better short- and long-term prognosis. *Eur Clin Respir J* 2020; 7: 1757274.

[91] Louie A, Feiner JR, Bickler PE, et al. Four types of pulse oximeters accurately detect hypoxia during low perfusion and motion. *Anesthesiology* 2018; 128: 520–530.

[92] Stergiou GS, Alpert BS, Mieke S, et al. Validation protocols for blood pressure measuring devices in the 21st century. *J Clin Hypertens* 2018; 20: 1096–1099.

[93] Pedersen NE, Rasmussen LS, Petersen JA, et al. Modifications of the National Early Warning Score for patients with chronic respiratory disease. *Acta Anaesthesiol Scand* 2018; 62: 242–252.

[94] Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomised

controlled trial. *BMJ* 2010; 341: 927.

[95] O'Driscoll R, Bakerly N, Murphy P, et al. NEWS2 needs to be tested in prospective trials involving patients with confirmed hypercapnia. *Resuscitation* 2019; 139: 369–370.

[96] Pimentel MAF, Redfern OC, Gerry S, et al. A comparison of the ability of the National Early Warning Score and the National Early Warning Score 2 to identify patients at risk of in-hospital mortality: A multi-centre database study. *Resuscitation* 2019; 134: 147–156.

[97] Hodgson LE, Congleton J, Venn R, et al. NEWS 2 - too little evidence to implement? *Clin Med J R Coll Physicians London* 2018; 18: 371–373.

[98] Smith GB, Prytherch DR, Meredith P, et al. Early warning scores: unravelling detection and escalation. *Int J Health Care Qual Assur* 2015; 28: 872–875.

[99] Cameron L, Pilcher J, Weatherall M, et al. The risk of serious adverse outcomes associated with hypoxaemia and hyperoxaemia in acute exacerbations of COPD. *Postgraduate medical journal* 2012; 88: 684–689.

[100] MacDonald MI, Shafuddin E, King PT, et al. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016; 4: 138–148.

[101] Pavasini R, D'Ascenzo F, Campo G, et al. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis. *Int J Cardiol* 2015; 191: 187–193.

[102] Pizarro C, Herweg-Steffens N, Buchenroth M, et al. Invasive coronary angiography in patients with acute exacerbated COPD and elevated plasma troponin. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2081–2089.

[103] Lumb A, Biercamp C. Chronic obstructive pulmonary disease and anaesthesia. *Contin Educ Anaesthesia, Crit Care Pain* 2014; 14: 1–5.

[104] Ramachandran SK, Nafiu OO, Ghaferi A, et al. Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery. *Anesthesiology* 2011; 115: 44–53.

[105] DeVita M, Hillman K, Bellomo R. *Textbook of Rapid Response Systems: Concept and Implementation*. Springer International Publishing Switzerland, 2017.

[106] Carter C, Notter J. COVID-19 disease: a critical care perspective. *Clin Integr Care* 2020; 1: 100003.

[107] Aziz S, Arabi YM, Alhazzani W, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. *Intensive Care Med* 2020; 46: 1303–1325.

[108] Churpek MM, Yuen TC, Winslow C, et al. Multicenter Comparison of Machine Learning

Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards. *Crit Care Med* 2016; 44: 368–374.

[109] Muralitharan S, Nelson W, Di S, et al. Machine Learning-based Early Warning Systems for Clinical Deterioration: A Systematic Scoping Review. *J Med Internet Res* 2021; 23: e25187.

[110] Nielsen AB, Belling K, Nielsen AP, et al. Survival prediction in intensive-care units based on aggregation of long-term disease history and acute physiology : a retrospective study of the Danish National Patient Registry and electronic patient records. *Lancet Digit Heal* 2019; 1: e78–e89.

[111] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nature Medicine* 2019; 25: 44–56.

[112] Lundberg SM, Nair B, Vavilala MS, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. *Nat Biomed Eng* 2018; 2: 749–760.

[113] Rasmussen PS, Aasvang EK, Olsen RM, et al. Continuous peripheral perfusion index in patients admitted to hospital wards – An observational study. 2020; 1–9.

[114] Convertino VA, Wirt MD, Glenn JF, et al. The compensatory reserve for early and accurate prediction of hemodynamic compromise: A review of the underlying physiology. *Shock* 2016; 45: 580–590.

[115] Lermuzeaux M, Meric H, Sauneuf B, et al. Superiority of transcutaneous CO2 over end-tidal CO2 measurement for monitoring respiratory failure in nonintubated patients: A pilot study. *J Crit Care* 2016; 31: 150–156.

[116] Lellouche F, Bouchard PA, Roberge M, et al. Automated oxygen titration and weaning with FreeO2 in patients with acute exacerbation of COPD: A pilot randomized trial. *Int J COPD* 2016; 11: 1983–1990.

[117] Hansen EF, Hove JD, Bech CS, et al. Automated oxygen control with O2matic® during admission with exacerbation of COPD. *Int J COPD* 2018; 13: 3997–4003.

[118] Shah T, Churpek MM, Coca Perraillon M, et al. Understanding why patients with COPD get readmitted: a large national study to delineate the Medicare population for the readmissions penalty expansion. *Chest* 2015; 147: 1219–1226.

Studies 1 – 3

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ORIGINAL RESEARCH

Physiological abnormalities in patients admitted with acute exacerbation of COPD: an observational study with continuous monitoring

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) may rapidly require intensive care treatment. Evaluation of vital signs is necessary to detect physiological abnormalities (micro events), but patients may deteriorate between measurements. We aimed to assess if continuous monitoring of vital signs in patients admitted with AECOPD detects micro events more often than routine ward rounds. In this observational pilot study (NCT03467815), 30 adult patients admitted with AECOPD were included. Patients were continuously monitored with peripheral oxygen saturation (SpO_2), heart rate, and respiratory rate during the first 4 days after admission. Hypoxaemic events were defined as decreased SpO_2 for at least 60 s. Non-invasive blood pressure was also measured every 15–60 min. Clinical ward staff measured vital signs as part of Early Warning Score (EWS). Data were analysed using Fisher's exact test or Wilcoxon rank sum test. Continuous monitoring detected episodes of $SpO_2 < 92\%$ in 97% versus 43% detected by conventional EWS ($p < 0.0001$). Events of $SpO_2 < 88\%$ was detected in 90% with continuous monitoring compared with 13% with EWS ($p < 0.0001$). Sixty-three percent of patients had episodes of $SpO_2 < 80\%$ recorded by continuous monitoring and 17% had events lasting longer than 10 min. No events of $SpO_2 < 80\%$ was detected by EWS. Micro events of tachycardia, tachypnoea, and bradypnoea were also more frequently detected by continuous monitoring ($p < 0.02$ for all). Moderate and severe episodes of desaturation and other cardiopulmonary micro events during hospitalization for AECOPD are common and most often not detected by EWS.

Keywords Continuous monitoring · Wireless electronic devices · Vital signs · Physiological abnormalities · Deterioration · Chronic obstructive pulmonary disease

1 Introduction

Chronic obstructive pulmonary disease is the third leading cause of death worldwide [1] despite advances in medical therapy. Severe exacerbations (AECOPD) may urgently

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require intensive care treatment and carry a mortality rate of 4–11% during hospital stay, and 21–43% during the first year [2–5]. Standard ward care consists of bronchodilation with short-acting anti-muscarinic agents and short acting β-agonists, titrated oxygen treatment (to a SpO_2 of 88–92%) combined with supplemental intravenous drugs, and non-invasive ventilation for the most severe cases. However, clinical conditions may rapidly decline requiring more advanced care, i.e. mechanical ventilation and intensive care unit (ICU) admission occurring in 6% and 10% of patients respectively [2]. Failure to rescue deteriorating patients can lead to worse prognosis, because the condition may progress beyond the point-of-no-return (e.g. cardiac arrest or ICU admission). Failure to rescue consists of a combination of inadequate vital signs monitoring, lack of recognition, poor interpretation of parameters, and untimely corrective action. To reduce this so-called afferent limb failure by identifying patients at risk of deterioration, standardised track-and-trigger systems such as Early Warning Score (EWS) have been implemented in many hospitals with vital signs measured manually at regular intervals, usually 2–3 times a day with decreasing intervals in case of abnormal vital signs. However, clinical deterioration may also happen between these intermittent evaluations potentially leading to delay in critical diagnostics and interventions.

AECOPD is a condition, where the typical clinical presentation includes high respiratory rate, tachycardia, and oxygen requirement resulting in high EWS and thus increased observation, even though the observed abnormal physiology may be influenced by the patient's chronic deviation from normal values. This may lead to alarm fatigue with inappropriate diversion of attention to patients already stabilised or non-adherence to the escalation protocol. And thus an overall increased risk of failure to detect deterioration. Continuous 24/7 monitoring of vital signs in AECOPD may potentially improve patient care by early detection of physiological deterioration, allowing clinicians to intervene sooner than with intermittent monitoring. Thus, the aim of this pilot study was to assess if continuous monitoring of vital signs more often detects abnormal physiological values. We hypothesized that automatic continuous monitoring would detect abnormal vital signs more frequently than standard EWS monitoring.

2 Methods

The study was approved by the Danish Data Protection Agency (2012-58-0004) and registered at http://ClinicalTrials.gov (NCT03467815) and written informed consent was obtained from all participating patients. Approval was sought but waived by the regional ethics committee because it was an observational study (protocol number 18010815). The study is part of the Wireless Assessment of Respiratory and circulatory Distress (WARD) project.

2.1 Patient inclusion

Thirty patients were enrolled between February and June 2018 at Bispebjerg Hospital, Copenhagen, Denmark. Patients were eligible if they were adults, admitted with AECOPD as admission diagnosis. This diagnosis (regardless of previous lung function) had to be maintained in the patient record at time of inclusion. Patients were excluded if they were unable to give informed consent or if they were deemed by the investigator not to be cooperative to wear the monitoring equipment. Other exclusion criteria were: active therapy withdrawn (patients admitted for palliative care), expected duration of admission less than 24 h after possible enrolment or allergies to plastic, plaster or silicone.

2.2 Monitoring

EWS measurements were performed with routine equipment on the wards. Standard interval between measurements are 12 h with escalation of monitoring frequency to 6, 4 and 1 h(s) for aggregated EWS of 2, 3 and 7, respectively, and to every 30 min for scores ≥ 9 [6]. Continuous monitoring was performed using the WARD projects sensor network, including; Isansys Lifetouch (Isansys Lifecare, Oxfordshire, United Kingdom), Nonin WristOx 3150 (Nonin Medical inc., Minnesota, USA), and Meditech BlueBP-05 (Meditech Ltd., Hungary). Isansys Lifetouch is a wireless patch with two ECG electrodes for placement on the front left side of the thorax. It collects data on heart rate (HR) and respiratory rate (RR) derived from a single lead electrocardiogram and transmits via Bluetooth to a bedside gateway. Nonin WristOx 3150 is a wearable pulse oximeter for measuring arterial oxygen saturation (SpO_2) through standard fingertip measurement once every second and transmits data via Bluetooth to the gateway. Data from the Nonin WristOx included raw data with values per second and a calculated average per minute of at least 45 reliable measurements. The Meditech BlueBP-05 is a compact, wireless device for intermittent (not continuous) oscillometric measurements of blood pressure. The device was programmed at inclusion to measure the blood pressure every 15 min during daytime and every 30 min during night-time. If patients expressed discomfort from BP measurements, settings were changed to measure every 30 min during daytime and every hour during night-time. Data were sent from the gateway via secured hospital wi-fi connection to a hospital server. HR-, RR- and blood pressure data were automatically stored locally on the devices when a patient was out of Bluetooth range from the bedside tablet, enabling later transfer of data when Bluetooth connection to the bedside gateway was re-established. SpO_2-data from

the Nonin WristOx were not stored when patients were out of Bluetooth range. Clinical staff and patients were blinded to vital signs from the continuous monitoring equipment. Measurements started after informed consent and continued for 96 h if patient was hospitalised. Study personal attended patients daily to ensure data quality by encouraging patient compliance and change device batteries when needed.

2.3 Data analysis

In the Capital Region of Denmark, an EWS algorithm based on the national early warning score (NEWS) is used. In this system, each measured vital sign value is converted to a score from 0 to 3. An urgent clinical assessment by on-call physician is required when a patient has a single parameter score of 3 or a cumulated score of more than 5 [7]. To compare the EWS versus the continuous data, we selected thresholds for micro events to be similar to those defined in the EWS, and we considered a micro event to be present if the average was below the threshold for at least 60 s: Hypoxaemia was defined as $SpO_2 < 92\%$ (calculated average of 60 s), tachycardia as > 130 beats/min, bradycardia as < 41 beats/min, tachypnoea as > 24 breaths/min, bradypnoea as < 9 breaths/min. BP micro events were considered present if measured in at least one measurement. Hypotension was defined as systolic blood pressure (sBP) < 90 mmHg, and hypertension as sBP > 219 mmHg. In COPD patients, due to chronic hypoxia and the risk of hypercapnic respiratory failure, a target oxygen saturation range of 88–92% is usually recommended [8] and therefore we also analysed the data to find micro events of $SpO_2 < 88\%$ (moderate desaturation) as well as $SpO_2 < 80\%$ (severe desaturation). In addition to comparing the frequency of events outside predefined thresholds, we also evaluated the duration of hypoxaemic events and these desaturation events detected by EWS was analysed based on a time-weighted average. The EWS is not designed to evaluate the duration of micro events. However, in case of abnormal vital signs, the time interval to next measurement is shortened according to the total aggregated score and we therefore used it as an estimate of duration of hypoxaemic events. Time below the SpO_2 threshold was assumed to start and end halfway between the normal and abnormal value and was counted as such. Artefacts from continuous monitoring were detected and removed before analysis: for SpO_2, any change larger than 4% within one second and values below 20% were considered artefacts [9], and to calculate a mean value, ≥ 45 measurements per minute were required. When the pulse rate from photoplethysmography deviated more than 20 beats/min from the HR-estimation calculated from the ECG signal, the SpO_2 value was discarded due to the risk of a poorly attached probe. The HR measurement was derived from the automatic detection of R-peak intervals in the ECG signal from the Lifetouch patch. For each minute of monitoring, 10 s of ECG was available. From these short ECG segments, it was investigated if noise was present using an algorithm inspired by Vallance et al. [10]. As both HR and RR were derived from the ECG, values of HR and RR during periods of noisy ECG-signal were denoted as artefacts and excluded from analysis.

2.4 Statistical analysis

Data are presented as numbers and frequency of patients with micro events or median and 5–95% range for the duration of hypoxaemic events. For the statistical analyses, SAS version 9.4 (SAS Institute, Cary, NC, USA) was used. Associations between categorical and continuous data were analysed with the Fisher's exact test and Wilcoxon rank sum test respectively, and we considered $p < 0.05$ statistically significant. Sample size was pragmatically determined based on available time and our pilot study design, allowing power calculations for future studies.

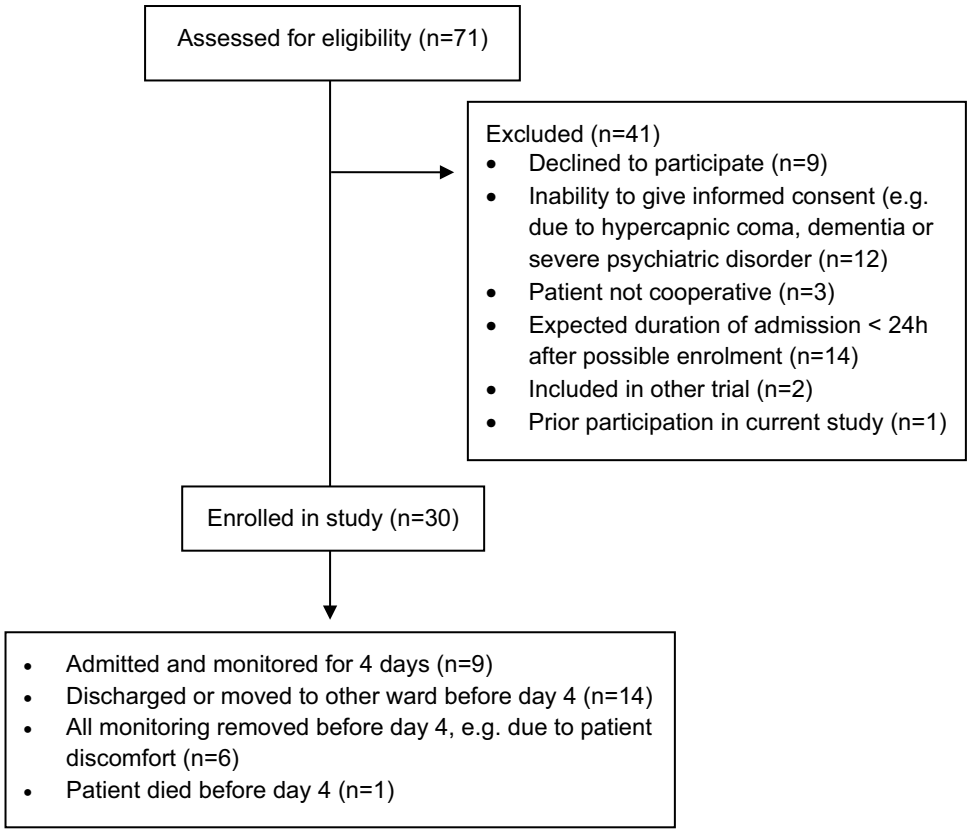
3 Results

Thirty patients were included in the study for a total of 2058 h of patient monitoring (median of 71 h, Fig. 1). Baseline characteristics are described in Table 1. All EWS measurements made during the study period were collected from the electronic patient record and a total of 328 complete EWS measurements were made which gave an average measurement interval of 6 h and 16 min.

3.1 Peripheral oxygen saturation

In total, 1248 h of continuous SpO_2 data were collected. After removal of artefacts (9% of total recorded time), 1135 h of continuous SpO_2 data were available for analysis. Average SpO_2 monitoring time per patient was 38 h corresponding to 55% of the total time. One or more events of desaturation to < 92% were found in 29 of 30 patients (97%) with continuous monitoring versus 13 patients (43%) with EWS ($p < 0.0001$, Fig. 2; Table 2). Seven patients had desaturation events with $SpO_2 < 92\%$ reported by EWS that were not detected by continuous monitoring, due to missing data from these time periods. Desaturation events with $SpO_2 < 88\%$ were detected in 90% of participants with continuous monitoring compared with 13% detected with EWS ($p < 0.0001$). One patient had a desaturation event with $SpO_2 < 88\%$ reported by EWS that was not captured by continuous monitoring, due to missing data from this period. The median duration among patients having desaturation below $SpO_2 < 88\%$ (median hypoxaemic time) detected by continuous monitoring was 156 min [5–95% range 0–1237]

Fig. 1 Study flowchart



versus 0 min [5–95% range 0–165] in the same patients measured with EWS ($p < 0.0001$). Figure 3 illustrates the average time of moderate desaturation ($SpO_2 < 88\%$) according to time of day. Desaturation events were detected on all days and the distribution of total hypoxaemic time throughout the day was as follows: 34% of total hypoxaemic time ($SpO_2 < 88\%$) was between 00 and 08, 36% between 08 and 16, and 31% between 16 and 24. Continuous monitoring detected severe desaturation events with $SpO_2 < 80\%$ in 19 patients (63%). Among patients with severe desaturation, the median cumulative duration with $SpO_2 < 80\%$ was 9 min [5–95% range 1–99], and 5 patients (17%) had these events lasting longer than 10 min. Events of $SpO_2 < 80\%$ were not detected for any patients by EWS.

3.2 Heart rate

The total time of collected HR data was 1570 h. After artefact removal (7% of total recorded time), 1462 h were available for analysis, corresponding to 71% of the total monitoring time. Continuous monitoring captured one or more tachycardic events with HR > 130/min in 15 patients (50%) versus only 4 patients (13%) reported with EWS ($p = 0.005$). All tachycardic events reported by EWS were also detected by continuous monitoring. Episodes of bradycardia were not detected.

3.3 Respiratory rate

Continuous RR was recorded for 1569 h with 7% artefacts, and 1458 h (71% of the total time) where available for analysis. One or more tachypnoeic events (RR > 24/min) were detected in 17 patients (57%) with continuous monitoring versus 7 patients (23%) detected with EWS ($p = 0.02$). Three patients had tachypnoeic events reported with EWS that were not captured by continuous monitoring, and 4 patients had events of tachypnoea registered in the EWS at a time were a normal respiration rate was recorded with continuous monitoring. Sixteen patients (53%) had bradypnoea (RR < 9/min) detected by continuous monitoring, however no episodes of RR < 9/min were reported with EWS ($p < 0.0001$).

3.4 Blood pressure

Total time of automatic wireless blood pressure monitoring with at least one measurement every hour was 1005 h (49% of total monitoring time). Seven patients (23%) were found to be hypotensive (sBP < 90 mmHg) at some point during the study period using the wireless device compared with 2 patients (7%) reported with EWS ($p = 0.15$). Three events of hypotension recorded in the EWS (all from the same patient) were not detected by wireless monitoring.

Table 1 Baseline characteristics

Parameter	n = 30
Sex, male/female	17/13
Age, years	74 [62–85]
BMI, kg/m^2	26 [14–39]
Medical history	
Smoking history (never/previously/current)	1/21/8
Alcohol consumption[a]	5 (17%)
Previous stroke or transitory ischaemic attack	4 (13%)
Other neurological disease	3 (10%)
Hypertension	15 (50%)
Paroxysmal atrial fibrillation	6 (20%)
Ischemic heart disease	7 (23%)
Congestive heart failure	3 (10%)
Other cardiovascular disease	4 (13%)
Pulmonary disease (other than COPD)	3 (10%)
Diabetes mellitus	5 (17%)
Gastrointestinal disease	4 (13%)
Chronic kidney disease	5 (17%)
Previous cancer diagnosis	4 (13%)
Other disease	19 (63%)
Classification of COPD	
Spirometrically confirmed diagnosis ($FEV_1/FVC < 0.7$)[b]	28 (93%)
FEV1 (% of predicted)	36 [18–72]
GOLD stage 1/2/3/4	0/11/7/10
mMRC dyspnea grade 0-1/2/3/4	0/6/13/11
Baseline measurements at hospital admission	
Early warning score	5 [1–10]
SpO_2	93 [81–99]
Heart rate	98 [73–144]
Respiratory rate	24 [16–36]
Systolic blood pressure	140 [113–206]
Arterial pH	7.42 [7.30–7.49]
Arterial PaO_2, kPa	9.3 [6.7–13.4]
Arterial $PaCO_2$, kPa	5.6 [4.2–10.6]
Arterial bicarbonate, mmol/L	25.5 [21.8–40.0]
Arterial lactate, mmol/L	1.1 [0.5–2.7]
Haemoglobin, mmol/L	8.4 [7.0–10.1]
White blood count, 10^9/L	11.1 [5.1–25.3]
C-Reactive protein, mg/L	34 [1–278]
Creatinine, µmol/L	86 [50–159]

Values are number (percentage) or median [5–95% range]

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity, *GOLD* global initiative for chronic obstructive pulmonary disease, *mMRC* modified Medical Research Council dyspnea scale, SpO_2 peripheral oxygen saturation

[a]Current alcohol consumption of more than recommended by the Danish Health Authority, which is 24 g/day for men or 12 g/day for women

[b]Spirometry values as recorded in electronic health records, which did not specify pre- or post-bronchodilator values consistently

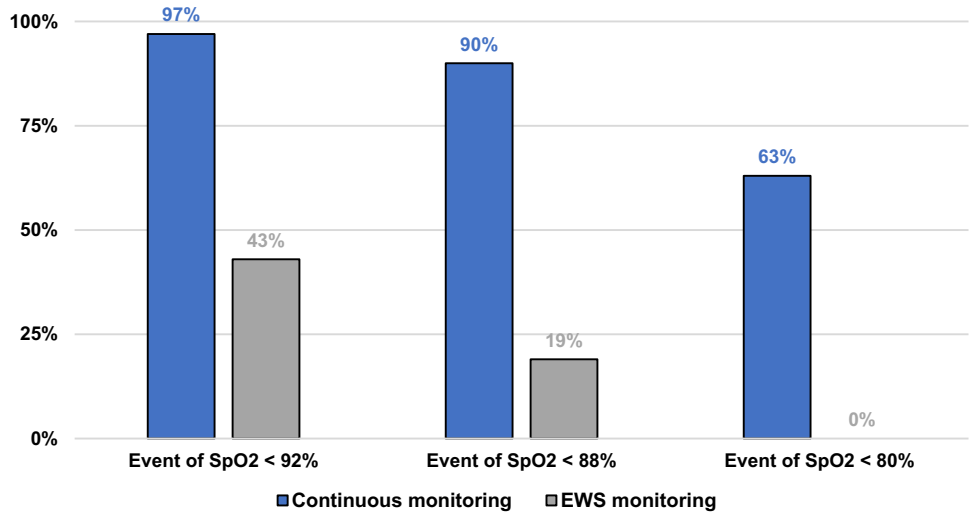


Fig. 2 Desaturation micro events during admission for acute exacerbation of COPD. Percent of patients with minimum one micro event of desaturation to $SpO_2 < 92\%$, $SpO_2 < 88\%$ and $SpO_2 < 80\%$ detected with continuous monitoring (blue) and EWS monitoring (grey), $p < 0.0001$ for all

Table 2 Cardiopulmonary micro events during admission for acute exacerbation of COPD

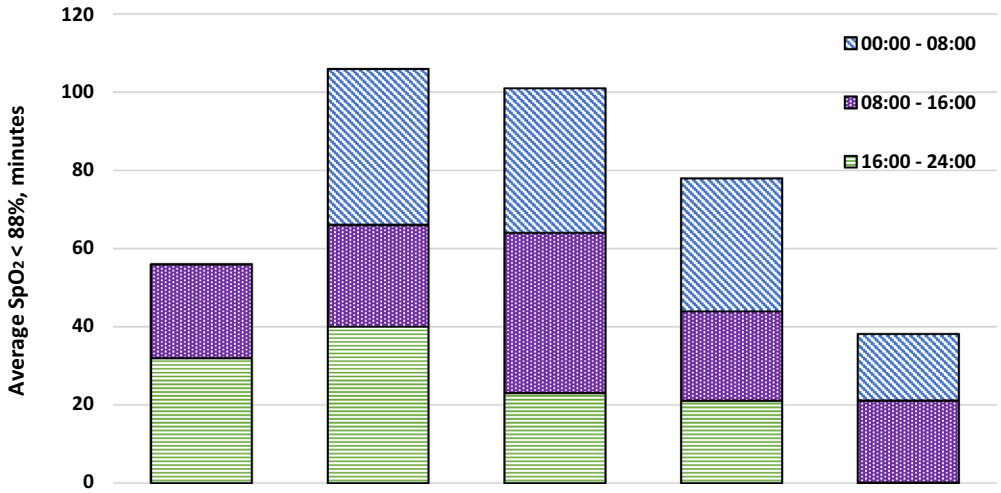
	Continuous monitoring, n = 30	EWS monitoring, n = 30	*p* value	Mean diff. (95% CI)
Desaturation micro events				
$SpO_2 < 92\%$				
Number of patients	29 (97%)	13 (43%)	< 0.0001	
Duration, minutes	996 [101–3123]	0 [0–2066]	< 0.0001	950 (475–1425)
Number of patients with at least one event lasting more than 60 min	24 (80%)	13 (43%)	0.01	
$SpO_2 < 88\%$				
Number of patients	27 (90%)	4 (13%)	< 0.0001	
Duration, minutes	156 [0–1237]	0 [0–165]	< 0.0001	359 (199–519)
Number of patients with at least one event lasting more than 60 min	11 (37%)	2 (7%)	0.01	
$SpO_2 < 80\%$				
Number of patients	19 (63%)	0	< 0.0001	
Duration, minutes	3 [0–79]	0	< 0.0001	13 (4–22)
Number of patients with at least one event lasting more than 10 min	5 (17%)	0	0.05	
Other cardiopulmonary micro events				
Heart rate > 130/min	15 (50%)	4 (13%)	0.005	
Heart rate < 41/min	0	0		
Respiratory rate > 24/min	17 (57%)	7 (23%)	0.02	
Respiratory rate < 9/min	16 (53%)	0	< 0.0001	
Systolic blood pressure < 90 mmHg	7 (23%)	2 (7%)	0.15	
Systolic blood pressure > 219 mmHg	2 (7%)	0	0.49	

Values are number (percentage), median [5–95% range] or mean difference (95% CI). Duration of hypoxaemia is calculated as median of the cumulative duration among all included patients

4 Discussion

Continuous monitoring detected statistically significant differences in frequency of desaturation, tachycardia, tachypnoea, and bradypnoea when compared with standard interval-based EWS monitoring in this pilot study of patients at high risk of ICU admission. Prolonged hypoxaemia of potential clinical significance was common in AECOPD, where moderate desaturation events ($SpO_2 < 88\%$) were detected in 90% of patients, and severe desaturation ($SpO_2 < 80\%$) were seen in more than half of patients. These events were only rarely reported with EWS.

The reported abnormal vital signs might reflect early stages of deterioration requiring critical diagnostics and interventions. Patients admitted with AECOPD are at risk



Days after inclusion	Day 0	Day 1	Day 2	Day 3	Day 4
Patients 00:00-08:00	0	30	25	20	11
Patients 08:00-16:00	22	30	25	19	10
Patients 16:00-24:00	30	25	21	11	2
Patients monitored during the day	30	30	25	20	11
Mean monitoring time	8 h	13 h	14 h	11 h	10 h

Fig. 3 Average time with $SpO_2 < 88\%$ per day of monitoring. Blue colour, desaturation at night time (00:00 to 08:00), purple colour, desaturation at day time (08:00 to 16:00), green colour, desaturation at evening time (16:00 to 24:00). Patients were recruited after 08:00 on day 0 and monitoring was stopped on day 4 (after 96 h of monitoring) if the patient was still hospitalised

of hypoxia during hospitalisation. Our results confirm that hypoxaemic micro events are very common in this population despite frequent administration of supplemental oxygen in medical wards specialised in respiratory disease. Patient deterioration is often preceded by unstable physiology reflected in abnormal vital signs, but several studies have reported that adverse trends in clinical observations are often missed or misinterpreted [11–14]. One response to this knowledge has been the introduction of EWS systems. However, the effectiveness of EWS to reduce morbidity and mortality has not been proven in prospective trials [15], and despite their wide implementation, preventable, serious adverse events still occur [16, 17]. Several studies have also reported problems with EWS data quality as well as poor compliance with the incorporated escalation protocols, both of which could affect manual EWS systems performance [16, 18–21]. Moreover, concern has been raised that most EWS systems lack specificity in the COPD population resulting in (alarmingly) high scores in relatively stable patients, especially due to the weighting of chronic hypoxia [22].

Therefore, alternative scores have been suggested to account for the chronically altered physiology in COPD patients [22, 23]. However, assigning lower oxygen saturation thresholds for scoring could cause high-risk patients to be categorized into a too-low risk group, thereby missing opportunities to intervene early.

The primary strength of this study was our ability to measure SpO_2, HR, and RR wirelessly and continuously after admission for AECOPD in consecutive patients in an optimised setting, thus indicating good external validity. Wireless and automatic blood pressure monitoring was also performed with decreased time interval compared with usual EWS monitoring. We were also able to compare these findings with routine care. However, several limitations deserve to be mentioned: First, we observed some amount of missing data. We found technical problems (battery power, Bluetooth connectivity issues or bedside Gateway being switched off) to be the main challenges, however, several of these issues were successfully resolved. Patient non-compliance was also the cause of data not being measured. For example, devices were occasionally pulled off by patients who felt physically restricted by the devices. Data were also lost when patients needed specific interventions or examinations requiring removal of equipment and when devices were removed unintendedly. We achieved continuous oxygen saturation data of acceptable quality in 55% of the time and it is likely that hypoxaemic episodes could have occurred during time periods without SpO_2-recordings. Our results therefore represent minimum durations. Other studies with continuous monitoring of vital signs in general wards have also reported issues with data incompleteness with comparable amount of missing data [24–26].

A second limitation is that invasive arterial blood gas analysis is required to obtain accurate data on the oxygen saturation of haemoglobin in blood (SaO_2). Pulse oximeters are widely used to estimate the arterial oxygen saturation in hospitalised patients. However, this has several limitations as they are subject to both patient-related variability and sensor variability as well as artefactual sources of error. Pulse oximeters are known to be unreliable in low perfusion states (e.g. due to pain/anxiety, hypotension, or hypothermia with vascular contraction) [27]. Severe anaemia and movement of the device can also influence the accuracy of pulse oximetry readings.

A third limitation is that SpO_2 artefacts accounted for 9% of total recorded time. This was most likely caused by motion artefacts and low peripheral perfusion.

A fourth limitation is that we were able to include less than half of patients assessed for eligibility. Some patients were unable to give informed consent due to severe dyspnoea or hypercapnic coma. These patients represent a group of patients with an even higher risk of deviating vital signs and deterioration, therefore our findings may only represent the tip of the iceberg of the real clinical problem, further strengthening the need for more intense observations. We also excluded patients with expected duration of admission less than 24 h, and our results thus represents patients with medium severity of AECOPD.

Limited data have been published regarding the clinical application of continuous multi-parameter wireless monitoring in hospitalised patients outside the ICU setting [17, 28], however a number of studies are currently ongoing. Studies have been conducted in different settings across specialties, but we were unable to find studies specifically in patients admitted with AECOPD. In the postsurgical setting, our group found similar results with high frequency of desaturation (e.g. 56% of patients had $SpO_2 < 80\%$ for at least 60 s) as well as other cardiopulmonary micro events [25]. Similarly, Turan et al. [29] reported common episodes of hypotension in patients after abdominal surgery (18% had mean arterial pressure lower than 65 mmHg). The clinical significance of these abnormal physiological values is debated. It has been shown that medical patients with desaturation events ($SpO_2 < 90\%$ for at least 5 consecutive minutes) within the first day of admission to a general ward have reduced survival compared with patients without hypoxaemic events [30]. However, this survival difference may be a result of the underlying disease (e.g. severe COPD) and the degree of hypoxaemia may be a marker of disease severity. Therefore, the individual contribution of hypoxaemia and other abnormal physiological values to development of adverse clinical outcomes is not fully described. More studies are needed to determine which vital parameters, thresholds and duration of micro events that are most predictive of adverse outcome. More precise prognostic information may be derived from the analyses of *trends* in physiological data [31] than currently available information of aggregated EWS from absolute values. Such trend analyses may be of particular interest in COPD patients who have chronically altered physiology. Correspondingly, the use of machine-learning algorithms on real-time physiological data may become of considerable prognostic value in the future [26, 32–35].

Continuous monitoring may improve track-and-trigger systems by allowing earlier detection of clinical deterioration across medical specialties [36, 37]. This could improve acute patient care by allowing for timely interventions to avoid clinical complications including transfer to ICU. The performance of track-and-trigger systems depends on both its ability to detect patients at risk of deterioration (the afferent limb) but also highly on the efferent part of the system, i.e. the quality and consistency of clinical interventions to improve vital signs and patient outcomes. This study was not powered to detect differences in clinical outcomes or health economics, but this is critical in future larger trials with enough power to substantiate the clinical effect of introducing continuous monitoring systems compared with standard interval-based observations.

5 Conclusion

Continuous monitoring in AECOPD patients showed an ability to detect and quantify more episodes of severe deterioration across physiological variables, than detected by the usual standard of care (EWS). These findings may aid in earlier detection of patients at risk of ICU transfer and should be confirmed in larger studies to aid in the development of preventive intervention trials on the clinical impact of continuous monitoring.

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Compliance with ethical standards

Conflict of interest M. E. reports departmental research funding from Merck Sharp & Dome Corp. outside the submitted work. C S. M. reports direct and indirect research funding from Ferring Pharmaceuticals, Merck Sharp & Dohme Corp., and Boehringer Ingelheim outside the submitted work. Other authors report none.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Global Health Estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva: World Health Organization; 2018. http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 22 Sep 2017.
2. Groenewegen KH, Schols AM, Wouters EFM. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124:459–67.
3. Eriksen N, Vestbo J. Management and survival of patients admitted with an exacerbation of COPD: comparison of two Danish patient cohorts. Clin Respir J. 2010;4:208–14.
4. Connors AF, Dawson NV, Thomas C, Harrell FE, Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996;154(4 Pt 1):959–67. https://doi.org/10.1164/ajrccm.154.4.8887592.
5. Almagro P, Calbo E, De Echagüen AO, Barreiro B, Quintana S, Heredia JL, et al. Mortality after hospitalization for COPD. Chest. 2002;121:1441–8.
6. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. Dan Med J. 2018;65:B5439.
7. Royal College of Physicians. National Early Warning Score (NEWS): standardising the assessment of acute illness severity in the NHS. Report of a working party. London: RCP; 2012. http://www.rcplondon.ac.uk/sites/default/files/documents/national-early-warning-score-standardising-assessment-acute-illness-severity-nhs.pdf.
8. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society R, Forni LG, Roderick PJ. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008;63(Suppl 6):vi1–68. https://doi.org/10.1136/thx.2008.102947.
9. Magalang UJ, Dmochowski J, Veeramachaneni S, Draw A, Mador MJ, El-Solh A, et al. Prediction of the apnea–hypopnea index from overnight pulse oximetry. Chest. 2003;124:1694–701. https://doi.org/10.1378/chest.124.5.1694.
10. Vallance D, Bonnici T, Tarassenko L, Charlton P, Orphanidou C, Clifton D. Signal quality indices for the electrocardiogram and photoplethysmogram: derivation and applications to wireless monitoring. IEEE J Biomed Heal Inform. 2014;19:1.
11. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. Resuscitation. 2004;62:137–41.
12. Kause J, Smith G, Prytherch D, Parr M, Flabouris A, Hillman K, et al. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and the United Kingdom: the ACADEMIA study. Resuscitation. 2004;62:275–82. https://doi.org/10.1016/j.resuscitation.2004.05.016.
13. Hodgetts TJ, Kenward G, Vlachonikolis IG, Payne S, Castle N. The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. Resuscitation. 2002;54:125–131. http://www.ncbi.nlm.nih.gov/pubmed/12161291. Accessed 21 Jan 2019.
14. Calzavacca P, Licari E, Tee A, Egi M, Haase M, Haase-Fielitz A, et al. A prospective study of factors influencing the outcome of patients after a medical emergency team review. Intensive Care Med. 2008;34:2112–6. https://doi.org/10.1007/s00134-008-1229-y.
15. Smith MEB, Chiovaro JC, O'Neil M, Kansagara D, Quiñones AR, Freeman M, et al. Early warning system scores for clinical deterioration in hospitalized patients: a systematic review. Ann Am Thorac Soc. 2014;11:1454–65. https://doi.org/10.1513/AnnalsATS.201403-102OC.
16. Petersen JA, Mackel R, Antonsen K, Rasmussen LS. Serious adverse events in a hospital using early warning score: what went wrong? Resuscitation. 2014;85:1699–703. https://doi.org/10.1016/j.resuscitation.2014.08.037.
17. Kellett J, Sebat F. Make vital signs great again: a call for action. Eur J Intern Med. 2017;45:13–9.
18. Pedersen NE, Rasmussen LS, Petersen JA, Gerds TA, Østergaard D, Lippert A. A critical assessment of early warning score records in 168,000 patients. J Clin Monit Comput. 2018;32:109–16.
19. Clifton DA, Clifton L, Sandu DM, Smith GB, Tarassenko L, Vollam SA, et al. "Errors" and omissions in paper-based early warning scores: the association with changes in vital signs-a database analysis. BMJ Open. 2015;5:1–7.
20. Kellett J, Woodworth S, Wang F, Huang W. Changes and their prognostic implications in the abbreviated Vitalpac™ early warning score (ViEWS) after admission to hospital of 18,853 acutely ill medical patients. Resuscitation. 2013;84:13–20. https://doi.org/10.1016/j.resuscitation.2012.08.331.
21. Petersen JA, Rasmussen LS, Rydahl-Hansen S. Barriers and facilitating factors related to use of early warning score among acute care nurses: a qualitative study. BMC Emerg Med. 2017;17:36. https://doi.org/10.1186/s12873-017-0147-0.
22. O'Driscoll BR, Bakerly ND, Murphy P, Decalmer S, Kane B, Nasir AA, et al. Concerns regarding the design of the bedside monitoring chart for use with the NEWS (National Early Warning System). Clin Med. 2013;13:319–20. https://doi.org/10.7861/clinmedicine.13-3-319.
23. Eccles SR, Subbe C, Hancock D, Thomson N. CREWS: improving specificity whilst maintaining sensitivity of the National Early Warning Score in patients with chronic hypoxaemia. Resuscitation. 2014;85:109–11. https://doi.org/10.1016/j.resuscitation.2013.08.277.
24. Jeffs E, Vollam S, Young JD, Horsington L, Lynch B, Watkinson PJ. Wearable monitors for patients following discharge from an intensive care unit: practical lessons learnt from an observational study. J Adv Nurs. 2016;72:1851–62.
25. Duus CL, Aasvang EK, Olsen RM, Sørensen HBD, Jørgensen LN, Achiam MP, et al. Continuous vital sign monitoring after major abdominal surgery: quantification of micro events. Acta Anaesthesiol Scand. 2018;62:1200–8.
26. Clifton L, Clifton DA, Pimentel MAF, Watkinson PJ, Tarassenko L. Predictive monitoring of mobile patients by combining clinical observations with data from wearable sensors. IEEE J Biomed Heal inform. 2014;18:722–30. https://doi.org/10.1109/JBHI.2013.2293059.
27. Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. Respir Med. 2013;107:789–99. https://doi.org/10.1016/j.rmed.2013.02.004.
28. Haahr-Raunkjær C, Meyhoff CS, Sørensen HBD, Olsen RM, Aasvang EK. Technological aided assessment of the acutely ill patient: the case of postoperative complications. Eur J Intern Med. 2017;45:41–5.
29. Turan A, Chang C, Cohen B, Saasouh W, Yang D, et al. Incidence, severity, and detection of blood pressure perturbations after abdominal surgery: a prospective blinded observational study. Anesthesiology. 2019;130:550–9.
30. Bowton DL, Scuderi PE, Haponik EF. The incidence and effect on outcome of hypoxemia in hospitalized medical patients. Am J Med. 1994;97:38–46.
31. Brekke IJ, Puntervoll LH, Pedersen PB, Kellett J, Brabrand M. The value of vital sign trends in predicting and monitoring clinical deterioration: a systematic review. PLoS ONE. 2019;14:e0210875.

32. Churpek MM, Adhikari R, Edelson DP. The value of vital sign trends for detecting clinical deterioration on the wards. Resuscitation. 2016;102:1–5. https://doi.org/10.1016/j.resuscitation.2016.02.005.
33. Steinhubl SR, Feye D, Levine AC, Conkright C, Wegerich SW, Conkright G. Validation of a portable, deployable system for continuous vital sign monitoring using a multiparametric wearable sensor and personalised analytics in an Ebola treatment centre. BMJ Glob Health. 2016;1:e000070. https://doi.org/10.1136/bmjgh-2016-000070.
34. Churpek MM, Yuen TC, Winslow C, Meltzer DO, Kattan MW, Edelson DP. Multicenter comparison of machine learning methods and conventional regression for predicting clinical deterioration on the wards. Crit Care Med. 2016;44:368–74.
35. Lundberg SM, Nair B, Vavilala MS, Horibe M, Eisses MJ, Adams T, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. Nat Biomed Eng. 2018;2:749–60. https://doi.org/10.1038/s41551-018-0304-0.
36. Tarassenko L, Hann A, Young D. Integrated monitoring and analysis for early warning of patient deterioration. Br J Anaesth. 2006;97:64–8. https://doi.org/10.1093/bja/ael113.
37. Downey CL, Chapman S, Randell R, Brown JM, Jayne DG. The impact of continuous versus intermittent vital signs monitoring in hospitals: a systematic review and narrative synthesis. Int J Nurs Stud. 2018;84:19–27.

Title:

Agreement between wireless and standard measurements of vital signs in acute exacerbation of chronic obstructive pulmonary disease: a clinical validation study

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Author contributions:

The guarantor of the study is CSM, from conception and design to conduct of the study, interpretation of results, and revised the manuscript. ME were responsible for measurements, conducted data analyses and drafted the manuscript. CJC conducted data analyses and revised the manuscript. CMP, SMR, KKG, CHR, HBDS and EKA contributed to conception and design of the study and revised the manuscript. All co-authors have provided important intellectual input and contributed considerably to the analyses and interpretation of the data. All authors have approved the final version of the manuscript.

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Role of the funding source:

No sponsor had any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Conflicts of interest:

The WARD-project has received grants from the Innovation Fund Denmark, the Novo Nordic Foundation, the Danish Cancer Society, Steno Diabetes Center Denmark, Copenhagen Center for Health Technology, Radiometer, A.P. Møller Foundation as well as internal institutional funding. CSM, EKA and HBDS have founded a start-up company, WARD247 ApS, with the aim of pursuing the regulatory and commercial activities of the WARD-project. WARD247 ApS has finalized terms for license agreement for any WARD-project software and patents. There are currently no patents pending or filed. None of the above entities have influence on the study design, conduct, analysis or reporting.

CSM also reports direct and indirect research funding from Ferring Pharmaceuticals, Merck, Sharp & Dohme Corp. and Boehringer Ingelheim outside the submitted work as well as lecture fees from

Radiometer. EKA also reports institutional research funding from Norpharma A/S outside the submitted work as well as lecture fees from Radiometer. ME: Received departmental funding from Merck, Sharp & Dohme Corp outside the submitted work.

Study registration: ClinicalTrials.gov (NCT04248842)

Running head: Agreement between wireless and standard measurements of vital signs in AECOPD

Keywords: Clinical monitoring, Wireless technology, Vital signs, Validation, Chronic Obstructive Pulmonary Disease, Circulatory and respiratory physiology

Word count manuscript: 3,577

Abstract

Objective: Wireless sensors for continuous monitoring of vital signs have potential to improve patient care by earlier detection of deterioration in general ward patients. We aimed to assess agreement between wireless and standard (wired) monitoring devices in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Approach: Paired measurements of vital signs were recorded with 15 minutes intervals for two hours. The primary outcome was agreement between wireless and standard monitor measurements using the Bland and Altman method to calculate bias with 95% limits of agreement (LoA). We considered LoA of less than ±5 beats/min (bpm) acceptable for heart rate (HR), whereas agreement of peripheral oxygen saturation (SpO_2), respiratory rate (RR), and blood pressure (BP) were acceptable if within ±3%-points, ±3 breaths/min (brpm), and ±10 mmHg, respectively.

Main results: 180 sample-pairs of vital signs from 20 with AECOPD patients were recorded for comparison. The wireless vs standard monitor bias was 0.03 (LoA -3.2 to 3.3) bpm for HR measurements, 1.4% (LoA -0.7 to 3.6%) for SpO_2, -7.8 (LoA -22.3 to 6.8) mmHg for systolic BP and -6.2 (LoA -16.8 to 4.5) mmHg for diastolic BP. The wireless vs standard monitor bias for RR measurements was 0.75 (LoA -6.1 to 7.6) brpm.

Significance: Commercially available wireless monitors could accurately measure heart rate in patients admitted with AECOPD compared to standard wired monitoring. Agreement for SpO_2 were borderline acceptable while agreement for RR and BP should be interpreted with caution.

Word count abstract: 240

1. Introduction

Deterioration of patients on general hospital wards often goes unnoticed for prolonged periods of time (Kause *et al* 2004, Duus *et al* 2018). This delay can potentially result in severe adverse outcomes such as cardiac arrest and need for admission to intensive care unit (Sax and Charlson 1987, McQuillan *et al* 1998, McGloin *et al* 1999). These complications occur despite the fact that, in most cases, measurable changes in physiological vital signs, could identify patients at risk and thereby provide opportunity for intervention (Schein *et al* 1990). Studies have shown poor quality of vital sign recordings from intermittent manual observations, which is the current standard monitoring practice in general wards (Difonzo 2019, Taenzer *et al* 2014). For example, significant interobserver variability of up to 6 breaths per minute (brpm) has been reported for respiratory rate (RR) measurements (Lim *et al* 2002, Edmonds *et al* 2002). The quality of manual vital sign recordings may also be limited by non-adherence to protocolled measurement intervals (Petersen *et al* 2014) or missing data (Pedersen *et al* 2018). Automated monitoring with wireless sensors could potentially counter these issues, by providing consistent monitoring either continuous or at a high sampling frequency without patients being connected to bedside monitors with cables limiting mobility.

Patients admitted with acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) carry a high risk of severe complications (Groenewegen *et al* 2003), and frequently have vital sign deviations, which are not detected with standard intermittent monitoring (Elvekjaer *et al* 2020). Therefore, continuous monitoring of vital signs using wireless technology could be particularly beneficial for this patient group. Vital sign changes associated with physiological instability should trigger a more comprehensive clinical evaluation (including arterial blood gas analyses) to assess the patient´s current status and possible requirement for intervention.

Numerous wireless monitoring devices have been marketed in recent years; however, devices need to be thoroughly tested before implementation in clinical practice. Importantly, validation of the accuracy and precision have most often not been performed in real clinical settings, during patient deterioration and/or in specific patient populations, despite European Conformity (CE) and/or Food and Drug Administration (FDA) approval.

The aim of this study was to assess agreement between vital sign measurements derived from wireless and standard wired monitoring systems. We hypothesized that agreement between wireless and standard device measurements would be within clinically acceptable limits of agreement (LoA)

defined as ±5 beats per minute (bpm) for heart rate (HR) and pulse rate (PR), ±3%-points for peripheral oxygen saturation (SpO_2), ±3 brpm for RR and ±10 mmHg for blood pressure recordings.

2. Methods

This observational method comparison study was part of the Wireless Assessment of Respiratory and circulatory Distress (WARD) project and was registered at ClinicalTrials.gov (NCT04248842). An application to the regional ethics committee (H-19023948) was waived and the study was approved by the hospital board of directors as a quality improvement study. All participating patients gave informed consent before inclusion.

2.1. Setting and study population

Twenty patients were enrolled between January and June 2020 at Bispebjerg Hospital in Copenhagen, Denmark. Patients were eligible if they were adults admitted to hospital with AECOPD as admission diagnosis. Exclusion criteria were: Implanted cardioverter defibrillator or pacemaker, severe allergy to plaster/silicone, isolation bed requirement, active treatment withheld, inability to give informed consent or if they were deemed by the investigator or clinical ward staff not to be able to cooperate in wearing the monitoring equipment. Patients were included during admission in the emergency department or pulmonary ward and each data collection period lasted for two hours.

2.2. Data sources

Paired measurements of HR, PR, RR, SpO_2, systolic (SBP) and diastolic blood pressure (DBP) were obtained from both wireless and standard wired monitors with 15-minute intervals. The measurements were performed during a single day between admission and day 6 of hospitalization.

2.2.1. Description of the wireless sensor system

Wireless monitoring consisted of the following devices: Lifetouch patch (Isansys Lifecare, Oxfordshire), Nonin $WristOx_2$ Model 3150 (Nonin Medical Inc., Minnesota, USA) and Meditech BlueBP-05 (Meditech Ltd., Hungary), relayed and displayed via the ISANSYS Patient Gateway. Isansys Lifetouch is a wireless patch for placement on the front left side of the thorax with two electrocardiogram (ECG) electrodes. It collects a single lead ECG continuously (1000 samples per second) and derives HR-data from the intervals between heart beats (R-peak intervals). The RR measurements in the Lifetouch sensor is derived from calculations of changes in the ECG signal (QRS complex amplitude) during the respiratory cycle due to changing impedance of the thoracic cavity. The HR and RR (sampled at one per minute) where automatically transmitted via Bluetooth to a bedside monitor from where values were recorded.

Nonin WristOx$_2$ 3150 is a wrist-born fingertip pulse oximeter with a short cable running between a soft finger sensor (8000SM-WO2) and the wrist unit with a display. It measures SpO_2 and PR sampled at 1 Hz and averaged at 4 beats. The Meditech BlueBP-05 is a compact device for non-invasive oscillometric blood pressure measurements with an upper arm cuff according to patient arm circumference (small, normal or large). It can be programmed for automatic intermittent monitoring and it stores measurements for later wireless transfer via Bluetooth.

2.2.2. Description of the standard monitoring system

The monitoring system for comparison was a standard bedside wired monitor (IntelliVue X2 connected to MP30 as host monitor, Philips, Amsterdam, The Netherlands) currently clinical standard at Bispebjerg Hospital. The system uses ECG leads (Philips M1672A) to measure HR and RR. HR measurements are derived from the ECG-signal and computed by averaging the 12 most recent R-peak intervals. RR measurements are derived from changes in thoracic impedance between two ECG electrodes producing a respiratory waveform. A fingertip pulse oximetry sensor (Philips M1191BL) was connected to the IntelliVue X2 for measuring SpO_2 and PR averaged at 10 seconds. A standard non-invasive oscillometric blood pressure cuff with size according to patient arm circumference (Philips M1573/M4555/M4557) was used to measure the blood pressure.

2.3. Monitoring procedure and signal analysis

Wireless and standard monitoring sensors were used according to device manuals and the data collection was completed with a study investigator at the bedside during measurements. Patient´s arm circumference was measured, and the appropriate blood pressure cuff size was chosen. Measurements were performed in a clinical stable period with a minimum of movement and conversation. The wireless measurements of HR and RR were performed by recording the value from the monitor (sampled at one per minute derived from the last 60 seconds) at the time when the value changed while simultaneously recording the value from the standard device. For RR measurements, we also compared values from the wireless and standard devices with manual count by direct observation (DO) of respirations. Respirations were counted for one minute by inspection of breathing movements. If breathing was not clearly visible, auscultation with a stethoscope applied in a single position was used. Recordings were performed as unobtrusive as possible with patients being unaware of ongoing measurements, and all observations were performed with patients breathing spontaneously. Automatic (wireless and standard) measurements of RR were performed simultaneous to DO. Pulse oximetry monitoring was performed by concurrent recordings of SpO_2 and PR from the two devices with the sensors applied to different fingers on the same hand.

The blood pressure was measured on the same arm with 2 minutes resting phase between measurements.

2.4. Outcomes and statistical analysis

The sample size by convenience was set at 20 patients each with 9 measurements per modality (two hours with measurements every 15 min), for a total of 180 sample-pairs for each parameter. The primary outcome was bias (mean difference) and 95% LoA between the wireless and standard devices. LoA were calculated summing the between subjects and within subjects variances to account for repeated measurements of the same individual as suggested by Bland and Altman (Bland and Altman 2007) and confidence interval estimation for LoA was based on the method of variance estimates recovery (MOVER) (Zou 2013). Results were plotted with standard Bland-Altman plots using statistical software R (v.3.6.2). All other analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Root mean square deviation (RMSD), a measure which reports accuracy as a function of both bias and precision, was also calculated. Percentage error was calculated as 1.96 × SD of bias / mean of the reference data. We considered HR and PR to be clinically acceptable if within ±5 bpm whereas measurements of SpO_2, RR and SBP/DBP were acceptable if within ±3%-points, ±3 brpm and ±10 mmHg, respectively.

3. Results

One hundred eight patients with a confirmed admission diagnosis of AECOPD were screened for eligibility, of which 20 patients were enrolled with 10 included in the emergency department and 10 in the pulmonary ward (figure 1). The main reasons for exclusion were lack of monitoring equipment and patients who had previously been enrolled. Ten patients were male, median age was 73 years and median BMI was 24 kg/m^2 (table 1).

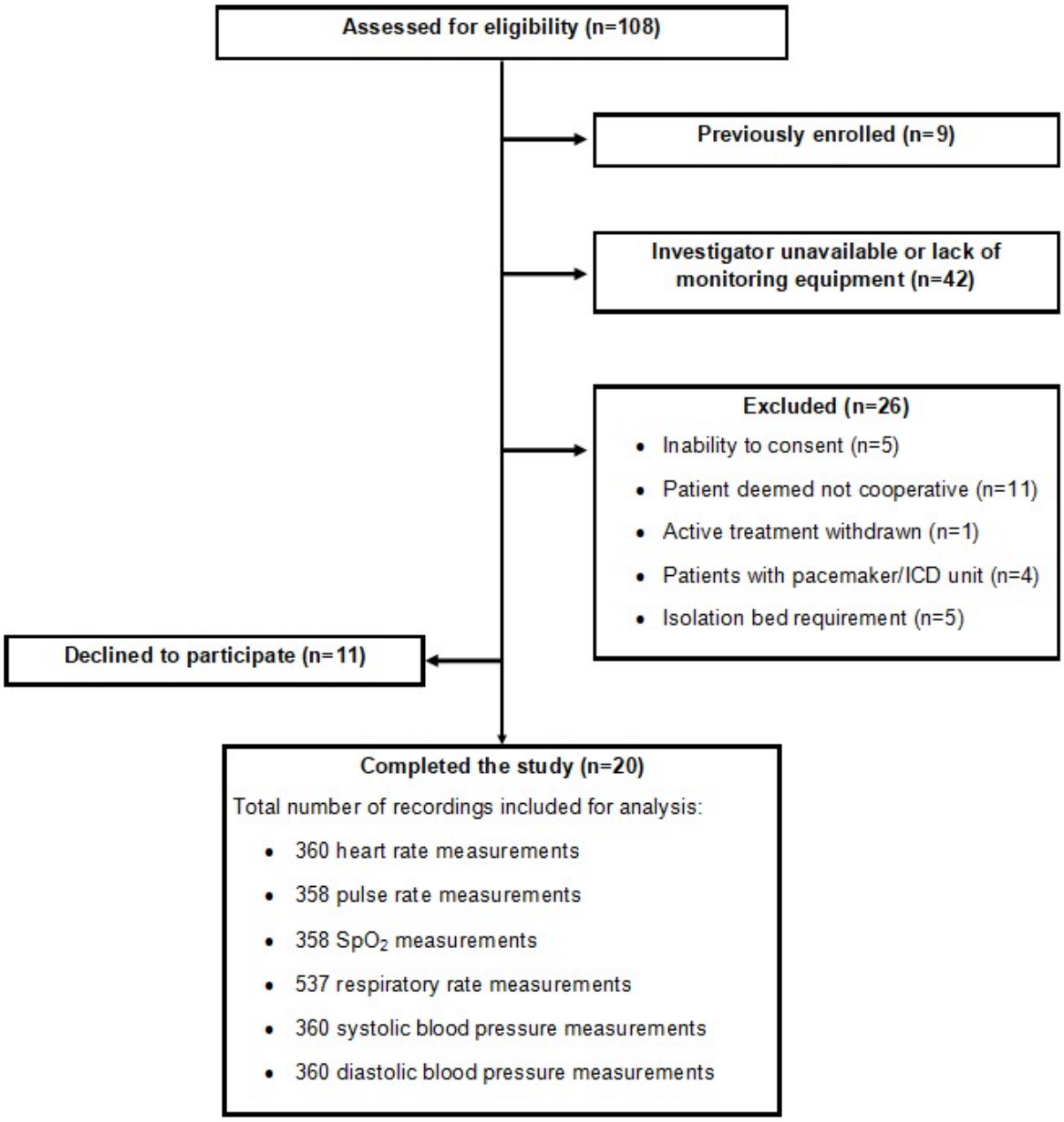

Figure 1. Flow chart of study base selection. ICD, implantable cardioverter defibrillator; SpO_2, peripheral oxygen saturation.

Table 1. Baseline characteristics

Parameter	n = 20
Sex, male / female	10 / 10
Age, years	73 [64-78]
BMI, kg/m^2	24 [21-29]
Smoking history, never / previously / current	1 / 14 / 5
Lifetime tobacco exposure, pack-years	43 [36-51]
Alcohol consumption[a]	3 (15%)
Medical history (age-adjusted Charlson comorbidity index)	
CCI score 2-3 / 4-5 / 6-7 / 8+	4 / 9 / 5 / 2
Classification of COPD	
Spirometry available[b]	18 (90%)
FEV1/FVC	0.5 [0.43-0.58]
GOLD grade, 1 / 2 / 3 / 4	1 / 6 / 7 / 4
mMRC dyspnea grade, 0-1 / 2 / 3 / 4	2 / 7 / 8 / 3
Baseline measurements at inclusion	
Early Warning Score	4 [3-7]
SpO_2, %	94 [90-96]
Oxygen supplementation, patients (n)	14 (70%)
Oxygen supplementation, liters/min	2 [1.5-3]
Heart rate, beats per minute	91 [78-100]
Respiratory rate, breaths per minute	21 [18-24]
Systolic blood pressure, mmHg	130 [114-144]
Hemoglobin, mmol/L	8.8 [8.1-10.0]
White blood count, 10^9/L	11.5 [8.6-15.1]
C-Reactive Protein, mg/L	12 [3-43]
Creatinine, µmol/L	72 [62-85]

Values are number (percentage) or median [interquartile range]. BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnea scale; SpO_2, peripheral oxygen saturation. [a]Current alcohol consumption of more than recommended by the Danish Health Authority, which is 24 g/day for men or 12 g/day for women. [b]Spirometry values as recorded in electronic health records, which did not specify pre- or post-bronchodilator values consistently.

3.1. Agreement between heart rate and pulse rate measurements

The HR dataset consisted of 180 sample-pairs whereas the PR dataset included 179 sample-pairs (one PR measurement was missing due to technical problems). The median HR for both standard and wireless measurements was 96 bpm with interquartile range (IQR) of 83 to 105 bpm. Overall,

98% of HR-measurements and 99% of PR-measurements were within ±5 bpm (acceptable limit) when comparing values from wireless and standard wired devices. Bias of HR measurements was 0.03 bpm with LoA of -3.2 to 3.3 bpm (figure 2a). The percentage error for HR measurements was 1% and the RMSD 1.7 bpm. The bias for PR measurements was -0.1 bpm with LoA of -3.1 to 3.0 (figure 2b).

3.2. Agreement between measurements of peripheral oxygen saturation

The SpO_2 dataset consisted of 179 sample-pairs (one SpO_2 measurement was missing due to technical problems). The median SpO_2 from the standard device was 92% (IQR 90-94) whereas the median SpO_2 from the wireless device was 90% (IQR 89-92). Overall, 98% of SpO_2 measurements were within the 3%-point acceptable limit when comparing values from the two devices. However, the recording from the wireless device was at least one percent-point lower than the standard device value in 87% of SpO_2 measurements, whereas 8% were numerically equal and 5% were at least one percent-point higher than the standard device value. The bias between SpO_2 measurements was 1.4% with LoA of -0.7 to 3.6% (figure 2c). The percentage error was 1% with RMSD of 1.8%.

3.3. Agreement between respiratory rate measurements

Three different methods (standard, wireless and DO) for measuring the respiratory rate were compared in the analysis (figure 2d-f). One set of measurements was missing due to technical problems and the dataset therefore consisted of 3 × 179 data points. The median RR was 22 brpm (IQR 19-25), 21 brpm (IQR 19-23) and 22 brpm (IQR 20-25) from standard, wireless and DO measurements, respectively. Overall, 77% of RR measurements were within the acceptable limit of ±3 brpm, when comparing values from wireless and standard devices. The bias between standard and wireless RR measurements was 0.75 brpm (LoA -6.1 to 7.5) and the bias between DO and wireless RR measurements was 1.02 (LoA -5.0 to 7.0).

3.4. Agreement between blood pressure measurements

The BP dataset consisted of 180 data points of SBP and DBP measurements and the standard device SBP was median 135 mmHg (IQR 97-156) as compared to 142 mmHg (IQR 101-162) with the wireless device. Overall, 62% of SBP measurements and 81% of DBP measurements were within 10 mmHg (acceptable limit) when comparing values from the wireless and standard device. The median standard device DBP was 71 mmHg (IQR 62-81) and the median wireless DBP was 78 mmHg (IQR 68-88). The bias between standard and wireless SBP was -7.8 mmHg with LoA of -22.3 to 6.8 mmHg (figure 2g).

Table 2. Summary of agreement between standard and wireless devices

	Heart rate (bpm)	Pulse rate (bpm)	Respiratory rate (breaths per min)			SpO_2 (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
	Standard vs Wireless	Standard vs Wireless	Standard vs Wireless	DO vs Standard	DO vs Wireless	Standard vs Wireless	Standard vs Wireless	Standard vs Wireless
Range of recordings	62 - 145	41 - 132	12 - 33	12 - 33	12 - 31	82 - 98	97 - 207	47 - 111
Bias (standard deviation)	0.03 (0.4)	-0.1 (0.5)	0.75 (2.7)	0.28 (1.2)	1.02 (2.6)	1.4 (0.6)	-7.8 (3.7)	-6.2 (2.9)
Lower LoA (95% CI)	-3.2 (-3.7 to -2.9)	-3.1 (-2.7 to -3.5)	-6.1 (-7.9 to -4.2)	-4.0 (-4.7 to -3.3)	-5.0 (-6.8 to -3.1)	-0.7 (-1.2 to -0.4)	-22.3 (-25.1 to -20.2)	-16.8 (-18.6 to -15.0)
Upper LoA (95% CI)	3.3 (2.9 to 3.7)	3.0 (2.6 to 3.4)	7.5 (6.0 to 9.9)	4.5 (3.8 to 5.3)	7.0 (5.4 to 9.4)	3.6 (3.2 to 4.1)	6.8 (4.7 to 9.6)	4.5 (2.7 to 6.3)
Percentage error	1%	1%	24%	11%	23%	1%	5%	8%
Root mean square deviation	1.7	1.6	3.5	2.2	3.2	1.8	10.7	8.2

Negative numbers indicate that the wireless monitor overestimates measurement values when compared to the standard monitor. Bpm, beats per minute; DO, direct observation; LoA, limits of agreement; SpO_2, peripheral oxygen saturation.

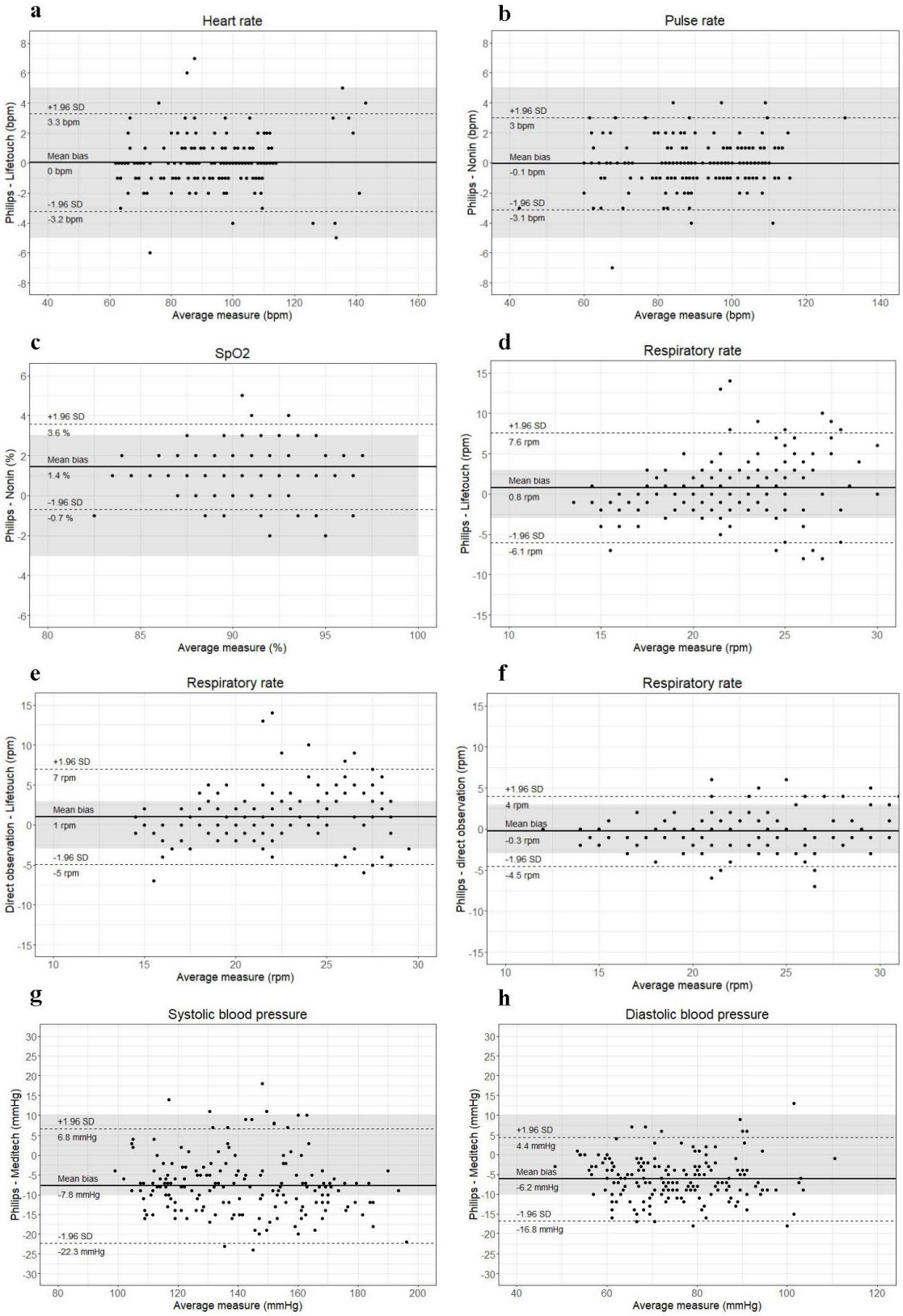

Figure 2. Bland-Altman plots of agreement between measurements of heart rate (figure 2a), pulse rate (figure 2b), peripheral oxygen saturation (figure 2c), respiratory rate (figure 2d-f), systolic blood pressure (figure 2g) and diastolic blood pressure (figure 2h). Solid line = bias; dotted lines = upper and lower 95% limits of agreement (LoA). The shaded area shows the predefined clinically acceptable LoA. Wireless measurements were performed with Isansys Lifetouch (heart rate, respiratory rate), Nonin WristOx$_2$ 3150 (pulse rate, SpO_2) and Meditech BlueBP-05 (blood pressure). Standard (wired) measurements were performed with the Phillips IntelliVue X2 system. bpm, beats per minute; brpm, breaths per minute; SpO_2, peripheral oxygen saturation.

4. Discussion

Agreement between vital sign measurements using a wireless sensor system and a standard monitoring system was within predefined acceptable limits for HR in patients admitted with AECOPD. SpO_2-values from the wireless device were within the acceptable limit of ±3%-points in 98% of measurements, but SpO_2-values was underestimated by 1.4%-point on average. RR measurements had low bias when comparing wireless and standard device measurements, but LoA was -6.1 to 7.5 brpm and thus wider than the clinically acceptable limit of ±3 brpm. The wireless device overestimated blood pressure measurements by 8 mmHg, and LoAs exceeded the clinically acceptable limit of 10 mmHg.

4.1. Comparison with previous research

The wireless patch used in the current study (Isansys Lifetouch) was also used in two recent studies involving patients with acute decompensation of cirrhosis (Jansen *et al* 2019) and hospitalized children (Duncan *et al* 2020). In the latter study, the Nonin $WristOx_2$ was also used for continuous pulse oximetry. However, agreement with other monitoring modalities was not reported in these studies.

In general, clinical validation studies of wireless devices for vital sign monitoring are few and difficult to compare due to different clinical settings, study populations, methodologies, and specific devices being investigated (Leenen *et al* 2020, Saugel *et al* 2020). Also, guidelines for acceptable accuracy and precision in studies of wireless monitoring are not universally agreed. For example, a recent systematic review (Leenen *et al* 2020) of continuous vital sign monitoring with wireless devices generally categorized wider LoAs as clinically acceptable than we did in our study. For SpO_2-validation studies, they defined acceptable bias of 3% and LoA of ±5%. Thus, our reported SpO_2-agreement (bias of 1.4%-point and LoA of -0.7 to 3.6%) would be acceptable by their criteria. In addition, we found a RMSD for SpO_2-measurements of 1.8% which is considered acceptable by most accuracy standards (e.g. the standard used by FDA), however this was not our primary outcome. Our results confirm the variable accuracy of vital sign measurements reported in other studies. In particular, several studies using both direct observation and wireless devices have reported difficulty in obtaining precise RR measurements (Breteler *et al* 2018, Weenk *et al* 2017, Amirav *et al* 2018, Edmonds *et al* 2002, Lim *et al* 2002, Brabrand *et al* 2018). Interestingly, the majority of the RR data points that fell outside confidence bounds in the Bland-Altman plot (figure 2d-e) were in the upper range of average RR suggesting inconsistent variability in the data which may introduce proportional bias (Montenij *et al* 2016). Thus, wireless RR measurements seems to

be less precise during tachypnea (RR > 20 brpm), which is a symptom commonly associated with AECOPD and the absolute values of RR derived from wireless monitoring should therefore be interpreted with caution in this clinical setting. On the other hand, a wireless warning system may alert staff in any situation with RR > 20 brpm, and the absolute value may thus be of less importance.

Hernandez-Silveira et al. compared RR- and HR-recordings from a different wearable patch sensor (SensiumVitals, Sensium Healthcare Ltd, Abingdon, UK) with measurements using the Phillips IntelliVue MP30 that was also used for comparison of measurements in the current study (Hernandez-Silveira *et al* 2015). In the clinical part of the study, 41 general ward patients with comorbidities were monitored for up to two hours with recordings every 2 minutes. Acceptable agreement of HR-measurements with bias of 0.1 bpm was reported. For RR recordings, a small bias of 0.2 brpm was also reported, but with relatively wide LoA of -8.1 to 8.5 brpm which is comparable to our findings. In contrast, a study with RR monitoring using pulse oximeter waveforms to derive the respiratory rate, with end-tidal CO_2-based monitoring as reference, reported more promising results with bias of 0.07 brpm and LoA of -3.84 to 3.97 brpm (Bergese *et al* 2017). A recently published clinical validation study in the postoperative setting (Breteler *et al* 2020), compared 4 different wireless sensors (SensiumVitals [Sensium Healthcare Ltd., UK], Healthpatch [VitalConnect, USA], EarlySense [EarlySense Ltd., Israel] and Masimo Radius-7 [Masimo Corporation, USA]) for measurement of HR and RR. Again, all sensors were accurate for HR. For RR measurements, bias was low for most sensors (although the HealthPatch overestimated the RR by 4.4 brpm), however, LoA was wider than ±5 brpm for all sensors indicating relatively poor precision. Interestingly, the study also included an analysis of the clinical relevance of measurement differences using error-grid to provide information about the consequences of incorrect treatment decisions triggered by measurements with the devices. This so-called *clinical* accuracy was nearly 100% for all sensors. A non-contact HR and RR monitoring method based on a computer vision system was evaluated in a study involving preterm infants (Gibson *et al* 2019). The system had previously been demonstrated to be accurate in a controlled setting among adult participants (Al-Naji *et al* 2019, Al-Naji and Chahl 2017), but the clinical study on neonates showed unacceptable results highlighting the importance of testing in various clinical settings.

4.2. Strengths and limitations

The primary strength of this study is measurements performed in a real-world clinical acute care setting in a highly relevant patient group. The clinical situation with respiratory distress associated

with AECOPD often resulted in deviating vital signs that may challenge measurement accuracy and the reported agreement between devices therefore reflects a situation with some degree of abnormal physiology. Many validation studies have been conducted in healthy volunteers, which may introduce a falsely high accuracy and precision. Also, measurements were performed by investigators, who inspected the signal quality from recordings throughout the monitoring period.

The study also has important limitations: When evaluating the accuracy of a wireless device, the limitations of the reference method must be considered, especially when this is not considered a gold standard. The most widely accepted method for evaluating pulse oximeter accuracy is by direct comparison of SpO_2 with arterial oxygen saturation, which was not available in our study. Estimation of arterial oxygen saturation from pulse oximetry has several limitations and the performance of any pulse oximeter is subject to both biological and sensor variability (Louie *et al* 2018). Sensor accuracy is mainly determined by the wavelength of the light emitting diode in the sensor, which varies across manufacturers (Nitzan *et al* 2014). The pulse oximeters compared in this study are both FDA-approved and CE-marked. Capnography is usually considered the gold standard for RR monitoring; however, it has several disadvantages in non-intubated patients (e.g. displacing of its nasal cannula) and is rarely used for continuous monitoring in general wards. Wireless monitoring was therefore compared with wired measurements of RR using a standard impedance technique device which is the current bedside routine standard for continuous RR monitoring. RR measurements through manual count (DO) is also widely used and we therefore chose this method as a second reference. Most validation studies of BP devices are conducted in a controlled (non-clinical) setting which is advantageous when measurements are performed in accordance with international requirements of validation protocols (Stergiou *et al* 2018). Moreover, a mercury sphygmomanometer or invasive blood pressure monitoring are usually recommended as reference for BP measurements, but this was not feasible in the acute-care clinical setting.

Another limitation is the fact that we did not assess device performance during motion as data were obtained during supervised conditions with a minimum of movement. All measurements could be influenced by motion artefacts (e.g. due to movement, talking, coughing or displacement of the pulse oximeter) and this is relevant when devices are intended for use as a continuous monitoring method. Further studies must describe if adjustments for ambulating patients is needed.

We included a subset of patients from a larger research project; however, we do not expect this to introduce major selection bias as the primary reasons for exclusion were investigators unavailable and lack of monitoring equipment. Also, a formal power calculation was not feasible due to the lack

of preexisting data from the wireless monitoring devices. Therefore, we enrolled 20 patients with AECOPD (each with repeated measurements) as our convenience sample and the observed results may not be generalizable to other patient populations.

4.3. Implications and future research

Remote monitoring systems utilize wireless non-invasive technology with wearable sensors that continuously track physiological variables. A major advantage of continuous vital signs monitoring is the inherent opportunity to analyze trends in recorded physiological parameters. More accurate prognostic information may be derived from such trend analysis than from EWS data derived from absolute values of spot measurements (Churpek *et al* 2016). This may be of particular interest in AECOPD patients with chronic deviations of vital signs, i.e. hypoxemia and tachypnea. Correspondingly, the use of machine-learning techniques on physiological data may become of significant value in the future to incorporate smart alarm algorithms. Importantly, such algorithms should also increase specificity of alarms and thereby decrease false-alarm rates. More studies are needed to determine which physiological parameters that are most predictive of clinical complications in different patient categories. It should be emphasized that even with a completely operational remote vital sign monitoring system, other markers of clinical deterioration (e.g. changes in blood pH-levels, respiratory fatigue etc.) are important and needs to be repeatedly evaluated as part of the clinical assessment. Method comparison studies using Bland-Altman analysis can provide a reliable measure of bias and precision of spot measurements, however, they do not evaluate the trending ability of the monitoring device. Thus, future validation studies of monitoring devices should incorporate statistical approaches with trend analyses.

5. Conclusion

Monitoring of heart rate and pulse rate were accurate and precise in patients with AECOPD when comparing wireless and wired devices. Agreement between measurements of SpO_2 were borderline acceptable, whereas measurements of respiratory rate and blood pressure should be interpreted with caution.

References

Al-Naji A and Chahl J 2017 Noncontact Heart Activity Measurement System Based on Video Imaging Analysis *Int. J. Pattern Recognit. Artif. Intell.* **31**

Al-Naji A, Chahl J and Lee S H 2019 Cardiopulmonary signal acquisition from different regions using video imaging analysis *Comput. Methods Biomech. Biomed. Eng. Imaging Vis.* **7** 117–31 Online: https://www.tandfonline.com/doi/abs/10.1080/21681163.2018.1441075

Amirav I, Masumbuko C K and Hawkes M T 2018 Poor agreement and imprecision of respiratory rate measurements in children in a low-income setting *Am. J. Respir. Crit. Care Med.* **198** 1462–3 Online: https://pubmed.ncbi.nlm.nih.gov/30192633/

Bergese S D, Mestek M L, Kelley S D, McIntyre R, Uribe A A, Sethi R, Watson J N and Addison P S 2017 Multicenter study validating accuracy of a continuous respiratory rate measurement derived from pulse oximetry: A comparison with capnography *Anesth. Analg.* **124** 1153–9

Bland J M and Altman D G 2007 Agreement between methods of measurement with multiple observations per individual *J. Biopharm. Stat.* **17** 571–82

Brabrand M, Hallas P, Folkestad L, Lautrup-Larsen C H and Brodersen J B 2018 Measurement of respiratory rate by multiple raters in a clinical setting is unreliable: A cross-sectional simulation study *J. Crit. Care* **44** 404–6 Online: https://doi.org/10.1016/j.jcrc.2017.12.020

Breteler M J M, Huizinga E, Van Loon K, Leenen L P H, Dohmen D A J, Kalkman C J and Blokhuis T J 2018 Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: A clinical validation study *BMJ Open* **8** e020162

Breteler M J M, KleinJan E J, Dohmen D A J, Leenen L P H, van Hillegersberg R, Ruurda J P, van Loon K, Blokhuis T J and Kalkman C J 2020 Vital signs monitoring with wearable sensors in high-risk surgical patients a clinical validation study *Anesthesiology* 424–39

Churpek M M, Adhikari R and Edelson D P 2016 The value of vital sign trends for detecting clinical deterioration on the wards *Resuscitation* **102** 1–5 Online: http://www.ncbi.nlm.nih.gov/pubmed/26898412

Difonzo M 2019 Performance of the Afferent Limb of Rapid Response Systems in Managing Deteriorating Patients: A Systematic Review *Crit. Care Res. Pract.* **2019**

Duncan H P, Fule B, Rice I, Sitch A J and Lowe D 2020 Wireless monitoring and real-time adaptive predictive indicator of deterioration *Sci. Rep.* **10** 1–8 Online: https://doi.org/10.1038/s41598-020-67835-4

Duus C L, Aasvang E K, Olsen R M, Sørensen H B D, Jørgensen L N, Achiam M P and Meyhoff C S 2018 Continuous vital sign monitoring after major abdominal surgery—Quantification of micro events *Acta Anaesthesiol. Scand.* **62** 1200–8

Edmonds Z V., Mower W R, Lovato L M and Lomeli R 2002 The reliability of vital sign measurements *Ann. Emerg. Med.* **39** 233–7 Online: https://pubmed.ncbi.nlm.nih.gov/11867974/

Elvekjaer M, Aasvang E K, Olsen R M, Sørensen H B D, Porsbjerg C M, Jensen J U, Haahr-Raunkjær C and Meyhoff C S 2020 Physiological abnormalities in patients admitted with acute exacerbation of COPD : an observational study with continuous monitoring *J. Clin. Monit. Comput.* **34** 1051–60 Online: https://doi.org/10.1007/s10877-019-00415-8

Gibson K, Al-Naji A, Fleet J, Steen M, Esterman A, Chahl J, Huynh J and Morris S 2019 Non-contact heart and respiratory rate monitoring of preterm infants based on a computer vision system: a method comparison study *Pediatr. Res.* **86** 738–41 Online: http://dx.doi.org/10.1038/s41390-019-0506-5

Groenewegen K H, Schols A M and Wouters E F M 2003 Mortality and Mortality-Related Factors After Hospitalization for Acute Exacerbation of COPD *Chest* **124** 459–67

Hernandez-Silveira M, Wieczorkowski-Rettinger K, Ang S and Burdett A 2015 Preliminary assessment of the SensiumVitals®: A low-cost wireless solution for patient surveillance in the general wards *Annu Int Conf IEEE Eng Med Biol Soc* pp 4931–7

Jansen C, Chatterjee D A, Thomsen K L, Al-Kassou B, Sawhney R, Jones H, Gallego-Leon A, Lehmann J, Pohlmann A, Nickenig G, Strassburg C P, Andrié R, Jalan R, Linhart M, Trebicka J and Mookerjee R P 2019 Significant reduction in heart rate variability is a feature of acute decompensation of cirrhosis and predicts 90-day mortality *Aliment. Pharmacol. Ther.* **50** 568–79

Kause J, Smith G, Prytherch D, Parr M, Flabouris A, Hillman K, Intensive Care Society (UK) and Australian and New Zealand Intensive Care Society Clinical Trials Group 2004 A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia

and New Zealand, and the United Kingdom--the ACADEMIA study. *Resuscitation* **62** 275–82 Online: http://linkinghub.elsevier.com/retrieve/pii/S0300957204002473

Leenen J P L, Leerentveld C, van Dijk J D, van Westreenen H L, Schoonhoven L and Patijn G A 2020 Current evidence for continuous vital signs monitoring by wearable wireless devices in hospitalized adults: Systematic review *J. Med. Internet Res.* **22** e18636

Lim W S, Carty S M, Macfarlane J T, Anthony R E, Christian J, Dakin K S and Dennis P M 2002 Respiratory rate measurement in adults - How reliable is it? *Respir. Med.* **96** 31–3

Louie A, Feiner J R, Bickler P E, Rhodes L, Bernstein M and Lucero J 2018 Four types of pulse oximeters accurately detect hypoxia during low perfusion and motion *Anesthesiology* **128** 520–30 Online: https://pubmed.ncbi.nlm.nih.gov/29200008/

McGloin H, Adam S K and Singer M 1999 Unexpected deaths and referrals to intensive care of patients on general wards. Are some cases potentially avoidable? *J. R. Coll. Physicians Lond.* **33** 255–9

McQuillan P, Pilkington S, Allan A, Taylor B, Short A, Morgan G, Nielsen M, Barrett D, Smith G and Collins C H 1998 Confidential inquiry into quality of care before admission to intensive care *BMJ* **316** 1853–8

Montenij L J, Buhre W F, Jansen J R, Kruitwagen C L and De Waal E E 2016 Methodology of method comparison studies evaluating the validity of cardiac output monitors: A stepwise approach and checklist *Br. J. Anaesth.* **116** 750–8

Nitzan M, Romem A and Koppel R 2014 Pulse oximetry: Fundamentals and technology update *Med. Devices Evid. Res.* **7** 231–9

Pedersen N E, Rasmussen L S, Petersen J A, Gerds T A, Østergaard D and Lippert A 2018 A critical assessment of early warning score records in 168,000 patients *J. Clin. Monit. Comput.* **32** 109–16

Petersen J A, Mackel R, Antonsen K and Rasmussen L S 2014 Serious adverse events in a hospital using early warning score - What went wrong? *Resuscitation* **85** 1699–703 Online: http://dx.doi.org/10.1016/j.resuscitation.2014.08.037

Saugel B, Hoppe P and Khanna A K 2020 Automated continuous noninvasive ward monitoring validation of measurement systems is the real challenge *Anesthesiology* 407–10

Sax F L and Charlson M E 1987 Medical patients at high risk for catastrophic deterioration *Crit. Care Med.* **15** 510–5

Schein R M H, Hazday N, Pena M, Ruben B H and Sprung C L 1990 Clinical antecedents to in-hospital cardiopulmonary arrest *Chest* **98** 1388–92

Stergiou G S, Alpert B S, Mieke S, Wang J and O'Brien E 2018 Validation protocols for blood pressure measuring devices in the 21st century *J. Clin. Hypertens.* **20** 1096–9

Taenzer A H, Pyke J, Herrick M D, Dodds T M and McGrath S P 2014 A comparison of oxygen saturation data in inpatients with low oxygen saturation using automated continuous monitoring and intermittent manual data charting *Anesth. Analg.* **118** 326–31

Weenk M, van Goor H, Frietman B, Engelen L J, van Laarhoven C J, Smit J, Bredie S J and van de Belt T H 2017 Continuous Monitoring of Vital Signs Using Wearable Devices on the General Ward: Pilot Study. *JMIR mHealth uHealth* **5** e91 Online: http://www.ncbi.nlm.nih.gov/pubmed/28679490

Zou G Y 2013 Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual *Stat. Methods Med. Res.* **22** 630–42

Title: Clinical impact of vital sign abnormalities in patients admitted with acute exacerbation of chronic obstructive pulmonary disease – an observational study using continuous wireless monitoring

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ABSTRACT

Background: Early detection of abnormal vital signs is critical for timely management of acute medical patients in hospital wards. Continuous wireless monitoring may improve this, but the relation to clinical outcomes is not well described. We aimed to assess the association between preceding vital sign abnormalities and serious adverse events (SAE) in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (COPD).

Methods: In this observational study, 200 patients were wirelessly and continuously monitored with peripheral oxygen saturation, heart rate and respiratory rate as well as non-invasive blood pressure during the first 4 days after admission for acute exacerbation of COPD. The primary outcome was SAE at 30 days and the physiological data were analyzed for preceding abnormalities of respiratory and circulatory vital signs. Data were presented as the mean cumulative duration of vital sign abnormalities per 24 hours and analyzed using the Wilcoxon rank sum test.

Results: SAE during ongoing continuous monitoring occurred in 50 patients (25%), whereas 31 patients (16%) experienced SAE after the monitoring period within 30 days after inclusion. Patients suffering SAE during the continuous monitoring period had on average 455 minutes (SD 413) per 24 hours of any vital sign abnormality compared with 292 minutes (SD 246) in patients without SAE, $p = 0.08$, mean difference 163 minutes [95% CI 61 – 265]. Mean duration of bradypnea (respiratory rate < 11 min^{-1}) was 48 minutes (SD 173) compared with 30 minutes (SD 84) in patients without SAE, $p = 0.01$. Duration and frequency of other vital sign abnormalities were not significantly associated with SAE during or after monitoring.

Conclusion: Cumulated duration of physiological abnormalities was substantial in patients admitted with acute exacerbation of COPD, especially in patients with SAEs, including duration of bradypnea.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major and increasing cause of morbidity and the third leading cause of death worldwide.[1] Patients with COPD may suffer episodes of acute exacerbations (AECOPD) with profound clinical implications including approximately 115,000 and 1.2 million emergency hospitalizations per year in the UK and US.[2,3] Despite adequate care in hospital wards with standardized intermittent observations and treatments (bronchodilating agents, titrated oxygen treatment, intravenous drugs, and non-invasive ventilation), patients may rapidly require escalation of care. One-tenth of patients hospitalized with AECOPD are admitted to the intensive care unit (ICU) and one out of twenty end up requiring mechanical ventilation.[4] Early recognition and timely response are critical to rescue deteriorating patients. Physiological changes with abnormal vital signs often precede adverse events by hours.[5–7] Standard monitoring includes manual vital sign recordings at pre-specified intervals, usually starting at 12 hours and with decreasing intervals in case of abnormal values.[8] However, clinical deterioration may occur undetected between routine ward rounds potentially resulting in delay in critical diagnostics and interventions. Patients with AECOPD have a high rate of vital sign deviations that are usually not detected by intermittent standard monitoring, e.g. episodes of $SpO_2 < 80\%$ occurring in 63% of patients.[9] Wearable devices can monitor several physiological parameters continuously and this may improve patient care by allowing physiological deterioration to be detected earlier.[10]

New clinical support systems can alert staff of abnormal vital signs, but it is of paramount importance that these alerts only are given for deviations related to relevant upcoming or present complications. The association between these physiological abnormalities derived from continuous monitoring and subsequent serious adverse events (SAE) is not described, hindering assessment of the relevance of deviations and subsequently thresholds for alerts.

This study aimed to assess the association between abnormalities in continuously monitored vital signs and subsequent clinical complications in patients admitted with AECOPD. We hypothesized that the duration of abnormal vital signs would be longer in the time before SAE than in patients without SAE.

2 Methods

This prospective observational study was approved by the regional ethics committee (protocol number H-18026653), Danish Data Protection Agency (2012-58-0004) and registered at http://clinicaltrials.gov (NCT03660501). Written informed consent was obtained from all participating patients. The study is part of the Wireless Assessment of Respiratory and circulatory Distress (WARD) project, a collaboration between Bispebjerg and Frederiksberg Hospital, Rigshospitalet and the Technical University of Denmark. The results of the WARD project on surgical patients are described elsewhere (NCT03491137).

Patient eligibility

Patients were eligible if they were adults admitted to emergency departments or pulmonary wards (Bispebjerg Hospital or Gentofte Hospital in Copenhagen, Denmark) with AECOPD as admission diagnosis. This diagnosis (regardless of previous lung function) had to be sustained in the patient record at the time of inclusion. Eligibility also required an expected admittance longer than 24 hours and the possibility of an investigator to include the patient within 24 hours from admission. Patients were excluded if they were not expected to be cooperative to wear the monitoring equipment or if they were unable to give informed consent. Other exclusion criteria were: Implanted cardioverter defibrillator or pacemaker, severe allergy for plaster/silicone, and if patients were withheld active treatment.

Monitoring

Continuous monitoring was completed with the WARD projects body-sensor network: Isansys Lifetouch (Isansys Lifecare, Oxfordshire), Nonin WristOx 3150 (Nonin Medical inc., Minnesota, USA), and Meditech BlueBP-05 (Meditech Ltd., Hungary). Isansys Lifetouch is a wireless patch for placement on the front left side of the thorax with two electrocardiogram electrodes. It collects the

heart rate (HR) continuously and respiratory rate (RR) with a one-minute sampling frequency derived from automatic detection of the QRS complex and R-peaks in the single-lead electrocardiogram, digitized at 1000 samples per second. Nonin WristOx 3150 is a wearable fingertip pulse oximeter measuring peripheral oxygen saturation (SpO_2) with a sampling frequency of one per second. SpO_2-data included both raw values and a calculated average per minute of at least 45 reliable measurements. The Meditech BlueBP-05 is a compact, wireless device for intermittent non-invasive oscillometric measurements of blood pressure. The device was programmed to start blood pressure measurements every 30 minutes during daytime and every 60 minutes during night-time. Data from all three devices were transmitted through Bluetooth to a bedside gateway and from the gateway via secured hospital wi-fi connection to a hospital server. HR-, RR- and blood pressure data were automatically stored in devices when a patient was out of Bluetooth range from the gateway, enabling later transfer of data when Bluetooth connection was re-established. SpO_2-data were not stored when patients were out of Bluetooth range. Clinical ward staff observed and recorded the patient's vital signs according to the hospital´s usual standard of care and were (like patients) blinded to values from the continuous monitoring equipment. In the Capital Region of Denmark, an early warning score (EWS) system is used for detection of clinical deterioration and initiation of a timely and relevant clinical response.[11] Continuous monitoring was initiated after informed consent and continued for 96 hours if the patient was hospitalized, corresponding to the battery time of the Lifetouch patch. Study personnel attended patients daily to change device batteries when needed.

Data analysis

Exposure variables were duration and frequency of predefined abnormalities of respiratory and circulatory vital signs with *a priori* defined cut-off values. We analyzed the data for frequency of events and cumulative duration outside thresholds preceding clinical events. In patients with COPD, due to chronic hypoxia and the risk of hypercapnic respiratory failure, a target SpO_2 range of 88-92%

is recommended[12] and hypoxemia was therefore defined at three cut-offs (SpO_2 < 88%, < 85%, and < 80%). We pre-defined criteria for the duration of physiological abnormalities according to the severity of the different vital sign deviations: I.e. SpO_2 < 88% had to be sustained for 10 minutes to count in the frequency analysis whereas the duration criteria for SpO_2 < 80% was one minute. Severe hypertension was defined as events of systolic blood pressure (SBP) > 180 mmHg and hypotension was defined as episodes of SBP < 90 mmHg. Artifacts from continuous monitoring were detected and removed by dedicated algorithms before analysis. Changes in SpO_2 > 4% per second were considered artifacts. The HR measurement from the Lifetouch patch was derived from automatic detection of R-peak intervals in the electrocardiogram signal. For each minute of monitoring, 10 seconds of electrocardiogram were available, and after a filtration process, the quality of the 10-second segment was determined using correlation analysis between each QRS-complex and a template of the average QRS-complex of the segment created from the previous segment. Values of HR and RR derived from noisy electrocardiographic signals were defined as artifacts and excluded from the analysis.

The primary outcome was any SAE at 30 days after inclusion. SAEs were defined (according to the International Conference on Harmonisation guidelines for Good Clinical Practice[13]) as untoward medical occurrences that are life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability. Secondary outcomes were all-cause mortality, admission to ICU, and acute readmission to hospital within 30 days and exploratory outcomes were events within SAE categories (neurological, respiratory, cardiovascular, infectious, and other SAEs). A manual on the reporting of adverse events according to international definitions was written pre-analysis with the assistance of experts across medical specialties and aiming to include internationally agreed definitions where possible. Two qualified physicians (ME and KG) completed the outcome assessment through review of the electronic medical record of included patients. Patients were also contacted by telephone as part of the 30-day follow-up assessment of medical events

occurring out of hospital. If outcome criteria for pneumonia, atelectasis, pneumothorax and pleural effusion (diagnoses dependent on admission chest x-ray or computed tomography scan), were met within 24 hours from admission, these events were adjudicated as occurring at baseline and therefore not included in the outcome analysis. Similarly, any clinical event occurring before inclusion (start of monitoring time) was not analyzed. The analysis of exposure variables (vital sign abnormalities) was performed after the outcome assessment was completed. In the primary outcome analysis, we only counted the first SAE for each patient since vital signs after that may be affected by this first clinical event as well as by any corrective actions.

Statistical analysis

We estimated at least 25% of included patients to suffer any SAE and 50 patients with SAE were estimated to be required for the AECOPD patient population to be included in an upcoming spectral analysis for machine learning-based algorithm development in the WARD research project for automatic detection of deterioration in hospitalized patients. Thus, 200 patients were chosen as sample size.

Duration and frequency of vital sign abnormalities were primarily analyzed in summary for the 24 hours preceding the first SAE, and results are presented for patients suffering SAE during the monitoring period compared with patients without SAE. For patients with SAE occurring after monitoring ended and for patients without SAEs, we analyzed the total monitoring period for vital sign abnormalities and presented these as abnormalities per 24 hours to adjust for different exposure times. For example, a patient monitored for 2 days (48 hours) resulting in a cumulated duration of tachypnea (HR > 110 beats/min) of 60 minutes, are reported as 30 minutes of tachypnea per 24 hours.

As a supplemental analysis, we compared the frequency of vital sign abnormalities within the 12 hours before in-hospital SAE to the frequency of vital sign abnormalities in the first 12 hours of hospital admission in patients without SAE.

A statistical analysis plan was written after the collection of data. Descriptive statistics of vital sign abnormalities were calculated for patients with and without SAEs. Mean differences between vital sign abnormalities in patients with SAE during ongoing monitoring and patients without SAEs were calculated and associations were analyzed using Wilcoxon rank sum test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS Studio (Version 9.4, SAS Institute, Cary, NC, USA).

3 Results

Two-hundred patients were enrolled in the study between September 2018 and December 2019 (Fig. 1). Baseline characteristics are presented in Table 1. Eighty-nine patients (44%) were male, median age was 74 years, median body mass index was 25 kg/m^2 and 192 (96%) had a history of tobacco smoking.

Eighty-five patients (43%) were monitored for four days, 76 patients (38%) were discharged before day four and 38 patients (19%) had all monitoring equipment removed due to discomfort before day four (Fig. 1). One patient died before day four. Patients were included median 15 [IQR 8-20] hours after hospital admission and the median length of hospital stay was four days [IQR 3-7]. Continuous monitoring resulted in 13,263 patient monitoring hours with at least one sensor modality providing data (Fig. 1). HR- and RR-monitoring resulted in median 56 (IQR 29-82) hours of data per patient after artifact removal, and median SpO_2-monitoring time per patient was 35 (IQR 16-57) hours artifact removal. The median number of blood pressure measurements was 39 (IQR 16-80).

The 30-day follow-up identified at least one SAE in 81 (41%) of the 200 included patients, whereof 7 patients (4%) were admitted to ICU. After initial discharge, readmission occurred for 47 patients (24%) and 14 (7%) died within 30 days after inclusion. For most of the patients with complications (n=50), the first SAE occurred during ongoing vital sign monitoring and the median time from inclusion to first SAE was 43 hours (IQR 5-196).

Patients suffering SAE during the continuous monitoring period had on average 455 minutes (SD 413) per 24 hours duration of any vital sign abnormality compared with 292 minutes (SD 246) in patients without SAE, $p = 0.08$, mean difference 163 minutes [95% CI 61 – 265] (Table 2). In patients with SAE occurring during continuous monitoring the mean cumulative duration of bradypnea (RR < 11) was 48 minutes (SD 173) per 24 hours compared with 30 minutes (SD 84) in patients without SAE, p

= 0.01. The number of severe desaturation events per 24 hours defined as $SpO_2 < 80\%$ for more than one min was 7 (SD 12) for patients with SAE during monitoring compared with 5 (SD 5) for patients without SAE, p = 0.07. The duration and frequency of other vital sign abnormalities were not significantly associated with SAE (Table 3). Severe desaturation events occurred in 62% of patients in the 12 hours preceding the first SAE compared with 73% of patients without SAEs with data analyzed for the first 12 hours of monitoring, OR = 0.60 (95% CI 0.26 to 1.41) (Supplemental Digital Content, Table S1). Patients with a cardiovascular SAE had a mean cumulative duration of $SpO_2 < 85\%$ for 83 minutes per 24 hours on average compared with 41 minutes per 24 hours for patients without SAE (Supplemental Digital Content, Table S2). The 30-day follow-up identified twelve patients (6%) with a myocardial infarction and 19 patients (10%) had new-onset heart failure diagnosed within 30 days from inclusion (Supplemental Digital Content, Table S3).

4 Discussion

One-fourth of patients admitted with AECOPD had serious adverse events during ongoing continuous vital sign monitoring. There were no statistical differences between the overall duration of physiological abnormalities between patients with and without SAEs. However, the durations were long and there was a significant mean difference between the duration of any vital sign deviation occurring before SAEs compared with patients without SAEs. The cumulative duration of bradypnea episodes (RR < 11) was significantly longer in patients with SAE, with a mean difference of 18 minutes.

Hospitalized patients may deteriorate without being noticed, leading to severe clinical complications and escalation of care that could have been prevented with timely intervention. Patient deterioration is often preceded by clinical instability reflected in subtle changes in physiologic parameters, but several studies have reported that abnormal trends in clinical observations are often missed or misinterpreted.[14,15] A retrospective audit of patient records following major surgery from 2003 to 2005 at five Australian hospitals reported that only 17% had complete documentation of vital signs; the respiratory rate was the most commonly absent observation and was not documented in 15.4% of records[16] and a study from Denmark found that 10% of vital sign records had one or more missing value.[11] Therefore, track-and-trigger systems, such as early warning score (EWS) have been implemented in many health care systems with vital signs measured at regular intervals. However, EWS systems have not been prospectively proven to reduce morbidity and mortality[17], and despite their wide implementation, preventable, serious adverse events still occur in large numbers.[15,18] Moreover, manually measured vital signs are often inaccurate and fail to reflect the patient's clinical condition.[19,20] COPD is a condition associated with chronic deviations of vital signs, and the typical clinical presentation of patients hospitalized for AECOPD includes varying degrees of tachypnea, tachycardia, and hypoxemia with supplemental oxygen requirement. This results in a high EWS for

most patients and thus an increased level of observation, even for relatively stable patients. Concern has been raised that this lack of specificity may lead to alarm fatigue with an inappropriate diversion of attention to clinically stable patients or non-adherence to the EWS escalation protocol.[21,22] Continuous multi-parameter monitoring in the general care setting could surpass the inadequacy of intermittent manual collection of vital signs by allowing for earlier detection of deterioration. The clinical application of continuous and wireless multiparametric vital sign monitoring in non-ICU settings has been reported in a limited number of studies. These studies mainly report feasibility or validation data in various settings, usually without clinical outcomes.[23]

Overall, the importance of vital signs for evaluating the need for treatment, outcome predictions and clinical course monitoring seems firmly established.[15] However, the specific contributions of different abnormalities of physiological parameters to the development of clinical complications are not entirely understood.

From this study and our recently published pilot study[9], it can be concluded that vital sign abnormalities are common and of substantial duration in AECOPD patients. Bowton *et al*. found that medical patients in a general ward with hypoxaemic events (Sp_{O_2} < 90% for 5 consecutive minutes) during the first day of admission have decreased survival rates compared with patients without hypoxaemic events.[24] However, this survival difference may be a result of the underlying disease and the degree of desaturation may thus be a marker of disease severity. In a study using one million vital sign spot measurements from 27,722 patients, individuals with one critical abnormal vital sign recording had in-hospital mortality of 0.9%, while patients with three critical abnormal values had a mortality rate of 24%.[25] A different study reported that neurological status (decreased or loss of consciousness), respiratory status (bradypnea, tachypnea and desaturation) and hypotension were independently associated with a high risk of subsequent mortality in hospitalized patients.[26]

We found relatively frequent episodes of abnormal vital signs of long cumulative duration in the first days after admission with AECOPD. For example, patients with SAE during monitoring had severe hypoxemia (SpO_2 < 80%) for an average of 17 minutes during the 24 hours preceding the SAE and such episodes of at least one-minute duration occurred on average 7 times per 24 hours. Notably, most categories of vital sign abnormalities were not associated with subsequent clinical complications in this sample. Although in general, we found that vital sign abnormalities in patients with subsequent SAE were more frequent and of longer cumulative duration when compared with patients without SAEs, this was not statistically significant. Episodes of severe desaturation (SpO_2 < 80%) occurred in 62% of patients in the 12 hours preceding SAE as compared with 73% of patients without SAEs in the first 12 hours of monitoring, OR = 0.60 (95% CI 0.26 to 1.41). Patients with a cardiovascular SAE had long cumulative duration of both respiratory and circulatory vital sign abnormalities, whereas those with infectious SAE had a long duration of only circulatory abnormalities. More than half of AECOPD patients have been reported also to have cardiovascular disease and about one-fifth of acute exacerbations might be triggered by worsening of underlying cardiovascular disease [99]. This is comparable with our results, as we found 39 patients (20%) with any cardiovascular SAE diagnosed within 30 days from inclusion.

Strengths, limitations and interpretation of the study

We continuously monitored vital signs for several days with reporting of serious clinical outcome data specifically in AECOPD patients. An important strength of the study is that patients were monitored in a real clinical setting and that the study addresses the association between deviating vital signs and clinical outcomes, which is often not the case for studies involving continuous monitoring. Further, deviating vital signs did not result in interventions since data were blinded to ward staff; thus, the physiological abnormalities observed should be clinically representative.

The study also has important limitations: First, we predefined cut-off values for abnormal vital signs based on track-and-trigger systems and usual target levels of vital signs in COPD populations, and such thresholds are to some extent arbitrary; nevertheless, they represent the best standard of care today. Second, observational studies cannot confirm or reject causality, and when performing multiple testing in exploratory studies there is an increased risk of significant results occurring by chance. Our findings must therefore be considered hypothesis-generating and should be verified in other patient samples. Third, several factors may potentially reduce the generalizability of our findings. Patients were primarily included from one study site and more than three-quarters of eligible patients had exclusion criteria or declined participation. The main reasons for exclusion were inability to consent or uncooperative patients, and these patients were typically severely affected with dyspnea and hypercapnia. Therefore, excluded patients´ vital signs may have deviated more. We included patients with an expected duration of admission of more than 24 hours and thus excluded patients with less severe AECOPD. Our study likely represents patients with medium severity of AECOPD, which is also reflected in only 4% of included patients admitted to ICU, which is less than half of that previously reported.[4] This can be attributed to the fact that we also included patients with “do not resuscitate” and “do not intubate” orders, which decreased ICU admission rates.

Data incompleteness is a common challenge in studies with continuous monitoring of vital signs in general wards. We achieved continuous SpO_2 data for 57% of the time after artifact removal while heart and respiratory rate were available during 83% of the total time, and physiological abnormalities could like have occurred during periods without recordings. Thus, our results represent the minimum frequency and duration of deviations. Comparable challenges with missing data have been reported in other studies with continuous monitoring of vital signs including SpO_2.[27–30] Technical issues were the main reason for missing data, but patient non-compliance also occurred. If patients felt physically restricted by devices, they would occasionally remove them and sometimes devices fell off

unintentionally. This could be accounted for by calculating the frequency and duration *per 24 hours*. But exposure time should also be noted in the interpretation of this as the mean monitoring time with at least one modality providing data for patients with SAE was 77 hours as compared with 59 hours for patients without SAE.

Implications for future research

The success of rapid response systems is highly dependent on early detection of deterioration and notification of relevant clinical staff (e.g. nurse or response teams). This so-called "afferent limb" can potentially benefit from remote monitoring systems utilizing non-invasive wearable sensors that continuously track physiological variables.

A key feature of continuous vital sign monitoring is the inherent opportunity to record and analyze trends in the data. More important prognostic information may be derived from such trend analysis of physiological data[31]; in particular for AECOPD patients with chronically deviating vital signs (i.e. hypoxemia and tachypnea). Importantly, such systems could also increase alarm specificity and thus decrease false-alarm rates. The use of machine learning-based algorithms on real-time physiological data may increase the performance of deterioration prediction in the future.[32–34] Future large interventional trials are needed to test the benefit of continuous monitoring systems in AECOPD patients as well as other high-risk patient populations.

In conclusion, we found substantial episodes of abnormal vital signs of long cumulative duration in AECOPD patients. Apart from bradypnea, the cumulated duration of preceding physiological abnormalities was not statistically significantly different in patients with or without serious adverse events.

References

1. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization, 2018

2. Overview of potential to reduce lives lost from Chronic Obstructive Pulmonary Disease (COPD). 2014 at <http://www.england.nhs.uk/wp-content/uploads/2014/02/rm-fs-6.pdf>

3. Perera P, Armstrong E, Sherrill D, Skrepnek G: Acute exacerbations of COPD in the United States: Inpatient burden and predictors of costs and mortality. COPD J Chronic Obstr Pulm Dis 2012; 9:131–41

4. Groenewegen KH, Schols AM, Wouters EFM: Mortality and Mortality-Related Factors After Hospitalization for Acute Exacerbation of COPD. Chest 2003; 124:459–67

5. McGloin H, Adam SK, Singer M: Unexpected deaths and referrals to intensive care of patients on general wards. Are some cases potentially avoidable? J R Coll Physicians Lond 1999; 33:255–9

6. Schein RMH, Hazday N, Pena M, Ruben BH, Sprung CL: Clinical antecedents to in-hospital cardiopulmonary arrest. Chest 1990; 98:1388–92

7. Buist MD, Jarmolowski E, Burton PR, Bernard SA, Waxman BP, Anderson J: Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. Med J Aust 1999; 171:22–5

8. Alam N, Hobbelink EL, Tienhoven AJ van, Ven PM van de, Jansma EP, Nanayakkara PWB: The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. Resuscitation 2014; 85:587–94

9. Elvekjaer M, Aasvang EK, Olsen RM, Sørensen HBD, Porsbjerg CM, Jensen JU, Haahr-Raunkjær C, Meyhoff CS: Physiological abnormalities in patients admitted with acute exacerbation of COPD : an observational study with continuous monitoring. J Clin Monit Comput 2020; 34:1051–60

10. Haahr-Raunkjær C, Meyhoff CS, Sørensen HBD, Olsen RM, Aasvang EK: Technological aided assessment of the acutely ill patient – The case of postoperative complications. Eur J Intern Med 2017; 45:41–5

11. Pedersen NE, Rasmussen LS, Petersen JA, Gerds TA, Østergaard D, Lippert A: A critical assessment of early warning score records in 168,000 patients. J Clin Monit Comput 2018; 32:109–16

12. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society R, Forni LG, Roderick PJ: BTS guideline for emergency oxygen use in adult patients. Thorax 2008; 63 Suppl 6:vi1-68

13. European Medicines Agency (EMA): Guideline for good clinical practice E6(R2). 2018

14. Calzavacca P, Licari E, Tee A, Egi M, Haase M, Haase-Fielitz A, Bellomo R: A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. Intensive Care Med 2008; 34:2112–6

15. Kellett J, Sebat F: Make vital signs great again – A call for action. Eur J Intern Med 2017; 45:13–9

16. McGain F, Cretikos MA, Jones D, Dyk S van, Buist MD, Opdam H, Pellegrino V, Robertson MS, Bellomo R: Documentation of clinical review and vital signs after major surgery. Med J Aust 2008; 189:380–3

17. Smith MEB, Chiovaro JC, O'Neil M, Kansagara D, Quiñones AR, Freeman M, Motu'apuaka

ML, Slatore CG: Early Warning System Scores for Clinical Deterioration in Hospitalized Patients: A Systematic Review. Ann Am Thorac Soc 2014; 11:1454–65

18. Petersen JA, Mackel R, Antonsen K, Rasmussen LS: Serious adverse events in a hospital using early warning score - What went wrong? Resuscitation 2014; 85:1699–703

19. Difonzo M: Performance of the Afferent Limb of Rapid Response Systems in Managing Deteriorating Patients: A Systematic Review. Crit Care Res Pract 2019; 2019

20. Taenzer AH, Pyke J, Herrick MD, Dodds TM, McGrath SP: A comparison of oxygen saturation data in inpatients with low oxygen saturation using automated continuous monitoring and intermittent manual data charting. Anesth Analg 2014; 118:326–31

21. O'Driscoll BR, Bakerly ND, Murphy P, Decalmer S, Kane B, Nasir AA, Simpson F, Turkington PM: Concerns regarding the design of the bedside monitoring chart for use with the NEWS (National Early Warning System). Clin Med 2013; 13:319–20

22. Kane B, Decalmer S, Murphy P, Turkington P, O'Driscoll B: S29 The Proposed National Early Warning System (NEWS) Could Be Hazardous For Patients Who Are at Risk of Hypercapnic Respiratory Failure. Thorax 2012; 67:A16-17

23. Leenen JPL, Leerentveld C, Dijk JD van, Westreenen HL van, Schoonhoven L, Patijn GA: Current evidence for continuous vital signs monitoring by wearable wireless devices in hospitalized adults: Systematic review. J Med Internet Res 2020; 22:e18636

24. Bowton DL, Scuderi PE, Haponik EF: The incidence and effect on outcome of hypoxemia in hospitalized medical patients. Am J Med 1994; 97:38–46

25. Bleyer AJ, Vidya S, Russell GB, Jones CM, Sujata L, Daeihagh P, Hire D: Longitudinal analysis of one million vital signs in patients in an academic medical center. Resuscitation

2011; 82:1387–92

26. Buist M, Bernard S, Nguyen T V., Moore G, Anderson J: Association between clinically abnormal observations and subsequent in-hospital mortality: A prospective study. Resuscitation 2004; 62:137–41

27. Sun Z, Sessler DI, Dalton JE, Devereaux P, Shahinyan A, Naylor AJ, Hutcherson MT, Finnegan PS, Tandon V, Darvish-Kazem S, Chugh S, Alzayer H, Kurz A: Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. Anesth Analg 2015; 121:709–15

28. Gögenur I, Rosenberg-Adamsen S, Lie C, Carstensen M, Rasmussen V, Rosenberg J: Relationship between nocturnal hypoxaemia, tachycardia and myocardial ischaemia after major abdominal surgery. Br J Anaesth 2004; 93:333–8

29. Duus C, Aasvang E, Olsen R, Sørensen H, Jørgensen L, Achiam M, Meyhoff C: Continuous Vital Sign Monitoring after Major Abdominal Surgery—Quantification of Micro Events. Acta Anaesthesiol Scand 2018:1–9

30. Jeffs E, Vollam S, Young JD, Horsington L, Lynch B, Watkinson PJ: Wearable monitors for patients following discharge from an intensive care unit: practical lessons learnt from an observational study. J Adv Nurs 2016; 72:1851–62

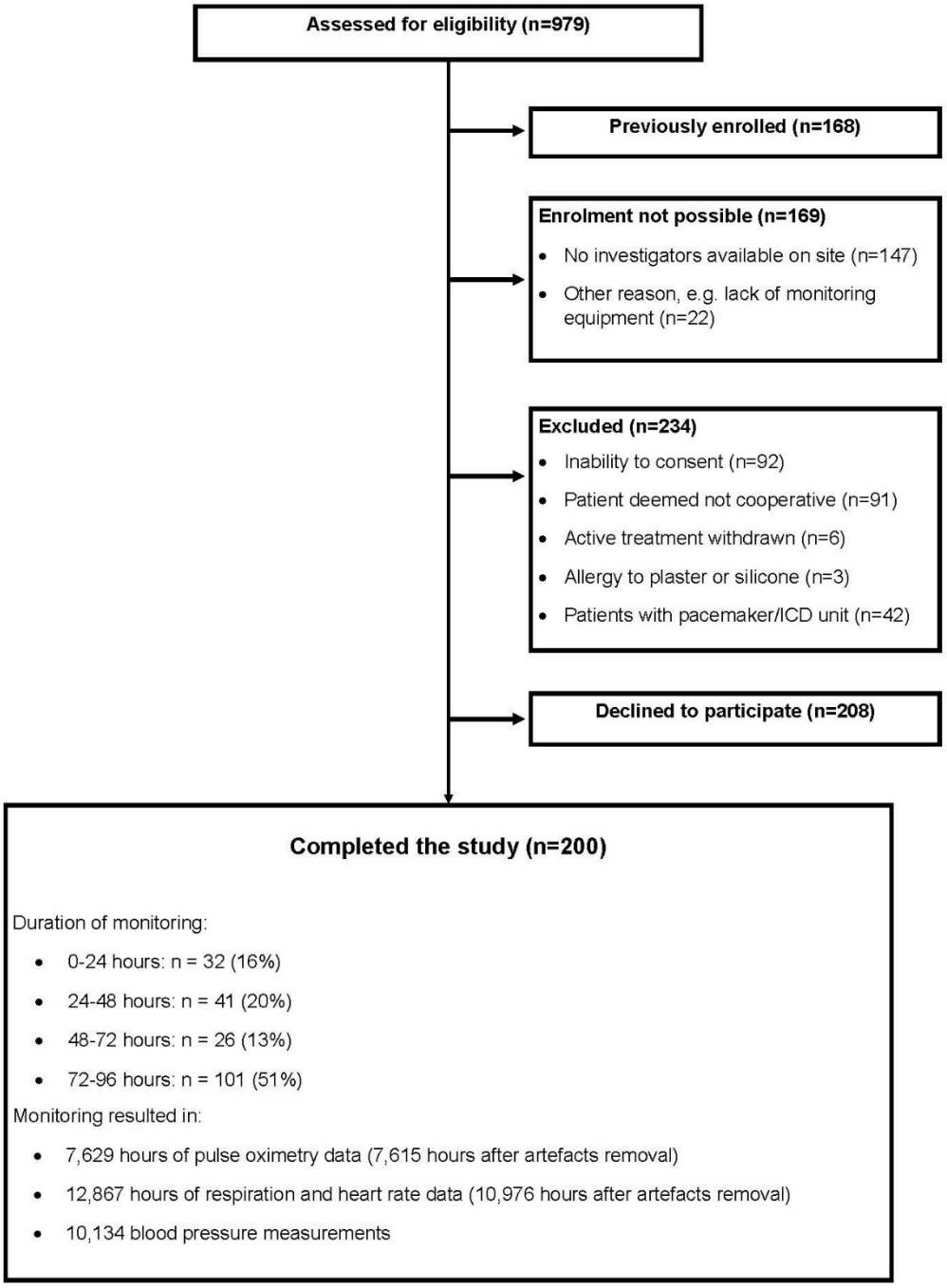
31. Churpek MM, Adhikari R, Edelson DP: The value of vital sign trends for detecting clinical deterioration on the wards. Resuscitation 2016; 102:1–5

32. Clifton L, Clifton DA, Pimentel MAF, Watkinson PJ, Tarassenko L: Predictive monitoring of mobile patients by combining clinical observations with data from wearable sensors. IEEE J Biomed Heal informatics 2014; 18:722–30

33. Churpek MM, Yuen TC, Winslow C, Meltzer DO, Kattan MW, Edelson DP: Multicenter Comparison of Machine Learning Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards. Crit Care Med 2016; 44:368–74

34. Lundberg SM, Nair B, Vavilala MS, Horibe M, Eisses MJ, Adams T, Liston DE, Low DK-W, Newman S-F, Kim J, Lee S-I: Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. Nat Biomed Eng 2018; 2:749–60

Fig. 1. Flow chart of study base selection



TABLES

TABLE 1. Baseline characteristics

Parameter	n = 200
Sex, male / female	89 (44%) / 111 (56%)
Age, years	74 [65-81]
Body mass index, kg/m^2	25 [21-30]
Smoking history, never / previously / current	8 (4%) / 112 (56%) / 80 (40%)
Lifetime tobacco exposure, pack-years	41 [30-60]
Excessive alcohol consumption[a]	35 (18%)
Any treatment limitation at inclusion (e.g. DNR), yes / no	30 (15%) / 170 (85%)
Nursing home resident, yes / no	26 (13%) / 174 (87%)
Assistance with activities of daily living, yes / no	74 (37%) / 126 (63%)
Medical history (age-adjusted Charlson comorbidity index)	
Charlson comorbidity index score 2-3 / 4-5 / 6-7 / 8+	46 (23%) / 85 (42%) / 51 (26%) / 18 (9%)
Classification of COPD	
Spirometry available[b]	185 (93%)
FEV_1/FVC	0.52 [0.43-0.61]
GOLD grade[c], 1 / 2 / 3 / 4	15 (8%) / 58 (31%) / 71 (39%) / 41 (22%)
mMRC dyspnea grade, 0-1 / 2 / 3 / 4	13 (7%) / 42 (21%) / 90 (45%) / 55 (27%)
Baseline measurements at inclusion	
Early Warning Score	4 [3-6]
Sp_{O_2}, %	94 [92-96]
Heart rate, beats per minute	92 [81-102]
Respiratory rate, breaths per minute	20 [18-22]
Systolic blood pressure, mmHg	126 [115-140]
Arterial pH	7.41 [7.37-7.45]
Arterial Pa_{O_2}, mmHg	64 [56-73]
Arterial Pa_{CO_2}, mmHg	44 [38-53]
Arterial bicarbonate, mmol/L	27 [25-29]
Arterial lactate, mmol/L	1.1 [0.8-1.7]
Haemoglobin, mmol/L	8.2 [7.3-9.0]
White blood count, 10^9/L	10.7 [8.1-15.3]
C-Reactive Protein, mg/L	29 [8-91]
Creatinine, µmol/L	76 [58-98]

Values are number (percentage) or median [interquartile range]. COPD, chronic obstructive pulmonary disease; DNR, do not resuscitate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnea scale; Sp_{O_2}, peripheral oxygen saturation. [a]Current alcohol consumption of more than recommended by the Danish Health Authority, which is 24 g/day for men or 12 g/day for women. [b]Spirometry values available as recorded in electronic health records, which did not specify pre- or post-bronchodilator values consistently. [c]Classification of airflow limitation severity in COPD.

TABLE 2. Summary of the association between preceding cardiopulmonary abnormalities duration and serious adverse events within 30 days in 200 patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	Patients with SAE		Patients without SAE	Mean difference*	P-value*
	SAE during monitoring (n=50)	SAE after monitoring (n=31)	(n=119)	[95% CI]	
Any vital sign abnormality					
Mean cumulative duration per 24 h	455 (413)	289 (264)	292 (246)	163 [61 to 265]	0.08
Median cumulative duration per 24 h	318 [12 – 710]	235 [54 – 451]	191 [110 – 425]		
Any respiratory abnormality					
Mean cumulative duration per 24 h of respiratory abnormalities	333 (367)	199 (226)	214 (186)	118 [34 to 203]	0.42
Median cumulative duration per 24 h of respiratory abnormalities	148 [0 – 535]	116 [35 – 298]	155 [77 – 324]		
Any circulatory abnormality					
Mean cumulative duration per 24 h of circulatory abnormalities	194 (326)	135 (212)	119 (216)	75 [-9 to 160]	0.69
Median cumulative duration per 24 h of circulatory abnormalities	35 [0 – 240]	60 [7 – 121]	29 [6 – 115]		

Values are mean (SD) or median [interquartile range] cumulative duration in minutes. Data for patients with SAE occurring during monitoring were analyzed for vital sign abnormalities in the 24h period preceding the SAE. Data for patients with SAE occurring after monitoring and patients without SAE were analyzed for vital sign abnormalities in the complete monitoring period (up to 4 days). All values are presented as frequency and duration of vital sign abnormalities *per 24 hours* to adjust for different exposure time.
*Mean differences and p-values are calculated for patients with SAE during monitoring vs patients without SAE.

TABLE 3. Association of preceding cardiopulmonary abnormalities duration and frequency and serious adverse events within 30 days in 200 patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	Patients with SAE/death		Patients without SAE	Mean difference*	P-value*
	SAE during monitoring (n=50)	SAE after monitoring (n=31)	(n=119)	[95% CI]	
Respiratory abnormalities					
Sp_{O_2} <88%					
Mean (SD) cumulative duration per 24 h	194 (282)	127 (132)	115 (150)	78 [11 to 146]	0.28
Median [IQR] cumulative duration per 24 h	79 [0 – 535]	60 [21 – 209]	71 [21 – 141]		
Mean (SD) number of events per 24 h (> 10 min)	6 (10)	4 (5)	4 (4)	2 [0 to 4]	0.50
Sp_{O_2} <85%					
Mean (SD) cumulative duration per 24 h	78 (135)	61 (73)	41 (84)	37 [3 to 72]	0.97
Median [IQR] cumulative duration per 24 h	14 [0 – 71]	19 [5 – 100]	17 [4 – 43]		
Mean (SD) number of events per 24 h (> 5 min)	4 (9)	4 (4)	3 (3)	1 [-0.3 to 4]	0.17
Sp_{O_2} <80%					
Mean (SD) cumulative duration per 24 h	17 (38)	14 (26)	9 (22)	8 [-1 to 18]	0.07
Median [IQR] cumulative duration per 24 h	0 [0 – 11]	3 [0.3 – 10]	2 [0.5 – 7]		
Mean (SD) number of events per 24 h (> 1 min)	7 (12)	7 (7)	5 (5)	2 [-0.9 to 4]	0.07
Tachypnea RR > 24					
Mean (SD) cumulative duration per 24 h	135 (275)	80 (172)	79 (124)	56 [-5 to 117]	0.46
Median [IQR] cumulative duration per 24 h	18 [0 – 87]	2 [0.1 – 22]	11 [0.9 – 99]		
Mean (SD) number of events per 24 h (> 5 min)	7 (15)	4 (8)	4 (7)	3 [-0.7 to 6]	0.64
Tachypnea RR > 30					
Mean (SD) cumulative duration per 24 h	9 (40)	15 (47)	4 (11)	5 [-3 to 13]	0.39
Median [IQR] cumulative duration per 24 h	0 [0 – 1]	0 [0 – 0.5]	0 [0 – 1]		
Mean (SD) number of events per 24 h (> 1 min)	8 (39)	7 (19)	3 (7)	5 [-2 to 12]	0.51
Bradypnea RR < 11					
Mean (SD) cumulative duration per 24 h	48 (173)	15 (39)	30 (84)	18 [-21 to 57]	0.01
Median [IQR] cumulative duration per 24 h	0 [0 – 7]	0.8 [0 – 4]	3 [0 – 11]		
Mean (SD) number of events per 24 h (> 5 min)	2 (8)	0.6 (2)	1 (4)	0.8 [-1 to 3]	0.01
Circulatory abnormalities					
Heart rate > 110/min					
Mean (SD) cumulative duration per 24 h	188 (328)	133 (213)	116 (217)	72 [-13 to 157]	0.55
Median [IQR] cumulative duration per 24 h	24 [0 – 219]	54 [5 – 120]	24 [4 – 109]		
Mean (SD) number of events per 24 h (> 60 min)	0.8 (2)	0.8 (2)	0.6 (1)	0.2 [-0.3 to 0.7]	0.34
Heart rate > 130/min					
Mean (SD) cumulative duration per 24 h	18 (48)	19 (76)	16 (56)	2 [-16 to 20]	0.27
Median [IQR] cumulative duration per 24 h	0 [0 – 7]	0.3 [0 – 7]	0.3 [0 – 4]		
Mean (SD) number of events per 24 h (> 30 min)	0.4 (2)	0.2 (0.5)	0.2 (0.5)	0.2 [-0.1 to 0.7]	0.53
Heart rate < 40/min					
Mean (SD) cumulative duration per 24 h	0.3 (1)	1 (4)	2 (11)	-1 [-5 to 2]	0.02
Median [IQR] cumulative duration per 24 h	0 [0 – 0]	0 [0 – 0.6]	0 [0 – 0.3]		
Mean (SD) number of events per 24 h (> 5 min)	0	0	0.1 (0.6)	0.1 [-0.2 to 0.1]	0.09
Systolic Blood Pressure < 90 mmHg					
Mean (SD) number of events per 24 h	4 (14)	0.3 (0.8)	0.3 (1)	4 [1 to 7]	0.22
Systolic Blood Pressure > 180 mmHg					
Mean (SD) number of events per 24 h	3 (9)	0.6 (1)	0.8 (3)	2 [-0.1 to 4]	0.06

Values are mean (SD) or median [interquartile range] cumulative duration per 24 hours in minutes and mean (SD) number of events. Data for patients with SAE occurring during monitoring were analyzed for vital sign abnormalities in the 24h period preceding the SAE. Data for patients with SAE occurring after monitoring and patients without SAE were analyzed for vital sign abnormalities in the complete monitoring period (up to 4 days). All values are presented as frequency and duration of vital sign abnormalities per 24 hours to adjust for different exposure time. *Mean differences and p-values are calculated for patients with SAE during monitoring vs patients without SAE.

TABLE S1. Association of preceding cardiopulmonary abnormalities frequency to serious adverse events and mortality within 30 days in patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	Patients with SAE during monitoring (n = 29)	Patients with SAE after monitoring (n = 31)	Patients without SAE (n = 119)		Odds ratio* (95% CI)
	Vital sign abnormalities during 12 h before SAE	Vital sign abnormalities during last 12 h of monitoring	Vital sign abnormalities during first 12 h of monitoring	Vital sign abnormalities during last 12 h of monitoring	
Respiratory abnormalities					
Mean (SD) SpO_2 monitoring time, hours	6.2 (4.4)	4.4 (4.3)	8.2 (3.4)	5.4 (4.2)	
SpO_2 <88%					
Patients with at least one event (duration > 10 min)	16 (55%)	17 (55%)	72 (61%)	61 (51%)	0.80 (0.35 – 1.82)
SpO_2 <85%					
Patients with at least one event (duration > 5 min)	12 (41%)	12 (39%)	59 (50%)	49 (41%)	0.72 (0.32 – 1.63)
SpO_2 <80%					
Patients with at least one event (duration > 1 min)	18 (62%)	17 (55%)	87 (73%)	66 (55%)	0.60 (0.26 – 1.41)
Mean (SD) respiratory rate monitoring time, hours	9.4 (3.5)	7.5 (4.8)	9.8 (3.1)	7.4 (4.2)	
Tachypnea RR > 24					
Patients with at least one event (duration > 5 min)	10 (34%)	6 (19%)	45 (38%)	29 (24%)	0.87 (0.37 – 2.03)
Tachypnea RR > 30					
Patients with at least one event (duration > 1 min)	6 (21%)	5 (16%)	27 (23%)	17 (14%)	0.89 (0.33 – 2.41)
Bradypnea RR < 11					
Patients with at least one event (duration > 5 min)	4 (14%)	2 (6%)	12 (10%)	18 (15%)	1.43 (0.42 – 4.80)
Circulatory abnormalities					
Mean (SD) heart rate monitoring time, hours	9.1 (3.9)	7.6 (4.7)	9.1 (3.1)	7.5 (4.2)	
Heart rate > 110/min					
Patients with at least one event (duration > 60 min)	5 (17%)	7 (23%)	31 (26%)	22 (18%)	0.6 (0.2 – 1.7)
Heart rate > 130/min					
Patients with at least one event (duration > 30 min)	3 (10%)	2 (6%)	9 (8%)	9 (8%)	1.4 (0.4 – 5.6)
Heart rate < 40/min					
Patients with at least one event (duration > 5 min)	0	0	0	1 (1%)	4.1 (0.08 – 208)
Mean (SD) blood pressure measurements, n	8.2 (7.6)	3.8 (5.5)	16 (8.3)	4.9 (5.9)	
Systolic Blood Pressure < 90 mmHg					
Patients with at least one event	1 (3%)	2 (6%)	4 (3%)	2 (2%)	1.03 (0.11 – 9.55)
Systolic Blood Pressure > 180 mmHg					
Patients with at least one event	0	1 (3%)	11 (9%)	1 (1%)	0.16 (0.01 – 2.79)

Values are numbers (percentage) or mean (SD). Data for patients with SAE occurring during monitoring (n = 29) were analyzed for vital sign abnormalities in the 12-hour period preceding the first SAE. Data for patients with first SAE occurring after ended monitoring (n = 31) were analyzed for vital sign abnormalities in the last 12 hours of monitoring, whereas data for patients without SAE (n = 119) were analyzed for vital sign abnormalities in the first AND last 12 hours of monitoring. Patients with first SAE occurring within 6 hours from inclusion (n = 21) was not included in this analysis. Therefore, the data included are derived from 6-12 hours of monitoring. *Odds ratios were calculated for patients with SAE during monitoring vs. patients without SAE (first 12 hours of monitoring).

TABLE S2. Preceding cardiopulmonary abnormalities in serious adverse event categories within 30 days in patients admitted with acute exacerbation of chronic obstructive pulmonary disease

	No SAE (n = 119)	Neurological SAE (n = 13)	Pulmonary SAE (n = 31)	Cardiovascular SAE (n=39)	Infectious SAE (n= 28)	Other SAE (n = 22)
Respiratory abnormalities						
Mean (SD) cumulative duration per 24h of respiratory abnormalities	214 (186)	205 (249)	300 (322)	336 (357)	389 (442)	230 (320)
SpO_2 <88%						
Mean (SD) cumulative duration per 24 h	115 (150)	149 (194)	170 (221)	188 (225)	197 (303)	98 (99)
SpO_2 <85%						
Mean (SD) cumulative duration per 24 h	41 (84)	55 (103)	83 (133)	83 (126)	70 (106)	38 (50)
SpO_2 <80%						
Mean (SD) cumulative duration per 24 h	9 (22)	8 (24)	18 (61)	24 (43)	10 (18)	10 (18)
Tachypnea RR > 24						
Mean (SD) cumulative duration per 24 h	79 (124)	77 (173)	91 (175)	145 (295)	142 (317)	85 (202)
Tachypnea RR > 30						
Mean (SD) cumulative duration per 24 h	4 (11)	8 (26)	7 (21)	15 (48)	22 (89)	9 (28)
Bradypnea RR < 11						
Mean (SD) cumulative duration per 24 h	30 (84)	10 (28)	58 (228)	43 (167)	74 (251)	66 (260)
Circulatory abnormalities						
Mean (SD) cumulative duration per 24h of circulatory abnormalities	119 (216)	182 (403)	181 (325)	189 (337)	103 (140)	163 (343)
Heart rate > 110/min						
Mean (SD) cumulative duration per 24 h	116 (217)	181 (403)	178 (326)	185 (338)	97 (142)	162 (343)
Heart rate > 130/min						
Mean (SD) cumulative duration per 24 h	16 (56)	1 (2)	26 (81)	22 (62)	14 (52)	15 (44)
Heart rate < 40/min						
Mean (SD) cumulative duration per 24 h	2 (11)	0 (0)	1 (2)	0 (1)	0 (1)	0 (1)
Systolic Blood Pressure < 90 mmHg						
Mean (SD) number of events per 24 h	0 (1)	0 (1)	0 (2)	2 (6)	5 (16)	1 (2)
Systolic Blood Pressure > 180 mmHg						
Mean (SD) number of events per 24 h	1 (3)	0 (1)	2 (10)	2 (6)	0 (2)	1 (2)

Values are mean (SD) cumulative duration per 24 hours in minutes. Data for patients with first SAE occurring during continuous monitoring were analyzed for vital sign abnormalities in the 24-hour period preceding the SAE. Data for patients with first SAE occurring after ended monitoring were analyzed for vital sign abnormalities in the last 24 hours of monitoring whereas data for patients without SAE were analyzed for vital sign abnormalities in the complete monitoring period (up to 4 days). All values are presented as duration or frequency of vital sign abnormalities *per 24 hours* to adjust for different exposure time.

TABLE S3. Frequency of serious adverse events categories within 30 days after hospitalization with acute exacerbation of chronic obstructive pulmonary disease

Serious adverse events	Number of patients (%) (n=200)
Any SAE	81 (41%)
All-cause mortality	14 (7%)
Acute readmission	47 (24%)
ICU admission	7 (4%)
Any neurological SAE	13 (7%)
Delirium	10 (5%)
Syncope	2 (1%)
Stroke	1 (0.5%)
Any respiratory SAE	31 (16%)
Respiratory failure	17 (9%)
Pneumonia	16 (8%)
Pleural effusion	3 (2%)
Atelectasis	2 (1%)
Pneumothorax	1 (0.5%)
Any cardiovascular SAE	39 (20%)
Heart failure	19 (10%)
Troponin elevation	18 (9%)
Myocardial infarction	12 (6%)
Atrial fibrillation	6 (3%)
Pulmonary embolism	3 (2%)
Non-fatal cardiac arrest	2 (1%)
Any infectious SAE	28 (14%)
Sepsis	18 (9%)
Urinary tract infection	12 (6%)
Any other SAE	22 (11%)
Acute renal failure	2 (1%)
Opioid intoxication	2 (1%)
Fracture	1 (0.5%)
Miscellaneous SAE	18 (9%)

Values are number (percent). Diagnosis had to be new-onset or clear worsening of symptoms. In case the criteria for a specific SAE was met before inclusion it was adjudicated as present at baseline and not included in the analysis. Specifically, if pneumonia, atelectasis, pneumothorax or pleural effusion occurred within 24 hours from admission they were not categorized as new-onset SAE. Some patients had more than one SAE included in the analysis. SAE, serious adverse event.