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

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Abstract

Purpose: 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.

Methods: 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 four days after admission. Hypoxaemic events were defined as decreased SpO_2 for at least 60 seconds. Non-invasive blood pressure was also measured every 15 to 60 minutes. 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.

Results: Continuous monitoring detected episodes of $\text{SpO}_2 < 92\%$ in 97% vs. 43% detected by conventional EWS ($p < 0.0001$). Events of $\text{SpO}_2 < 88\%$ was detected in 90% with continuous monitoring compared with 13% with EWS ($p < 0.0001$). Sixty-three percent of patients had episodes of $\text{SpO}_2 < 80\%$ recorded by continuous monitoring and 17% had events lasting longer than 10 minutes. No events of $\text{SpO}_2 < 80\%$ was detected by EWS. Micro events of tachycardia, tachypnoea, and bradypnoea were also more frequently detected by continuous monitoring ($p < 0.02$ for all).

Conclusion: 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 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 SpO₂ 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 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 24h 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 hours with 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 [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 minutes during daytime and every 30 minutes during night-time. If patients expressed discomfort from BP measurements, settings were changed to measure every 30 minutes 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. SpO₂-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 hours 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 vs. 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 seconds: Hypoxaemia was defined as SpO₂<92% (calculated average of 60 seconds), tachycardia as >130 beats per minute, bradycardia as <41 beats per minute, tachypnoea as >24 breaths per minute, bradypnoea as <9 breaths per minute. BP micro events were considered present if measured in at least one measurement. Hypotension were defined as systolic blood pressure (sBP)<90mmHg, and hypertension as sBP>219mmHg. 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 SpO₂<88% (moderate desaturation) as well as SpO₂<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 SpO₂ 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 SpO₂, 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 per minute from the HR-estimation calculated from the ECG signal, the SpO₂ 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 seconds 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 hours of patient monitoring (median of 71 hours, 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 hours and 16 minutes.

3.1 *Peripheral oxygen saturation*

In total, 1248 hours of continuous SpO₂ data were collected. After removal of artefacts (9% of total recorded time), 1135 hours of continuous SpO₂ data were available for analysis. Average SpO₂ monitoring time per patient was 38 hours 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 vs 13 patients (43%) with EWS ($p<0.0001$, Fig. 2 and Table 2). Seven patients had desaturation events with SpO₂<92% reported by EWS that were not detected by continuous monitoring, due to missing data from these time periods. Desaturation events with SpO₂<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 SpO₂<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 SpO₂<88% (median hypoxaemic time) detected by continuous monitoring was 156 minutes [5-95% range 0-1237] vs. 0 minutes [5-95% range 0-165] in the same patients measured with EWS ($p<0.0001$). Fig. 3 illustrates the average time of moderate desaturation (SpO₂<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 (SpO₂<88%) was between 00 and 08, 36% between 08 and 16, and 31% between 16 and 24. Continuous monitoring detected severe desaturation events with SpO₂<80% in 19 patients (63%). Among patients with severe desaturation, the median cumulative duration with SpO₂<80% was 9 minutes [5-95% range 1-99], and 5 patients (17%) had these events lasting longer than 10 minutes. Events of SpO₂<80% were not detected for any patients by EWS.

3.2 *Heart rate*

The total time of collected HR data was 1570 hours. After artefact removal (7% of total recorded time), 1462 hours 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%) vs 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 hours with 7% artefacts, and 1458 hours (71% of the total time) where available for analysis. One or more tachypnoeic events ($RR>24/\text{min}$) were detected in 17 patients (57%) with continuous monitoring vs 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 where a normal respiration rate was recorded with continuous monitoring. Sixteen patients (53%) had bradypnoea ($RR<9/\text{min}$) detected by continuous monitoring, however no episodes of $RR<9/\text{min}$ was 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 hours (49% of total monitoring time). Seven patients (23%) were found to be hypotensive ($sBP<90\text{mmHg}$) 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.

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 ($\text{SpO}_2 < 88\%$) were detected in 90% of patients, and severe desaturation ($\text{SpO}_2 < 80\%$) 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 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 SpO₂-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 (SaO₂). 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 SpO₂ 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 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 hours, 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 $\text{SpO}_2 < 80\%$ for at least 60 seconds) as well as other cardiopulmonary micro events [25]. Similarly, Turan et al. reported common episodes of hypotension in patients after abdominal surgery (18% had mean arterial pressure lower than 65 mmHg) [29]. The clinical significance of these abnormal physiological values is debated. It has been shown that medical patients with desaturation events ($\text{SpO}_2 < 90\%$ 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

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Conflict of Interest

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.

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Figure Captions:

Fig. 1 Study flowchart

Fig. 2 Desaturation micro events during admission for acute exacerbation of COPD

Percent of patients with minimum one micro event of desaturation to $\text{SpO}_2 < 92\%$, $\text{SpO}_2 < 88\%$ and $\text{SpO}_2 < 80\%$ detected with continuous monitoring (blue) and EWS monitoring (grey), $p < 0.0001$ for all

Fig. 3 Average time with $\text{SpO}_2 < 88\%$ 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 afternoon (after 96 hours of monitoring) if the patient was still hospitalised.