

# Automated Oxygen Administration Alleviates Dyspnea in Patients Admitted with Acute Exacerbation of COPD: A Randomized Controlled Trial

Charlotte Sandau<sup>1</sup>, Ejvind Frausing Hansen<sup>1</sup>, Thomas Jørgen Ringbæk<sup>2</sup>, Thomas Kallemose<sup>3</sup>, Dorthe Gaby Bove<sup>4</sup>, Ingrid Poulsen<sup>3,5</sup>, Vibeke Nørholm<sup>3</sup>, Lars Pedersen<sup>6</sup>, Jens Ulrik Stæhr Jensen<sup>7,8</sup>, Charlotte Suppli Ulrik<sup>1,9</sup>

<sup>1</sup>Department of Respiratory Medicine and Endocrinology, Pulmonary Section, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark;

<sup>2</sup>Allergy and Lung Clinic, Elsinore, Denmark; <sup>3</sup>Department of Clinical Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark;

<sup>4</sup>University College Absalon, Centre for Nursing, Roskilde, Denmark; <sup>5</sup>Research Unit Nursing and Health Care, Aarhus University, Aarhus, Denmark;

<sup>6</sup>Department of Respiratory Medicine and Infectious Diseases, Copenhagen University Bispebjerg Hospital, Copenhagen, Denmark; <sup>7</sup>Respiratory Medicine Section, Department of Medicine, Herlev-Gentofte Hospital, Hellerup, Denmark; <sup>8</sup>Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, København, Denmark; <sup>9</sup>Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence: Charlotte Sandau, Email [charlotte.sandau.bech.01@regionh.dk](mailto:charlotte.sandau.bech.01@regionh.dk)

**Objective:** Devices for Automated Oxygen Administration (AOA) have been developed to optimize the therapeutic benefit of oxygen supplementation. We aimed to investigate the effect of AOA on multidimensional aspects of dyspnea and as-needed consumption of opioids and benzodiazepines, as opposed to conventional oxygen therapy, in hospitalized patients with Acute Exacerbation of COPD (AECOPD).

**Method and Patients:** A multicenter randomized controlled trial across five respiratory wards in the Capital Region of Denmark. Patients admitted with AECOPD (n=157) were allocated 1:1 to either AOA (O2matic Ltd), a closed loop device automatically delivering oxygen according to the patient's peripheral oxygen saturation (SpO<sub>2</sub>), or conventional nurse-administered oxygen therapy. Oxygen flows and SpO<sub>2</sub> levels were measured by the O2matic device in both groups, while dyspnea, anxiety, depression, and COPD symptoms were accessed by Patient Reported Outcomes.

**Results:** Of the 157 randomized patients, 127 had complete data for the intervention. The AOA reduced patients' perception of overall unpleasantness significantly on the Multidimensional Dyspnea Profile (MDP) with a difference in medians of -3 ( $p=0.003$ ) between the intervention group (n=64) and the control group (n=63). The AOA also provided a significant between group difference in all single items within the sensory domain of the MDP (all  $p$ -values $\leq 0.05$ ) as well as in the Visual Analogue Scale – Dyspnea (VAS-D) within the past three days ( $p=0.013$ ). All between group differences exceeded the Minimal Clinical Important Difference of the MDP and VAS-D, respectively. AOA did not seem to have an impact on the emotional response domain of the MDP, the COPD Assessment Test, the Hospital Anxiety and Depression Scale, or use of as-needed opioids and/or benzodiazepines (all  $p$ -values $>0.05$ ).

**Conclusion:** AOA reduces both breathing discomfort and physical perception of dyspnea in patients admitted with AECOPD but did not seem to impact the emotional status or other COPD symptoms.

**Keywords:** dyspnea, oxygen, automated oxygen therapy, multidimensional dyspnea profile, COPD, hospital, admission, therapy

## Introduction

In patients with Chronic Obstructive Pulmonary Disease (COPD), acute exacerbations are a major cause of hospitalizations, and in most cases associated with dyspnea, anxiety, and hypoxemia.<sup>1,2</sup>

Supplemental oxygen is a key component of the in-hospital management of these patients. Titrated oxygen therapy to achieve oxygen saturation (SpO<sub>2</sub>) between 88 and 92% reduces the risk of hypercapnic acidosis and the need for assisted

ventilation compared to higher flow rates, reaching higher SpO<sub>2</sub> levels.<sup>3,4</sup> To optimize the administration of oxygen and thereby therapeutic impact, devices with Automatic Oxygen Administration (AOA), in response to the patient's SpO<sub>2</sub>, have been developed.<sup>5,6</sup> It has been shown that AOA significantly increases the proportion of time within the guideline-recommended ranges of SpO<sub>2</sub> compared to conventional oxygen therapy.<sup>5–8</sup>

Dyspnea is often associated with hypoxemia and is a major cause of suffering and therefore a treatment target. The clinical management of Acute Exacerbation in COPD (AECOPD) is complex and includes inhaled bronchodilators and oxygen therapy for hypoxemic patients. To reduce the intensity of dyspnea, these primary therapies may, if necessary, be supplemented by as-needed opioids or benzodiazepines for the related anxiety, despite their respiratory risk profiles.<sup>9–12</sup> Dyspnea is defined as “a subjective experience of breathing discomfort that consist of qualitatively distinct sensations that vary in intensity”.<sup>10</sup> The patient's experience of dyspnea is based on several afferent paths, which the brain processes into physical perceptions as well as affective responses often linked to emotions such as fear and anxiety.<sup>10,13</sup> Thus, dyspnea is a multidimensional symptom and can be measured as such by The Multidimensional Dyspnea Profile (MDP).<sup>14</sup> However, most studies investigating dyspnea as an outcome of supplemental oxygen therapy in patients with COPD have primarily been carried out in out-of-hospital settings measuring the symptom uni-dimensionally and based on recall of physical activity.<sup>15</sup> Hypoxemia, hypercapnia, and dyspnea are associated in healthy subjects<sup>16</sup>, whereas the relationship between hypoxemia, hypercapnia, and the perception of dyspnea in patients with COPD is unclear, and evidence is inconsistent on whether or not oxygen therapy can relieve dyspnea.<sup>17–19</sup>

We hypothesized that optimized oxygen therapy via AOA can reduce dyspnea and the need for as-needed opioids and benzodiazepines in patients hospitalized with AECOPD and hypoxemia. Therefore, the primary aim of this study was to investigate the effect of AOA, compared to conventional oxygen therapy, on patients' perception of dyspnea measured by the MDP, and secondary is the need for opioids and/or benzodiazepines in patients hospitalized with AECOPD.

## Materials and Methods

This study (ClinicalTrials.gov Identifier: NCT04370990) is a study nested within the open-labeled, multicenter randomized controlled trial “Automated oxygen-control with O2matic during admission with exacerbation in COPD” (ClinicalTrials.gov Identifier: NCT03661086). Patients were included and randomized 1:1 to either conventional oxygen therapy or automated oxygen therapy provided by O2matic. The study was approved by The Danish Medicines Agency, the Committee on Health Research Ethics of the Capital Region (H-17040114), and the Data Protection Authority (VD-2018-44, 6248) and conducted in accordance with the Declaration of Helsinki.

## Materials

Patients were recruited from five respiratory wards in the Capital Region of Denmark between December 2018 and April 2022. Patients were eligible for inclusion within the first 48 hours following admission if they had a primary diagnosis of COPD (International Classification of Diseases [ICD] code J440, J441, J448, or J449), an expected length of hospital stay (LOS) >24 hours, an SpO<sub>2</sub> <88% breathing room air, age ≥35 years, and cognitively able and willing to provide written informed consent to participate. A concomitant diagnosis of pneumonia was accepted.

Patients were excluded if they required mechanical ventilation within the first 48 hours of admission, had a verified pulmonary embolism within two weeks prior to admission, had concomitant asthma or any other disease requiring an SpO<sub>2</sub> >94%. Women <55 years of age had to have a negative pregnancy test to be eligible for inclusion.

## Baseline Assessment

Baseline data in the form of descriptive demographic, clinical, and paraclinical data and data on comorbidities were collected from the patients' medical records at inclusion.

The paraclinical data were obtained from the first measurement taken on arrival of the active admission. The descriptive demographic data and data on comorbidity were obtained from the latest registration in the medical records with pneumonia verified by radiology, whereas the clinical data were obtained from EWS registration at the time of inclusion.

The administration of medication during the intervention was collected retrospectively from the medical records.

## Intervention

The O2matic (O2matic Ltd, Herlev, Denmark) is a device that delivers AOA by a closed-loop system, that continuously measures patients' peripheral oxygen saturation by pulse oximetry and automatically titrates oxygen flows according to it. In the O2matic, acceptable ranges for SpO<sub>2</sub> and oxygen flows are individually defined and increments or decrements in oxygen flows are based on the average SpO<sub>2</sub> of the past 15 seconds input from the pulse oximeter. The proportional change in flow will be relative to the difference between defined and actual measurements of SpO<sub>2</sub>.

Before randomization and initiation of the intervention, the accepted SpO<sub>2</sub> range (88–92% or 90–94% depending on clinical evaluation of the risk of hypercapnia) and accepted range of oxygen flows (0–6 L/min, 0–10 L/min, or 0–15 L/min) were selected. Patients were randomized and allocated 1:1 using REDCap electronic data capture tools (REDCap consortium, Vanderbilt University Medical Center, Nashville, TN, USA) hosted by the Capital Region of Denmark to either an intervention of AOA by the O2matic device or to standard care with manually nurse administered supplemental oxygen via O2matic. In the standard care group, the O2matic was converted into a manual device only showing oxygen flow and range on screen, with no data on SpO<sub>2</sub>. When in manual mode, oxygen flows were administered manually by the nurses like it is done in conventional oxygen therapy by flowmeters. In both groups the O2matic saves records of patients' saturation levels and oxygen flows throughout the intervention. The intervention would last for a maximum of three days or until patients were titrated back to pre-admission Long Term Oxygen Therapy (LTOT) flow or no oxygen flows. The intervention would stop earlier if patients were non-compliant, wished to stop the intervention, were dismissed, were transferred to another ward, or needed Non-Invasive Ventilation (NIV). If patients died or needed mechanical ventilation it was considered a serious adverse event and the intervention would also be stopped.

## Outcomes

The effect of AOA on dyspnea was assessed by Patient Reported Outcome Measurements (PROMs). The PROMs were collected bedside, interview-based, and in paper form, before patients were connected to the O2matic and after completing the intervention, preferably while still connected to the O2matic (see Figure 1). There were three different procedures for collecting end of intervention data:

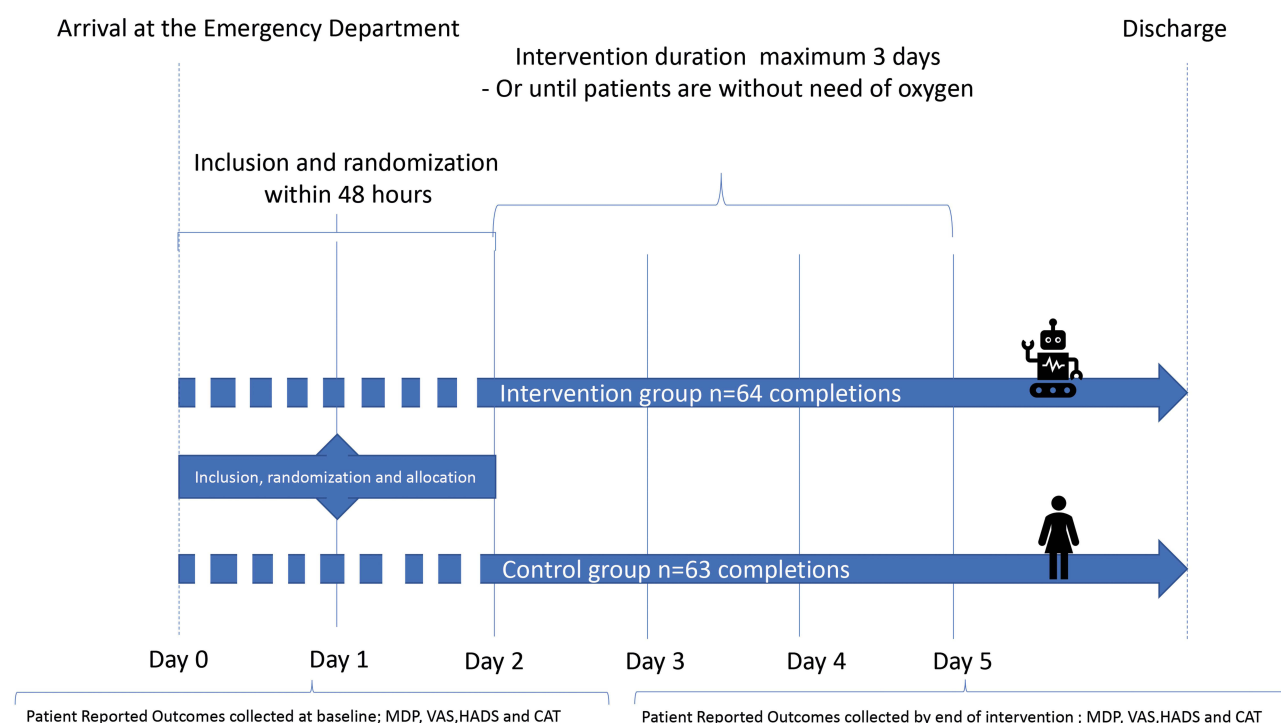
1. When the patients were back on the usual LTOT dose, the first author would come by the site, interview the patient who was still using the device, and discontinue the intervention afterward.
2. When the patients still had a need for supplemental oxygen throughout the intervention, in which case the intervention was ended after three days. Also, in this case, the first author would come by the site, interview the patient who was still using the device, and discontinue the intervention afterward.
3. The patients had become normoxic and weaned from oxygen within the three intervention days. In this case, patients were disconnected from the device by the ward nurses and the interviews would be conducted after weaning the intervention, but within a maximum of 12 hours.

Dyspnea was measured with the Multidimensional Dyspnea Profile (MPD)<sup>14,20</sup> and the Visual Analogue Scale – Dyspnea (VAS-D).<sup>21</sup> COPD symptoms were measured by the COPD Assessment Test (CAT)<sup>22–24</sup> and symptoms of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS).<sup>25,26</sup>

Primary outcome was the between group difference in perception of overall unpleasantness of dyspnea as assessed by the scale A1 on the MDP. The perception was assessed for the focal period of “past three days” at baseline and for “the duration of the intervention” by the end of intervention.

Secondary outcomes were the between group differences in:

- VAS-D assessed for the focal period of “current dyspnea” at baseline and at end of intervention, and VAS-D assessed for the focal period of “past three days” at baseline and for “the duration of the intervention” by the end of intervention.
- The sensory and emotional items of dyspnea as given on the MDP assessed for the focal period of “past three days” at baseline and for “the duration of the intervention” by the end of intervention.



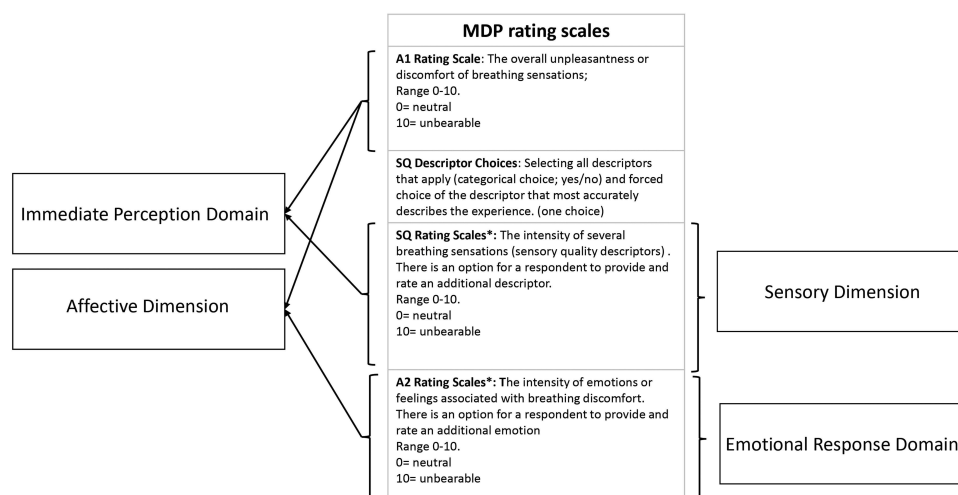
**Figure 1** Flow-chart describing the flow of included patients through the randomized design and data collection procedure. The flow-chart shows the patient-flow through the randomized design. It illustrates, on a day-to-day timeline, the inclusion of patients within first 48 hours of hospitalization and the randomization allocating patients to either the intervention or control group. In the intervention group, patients receive oxygen treatment by the device designed for Automated Oxygen Administration. In the control group, patients receive manual nurse-administered oxygen treatment. The intervention lasted a minimum of 4 hours and a maximum of three days and 21 hours or until patients were back on LTOT flow or without a need of oxygen supplementation. The procedures for data collection are shown at the bottom of the illustration. Patient Reported Outcome Measures (PROMs) are collected at inclusion (baseline) and by the end of intervention.

- The respiratory symptoms by CAT assessed for the focal period of “past three days” at baseline and for “the duration of the intervention” by the end of intervention.
- Anxiety and depression symptoms by the HADS assessed for the focal period of “past three days” at baseline and for “the duration of the intervention” by the end of intervention.
- The consumption of opioids and/or benzodiazepines reported in number of as-needed administrations for the duration of the intervention.

## The Multidimensional Dyspnea Profile

The MDP is a symptom specific questionnaire developed for clinical use. It has a user specified focus period, and measures dyspnea multidimensionally by a global scale A1 “Breathing discomfort” (range 0–10), a sensory dimension consisting of five single items (range 0–10, cumulated 0–40), and an emotional response domain also consisting of five single items (range 0–10, cumulated 0–40).<sup>14</sup> The higher the number, the more intense the symptom. The construct, dimensions, and domains are shown in Figure 2.

The questionnaire has a construct validity providing an ability to discriminate items and dimensions into separable components of dyspnea, making it possible to detect if a particular therapy may reduce a specific dyspnea sensation or emotional response by single items such as eg “air hunger” or “anxiety”.<sup>14</sup> The MDP questionnaire has been extensively tested and has shown a high reliability, validity, and sensitivity to clinical changes in different populations.<sup>27–30</sup> The MDP has been translated and linguistic validated for Danish.<sup>20</sup> The Minimal Clinical Important Difference (MCID) of the MDP has been given by Ekström et al in 2020 from a sample of cardiorespiratory outpatients.<sup>31</sup> The study found the mean (95% CI) of the COPD-specific MCIDs of the MDP A1 unpleasantness to be 0.58 (0.06–1.10) (n=35); MDP perception 3.02 (0.06–5.99) (n=28), and MDP emotional score 2.07 (–0.71 to 4.86) (n=37), respectively.<sup>31</sup>



**Figure 2** The construct, dimensions, and domains of the Multidimensional Dyspnea Profile. \*Additional descriptors (ie items) for SQ or A2 can be added if needed, using the same numerical rating scale and anchor statements for responses. The SQ descriptor Choices and the additional descriptors or emotions are also part of the MDP but are not incorporated in the domain scoring.

## Visual Analogue Scale – Dyspnea (VAS-D)

The VAS-D measures dyspnea on a 0–100 mm scale, anchored between extreme lowest or highest points, with 100 being most extreme dyspnea.<sup>32</sup> It is known that measures of “current dyspnea” and “usual dyspnea” correlate poorly,<sup>33,34</sup> thus we used the VAS-D to measure “dyspnea now” and “dyspnea over the past three days” at both inclusion and by the end of intervention. The MCID of VAS-D ranges from –13.9 mm to –9.5 mm, with effect sizes classed as large (–15.0 to –20.0 mm), moderate (–9.4 to –12.5 mm) and small (–4.7 to –6.3 mm).<sup>34</sup>

## COPD Assessment Test (CAT)

The CAT questionnaire is a COPD specific symptom screening tool that assesses disease severity.<sup>22,23,35</sup> The CAT consists of 8 items (range 0–40). A CAT score of 0–10 indicates low disease severity impact, a score of 11–20 medium impact, a score of 21–30 high impact, and 31–40 very high impact.<sup>36</sup> A change of 2 units is suggested as MCID.<sup>22,35</sup>

## Hospital Anxiety and Depression Scale (HADS)

The HADS has been developed to assess symptoms of depression or anxiety in hospitalized patients.<sup>26,37</sup> It consists of 14 items (range 0–3), with seven items reflecting symptoms of anxiety HADS-A scale (range 0–21) and seven reflecting symptoms of depression HADS-D scale (range 0–21). A score  $\geq 8$  in each scale is accepted as threshold for either clinical anxiety or depression.<sup>26</sup> The questionnaire has been extensively validated and has proved high sensitivity and specificity in both scales on somatic in-hospital populations.<sup>38</sup> It has also been validated in a COPD specific out of hospital population.<sup>39,40</sup> Based on effect sizes in a sample of 88 hospitalized patients with COPD, Puhan et al found the MCID for the HADS total score to be 1.17 and for the HADS anxiety and depression score the MCID was 1.32 and 1.40 respectively.<sup>41</sup>

## Statistical Analysis

As no MCID of the A1 scale of the MDP was published as we initiated this study, we assumed, based on literature, a reduction  $\geq 1$  unit on the MDP, with a standard deviation (SD) of 2 units, a sample size of 126 patients met the criterion of  $\alpha=5\%$  and  $\beta=20\%$ .<sup>27,42</sup> Only patients who received the intervention and had completed follow-up measurements were included in the present analysis (per protocol). In anticipation of a maximum 20% of lack of completion, our study was rounded up to a sample size of a minimum of 150 patients.

Estimates are presented as either frequency and percentage for categorical variables or mean/median with standard deviation (SD)/interquartile range (IQR) for continuous variables.

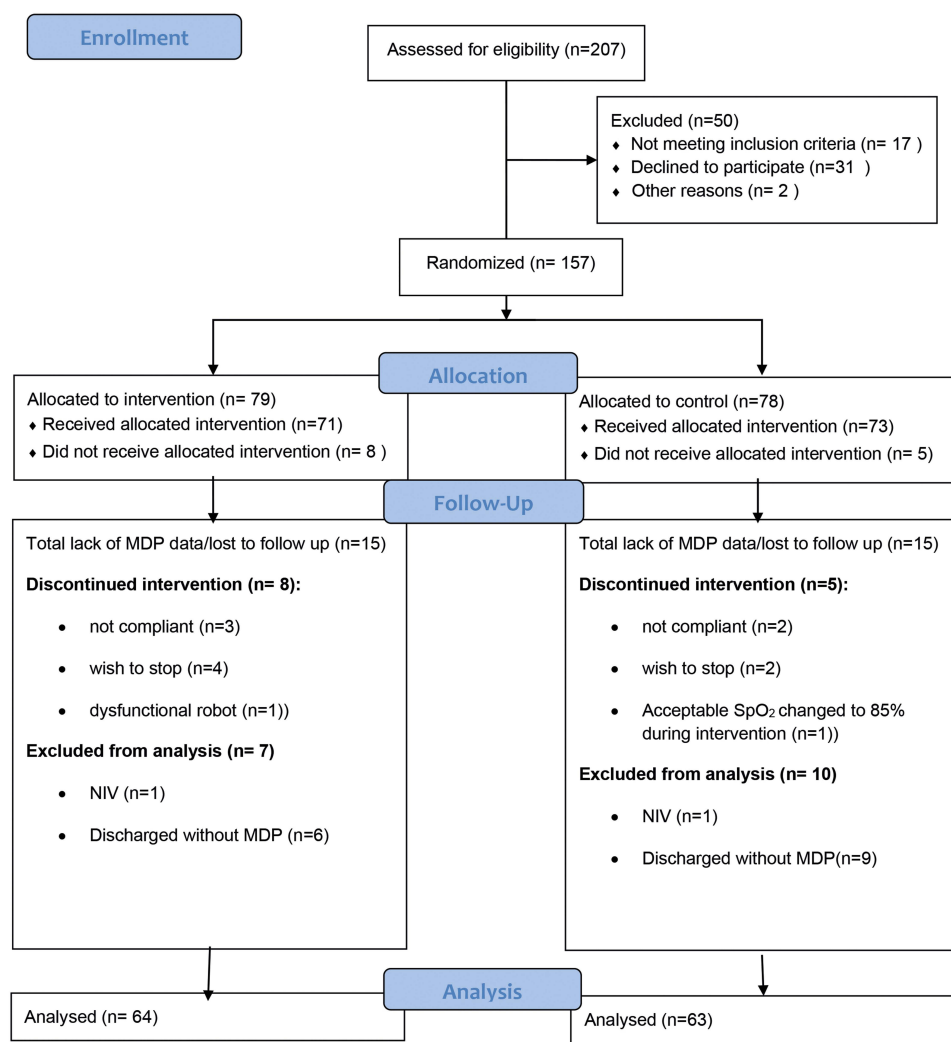
Changes from baseline to end of intervention of the primary and secondary outcomes were analyzed by either two-sample *t*-test or Wilcoxon rank sum test with continuity correction, if normality assumptions were not satisfied. Normality assumption of variables was evaluated by histograms and QQ-plots. Estimates from test are presented as mean or medians with *p*-values and 95% confidence intervals (CIs) where possible. Patients included in the primary analysis had no missing values on variables used in the analysis. *p*-Values of less than 0.05 were considered statistically significant. All analyses were done using R version 4.1.2.<sup>43</sup>

## Results

We included and randomized 157 patients allocated equally to either AOA (*n*=79) or conventional oxygen therapy (*n*=78), with a total of 127 patients completing the intervention and filling in questionnaires by end of intervention. Further details of inclusion and exclusion are displayed in Figure 3.

## Patient Characteristics

The patients' demographic characteristics, including markers of disease severity (MRC, comorbidity and exacerbation history), oxygen therapy, smoking status, spirometry values, and questionnaire scores, did not differ between groups at baseline (Table 1). However, the maintenance daily doses of morphine at baseline did differ slightly between the two groups (Table 2).



**Figure 3** Consort flow-chart of inclusion. Consort flow-chart of inclusion showing number of patients (*n*) assessed for eligibility, randomization, allocation, and completion for analysis of the primary outcome on the MDP.



**Table I** Characteristics of the Included Patients, n=157

Patient Characteristics by Inclusion			
Variables	Total	Intervention Group	Control Group
Female	85 (66.9%)	45 (70.3%)	40 (63.5%)
Age, years	75.3 (9.0)	76.6 (8.9)	74.0 (9.0)
Body mass index, kg/m <sup>2</sup>	25.4 (7.0)	24.4 (6.6)	26.3 (7.4)
Intervention time, days	2.1 (1.1)	2.1 (1.3)	2.0 (0.9)
Oxygen therapy at inclusion			
Peripheral oxygen saturation, %	90.4 (3.4)	90.3 (2.9)	90.5 (3.8)
Oxygen, L/min	2.1 (1.4)	2.0 (1.5)	2.1 (1.4)
LTOT yes	23 (18.5%)	11 (18%)	12 (19%)
LTOT dose, L/min	1.3 (0.5)	1.2 (0.3)	1.4 (0.6)
Smoking status			
Smoker	48 (38.7%)	23 (37.7%)	25 (39.7%)
Ex-smoker	74 (59.7%)	38 (62.3%)	36 (57.1%)
Never smoker	2 (1.6%)	0 (0%)	2 (3.2%)
Number of pack-years for current and former smokers	44.7 (22.0)	45.0 (19.9)	44.4 (24.0)
Spirometry			
FEV <sub>1</sub> , L	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)
FEV <sub>1</sub> , %pred	38.9 (15.7)	40.4 (17.6)	37.5 (13.7)
FVC, L	1.8 (0.7)	1.9 (0.7)	1.8 (0.7)
FVC, %pred	62.9 (22.0)	64.2 (25.1)	61.8 (19.2)
FEV <sub>1</sub> /FVC	0.48 (0.12)	0.47 (0.11)	0.48 (0.13)
Dyspnea MRC			
MRC 1	1 (0.8%)	1 (1.6%)	0 (0%)
MRC 2	7 (5.7%)	2 (3.3%)	5 (8.1%)
MRC 3	44 (35.8%)	20 (32.8%)	24 (38.7%)
MRC 4	31 (25.2%)	16 (26.2%)	15 (24.2%)
MRC 5	40 (32.5%)	22 (36.1%)	18 (29%)
Exacerbation history			
≤1 AECOPD/within last year	53 (42.7%)	26 (42.6%)	27 (42.9%)
≥2 AECOPD/within last year	71 (57.3%)	35 (57.4%)	36 (57.1%)
COPD admission ≥1	75 (60.5%)	39 (63.9%)	36 (57.1%)
Comorbidity			
Atrial fibrillation	16 (12.6%)	9 (14.1%)	7 (11.1%)
Ischemic heart disease	11 (8.7%)	5 (7.8%)	6 (9.5%)
Heart failure	13 (10.2%)	5 (7.8%)	8 (12.7%)
Diabetes type 1 and 2	18 (14.2%)	5 (7.8%)	13 (20.6%)
Cancer	6 (4.7%)	5 (7.8%)	1 (1.6%)
Pneumonia	29 (22%)	14 (22%)	15 (24%)
Bronchiectasis and/or interstitial lung diseases	14 (11%)	5 (7.8%)	9 (14.3%)
Arterial blood gas (ABG) and related oxygen flows			
pH	7.41 (0.046)	7.41 (0.047)	7.40 (0.044)
PaCO <sub>2</sub> (KPa)	6.5 (1.5)	6.6 (1.6)	6.4 (1.3)
PaO <sub>2</sub> (KPa)	8.6 (2.5)	8.5 (1.5)	8.7 (3.1)

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**Table 1** (Continued).

Standard bicarbonate	27.9 (5.9)	27.8 (7.2)	27.9 (4.4)
Oxygen flow, L/min	2.3 (1.2)	2.3 (1.1)	2.2 (1.3)
Blood values			
Hb, mmol/L	8.4 (2.2)	8.4 (2.4)	8.5 (1.9)
Leukocytes (10 <sup>9</sup> cells pr. L)	11.1 (5.3)	10.7 (5.7)	11.5 (4.8)
CRP, mg/L	59.4 (82.6)	59.1 (82.8)	59.8 (83.1)
Creatinine, µmol/L	83.2 (34.5)	81.1 (32.1)	85.3 (36.7)
Potassium, mmol/L	4.0 (0.5)	3.9 (0.4)	4.1 (0.5)

**Notes:** Data are presented as counted numbers with percentage (%), means with standard deviations. The descriptive data on patient characteristics, smoking status, spirometry, exacerbations and comorbidity were obtained from the latest registration in the medical records, with pneumonia confirmed by radiology. Data on arterial blood gasses and blood values were obtained from the first registration by arrival for the current admission. Oxygen therapy was registered by inclusion.

**Abbreviations:** LTOT, Long Term Oxygen Therapy; FEV<sub>1</sub>, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; MRC, Medical Research Council Dyspnea Scale; AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; GOLD 1–4, Global initiative for chronic Obstructive Lung Disease classification of airflow limitation severity in COPD; pH, potential of hydrogen; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; Hb, hemoglobin; CRP, C-reactive protein.

**Table 2** Baseline Symptom Scores are Given in Medians and Inter Quartile Ranges (IQR) and Fixed Daily Dose of Drugs in mg are Given in Mean (SD)

Baseline Symptom Scores Dyspnea “Overall unpleasantness” AI MDP (range 0–10)			
Variables	Total	Intervention Group	Control Group
MDP dyspnea, “overall unpleasantness”	8 (6: 9.5)	8 (7: 10)	8 (5: 9)
Intensity of five sensory qualities on the MDP (range 0–10)			
Physical breathing effort	8 (5: 9)	8 (6: 9)	8 (3: 9)
Air hunger	8 (5: 9.5)	8 (5: 9.25)	8 (5: 9.5)
Chest tightness	5 (0: 8)	6 (0: 9)	4 (0: 7)
Mental breathing effort	8 (5: 9)	8 (5: 9)	7 (5: 9)
Hypernea	8 (7: 9)	8 (8: 9)	8 (6: 9)
Intensity of five emotions on the MDP (item range 0–10)			
Depressed	2 (0: 7)	3 (0: 7)	1.5 (0: 5.75)
Anxious	5 (0.25: 9)	6.5 (2: 9)	5 (0: 8.75)
Frustrated	5 (0: 8)	5 (0: 8)	5 (0: 8)
Angry	0 (0: 5)	1 (0: 7)	0 (0: 5)
Afraid	5 (0: 9)	5 (0: 8)	5 (0: 9)
COPD Assessment Test (CAT) (total sum range 0–40)			
CAT total sum	24.5 (20: 29)	25 (22: 29)	23 (19: 29)
Hospitals Anxiety and Depression Scale (HADS) Composite anxiety (HADS-A) and composite depression (HADS-D) (ranges 0–21)			
HADS-A	9 (5: 13)	10 (6: 13)	7.5 (4.25: 12)
HADS-D	9 (5.75: 12)	9 (6: 12)	8 (4: 13)
Visual Analog Scale (VAS) (range 0–10)			
VAS-dyspnea now	50 (25: 66.75)	50 (25.75: 65)	47.5 (24.5: 70)
VAS-dyspnea past 3 days	92 (74.5: 97.25)	92.5 (75.75: 98)	91.5 (71.75: 97)

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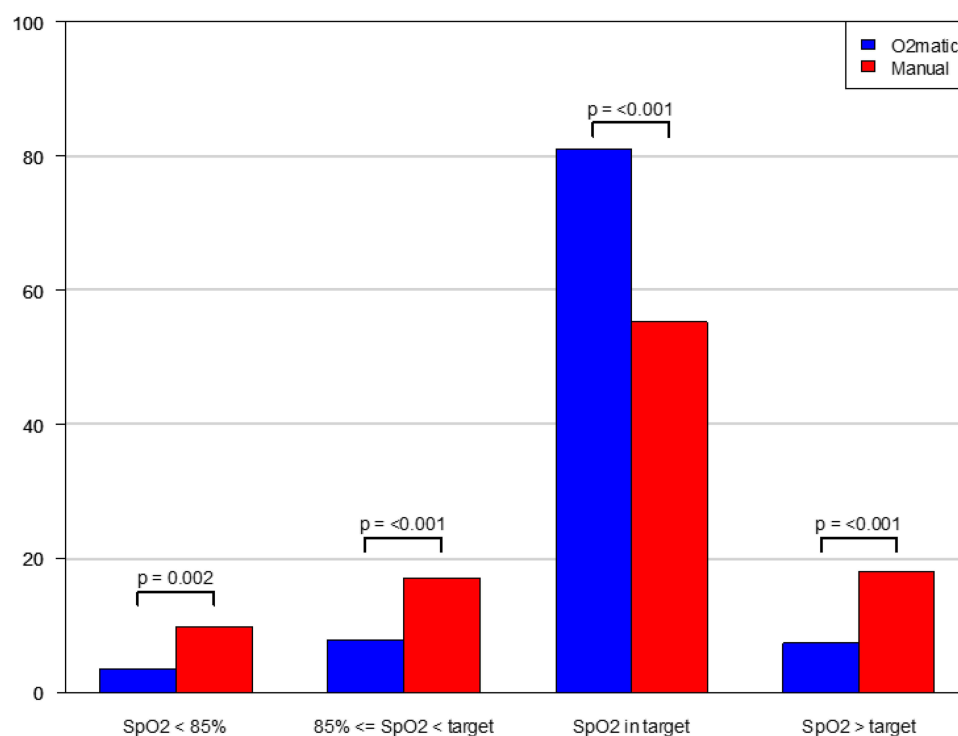


Table 2 (Continued).

Baseline Symptom Scores Dyspnea "Overall unpleasantness" AI MDP (range 0–10)			
Variables	Total	Intervention Group	Control Group
Opioids and benzodiazepines fixed daily dose mg at inclusion			
Morphine oral	4.1 (18.0)	2.5 (9.3)	5.8 (23.8)
Morphine IV	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Morphine (oral route)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Benzodiazepines	0.99 (5.78)	0.98 (5.80)	1.0 (5.81)
Lorazepam	0.02 (0.2)	0.0 (0.0)	0.05 (0.3)
Oxazepam	0.9 (5.7)	0.8 (5.7)	1.0 (5.8)
Diazepam	0.08 (0.9)	0.2 (1.2)	0.0 (0.0)
Sleep medicine	0.9 (2.7)	0.7 (2.0)	1.1 (3.3)
Imoclone	0.1 (1.3)	0.0 (0.0)	0.2 (1.9)
Zolpiclone	0.8 (2.4)	0.7 (2.0)	0.9 (2.8)

**Notes:** "Benzodiazepines" is a cumulation of Lorazepam, Oxazepam, and Diazepam. "Sleep medicine" is a cumulation of Imoclone and Zolpiclone. Baseline symptom scores are given in medians and Inter Quartile Ranges (IQR) and fixed daily dose of drugs in Mg are given in mean (SD).

The mean duration of the intervention was 40 hours in both groups and the median length of stay across the two groups was 6.0 days, whereas the median time from randomization to discharge was 5.7 days. The fraction of time with normoxemia ( $\text{SpO}_2$  in target, either 88–92% or 90–94%), hyperoxemia ( $\text{SpO}_2 > \text{target}$ ), hypoxemia ( $\text{SpO}_2$  between 85 and target), and severe hypoxemia ( $\text{SpO}_2 < 85\%$ ), respectively, are presented in Figure 4, for the intervention group and the control group.



**Figure 4** Fraction of time with different saturation levels. The figure shows the fraction of time spent with severe hypoxemia, hypoxemia, normoxemia, and hyperoxemia for the intervention group (O2matic, blue color) and the control group (manual oxygen administration, red color) respectively, with  $p$ -values for the difference between the groups.

## Primary Outcome

The overall unpleasantness of dyspnea on the A1 scale of the MDP was reduced significantly by AOA with a between group difference in medians of  $-3$  ( $p=0.003$ ), median [IQR] of  $-5$  [ $-6$ :  $-2$ ] in the intervention group and  $-2$  [ $-6$ :  $0$ ] in the control group. Overall unpleasantness on the MDP had an intensity at baseline of median [IQR]  $8$  [ $7$ :  $10$ ] in the intervention group and  $8$  [ $5$ :  $9$ ] in the control group. The intensities given by median [IQR] at follow-up were respectively  $3$  [ $2$ :  $5$ ] in the intervention group and  $4$  [ $2.5$ :  $7$ ] in the usual care group. The within group differences are illustrated in the spaghetti plots [Figure 5](#).

All within group changes are presented in [Table 3](#).

## Secondary Outcomes

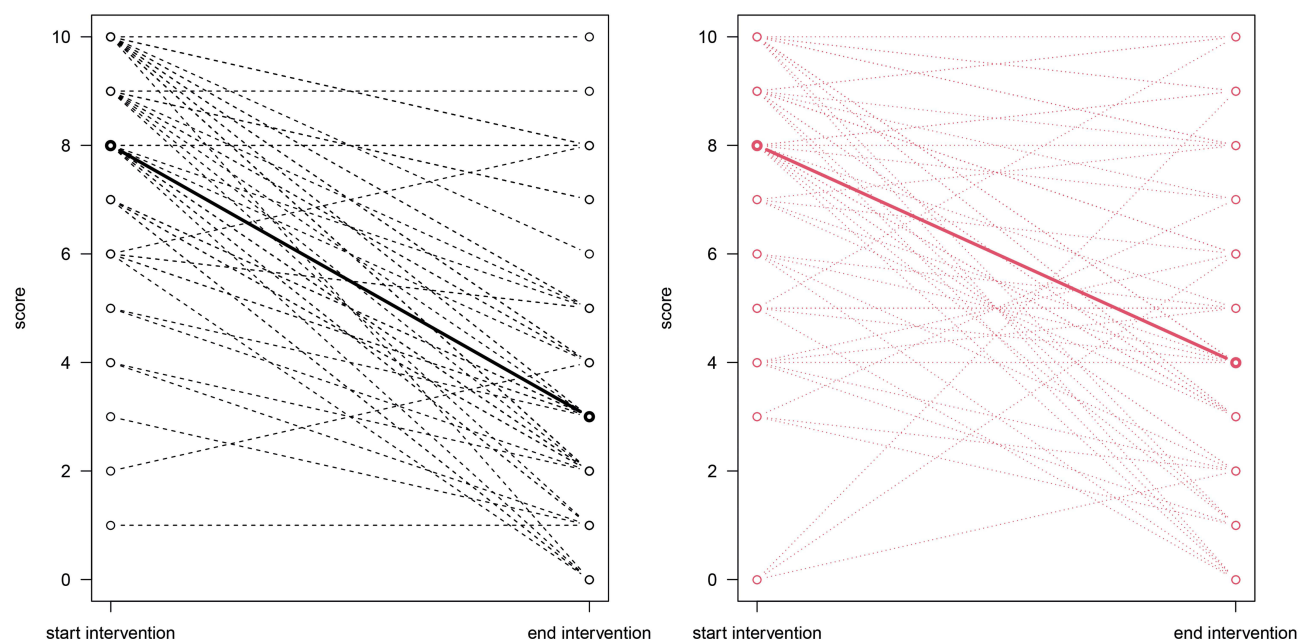
Differences in median change between the intervention group and the control group in the five items within the sensory dimension of the MDP and “VAS-dyspnea past three days” are given in medians [IQR] in [Table 4](#) (all  $p$ -values  $\leq 0.03$ ). No significant difference between groups was found for the CAT-score, HADS-A, HADS-D, or the cumulated number of as-needed administrations of opioids and/or benzodiazepines ( $p=0.061$ ).

The choice of “Air hunger” as the most accurate descriptor was reduced during the intervention from 26 to 6 patient choices in the intervention group as opposed to a reduction from 28 to 20 patient choices in the control group ([Table 3](#)).

## Discussion

This study shows that AOA reduces dyspnea overall unpleasantness, in patients hospitalized with AECOPD and hypoxemia, when compared to conventional oxygen therapy. The AOA also reduces all the five items within the sensory dimension of dyspnea, as well as dyspnea within past three days, significantly when compared to conventional oxygen therapy. All of these results were substantial in size and according to MCID the effect size, they should be considered clinically relevant.<sup>31,34</sup>

The effect of AOA on dyspnea measured on the A1 scale is clinically relevant, with a within group reduction in the intervention group of more than eight times the MCID and a between group difference of more than three times the reported MCID.<sup>31</sup> Furthermore, Stevens et al found an intensity of dyspnea on the A1 scale to be acceptable to patients if  $<4$  on the 0–10 rating scale,<sup>44</sup> underlining the clinical important impact of AOA in our study, as dyspnea on the A1 scale was reduced to a median of 3 in the intervention group and 4 in the control group.



**Figure 5** Spaghetti plots. The figures illustrate the within group difference in overall unpleasantness on the A1 scale for the intervention group (black spaghetti plot) and the control group (red spaghetti plot). Dashed lines represent patterns of change, that may include more than one patient ID, and bolded/fat lines illustrates the median within group difference between baseline and follow up.

**Table 3** Data are shown as medians with Inter Quartile Ranges [IQR].

Changes in Symptom Intensities within and Between Intervention and Control Group				
Variable	Within intervention-group changes; median [IQR]	Within control-group changes; median [IQR]	Difference in median change between the intervention and the control group	p-Value for between groups differences
Dyspnea overall unpleasantness, scale AI MDP (range 0–10)				
Dyspnea overall unpleasantness	–5 [–6: –2]	–2 [–6: 0]	–3	0.003*
Intensity of five sensory qualities on the MDP (item range 0–10)				
Physical breathing effort	–3 [–6: 0]	–1 [–3: 1]	–2	0.005*
Air hunger	–4 [–7: –1.25]	–1 [–3: 0]	–3	<0.001*
Chest tightness	–1 [–5: 0]	0 [–1: 0]	–1	<0.001*
Mental breathing effort	–4 [–7: 0]	–1 [–4: 0.5]	–3	0.029*
Hyperpnea	–3 [–6: 0]	–2 [–4.5: 0]	–1	0.032*
MDP sensory dimension				
Cumulated intensity of five sensory qualities	–16.5 [–26: –3.75]	–7 [–14: 2]	–9.5	<0.001*
Intensity of five emotions on the MDP (item range 0–10)				
Depressed	0 [–3: 0]	0 [–2: 0]	0	0.936
Anxious	–2 [–5: 0]	–0.5 [–4.75: 0]	–1.5	0.103
Frustrated	0 [–3.25: 0]	0 [–2.75: 0]	0	0.298
Angry	0 [–2: 0]	0 [0: 0]	0	0.247
Afraid	0 [–6.75: 0]	0 [–4: 0]	0	0.627
MDP affective dimension				
Cumulated intensity of five emotions**	–9.6 [–15.0: –4.1]	–6.7 [–12.1: –1.2]	–2.9 [–10.7: 4.9]	0.461
COPD Assessment Test (CAT) (total sum range 0–40)				
CAT total sum	–3 [–6: 0]	–1 [–5.75: 2.75]	–2	0.079
Hospital Anxiety and Depression Scale (HADS) (composite anxiety (HADS-A) or depression (HADS-D) range 0–21)				
HADS-A	–3 [–8: 0]	–2 [–5: 0]	–1	0.309
HADS-D	–1 [–5: 1]	–1 [–4.25: 2]	0	0.719
Visual Analog Scale (VAS) (range 0–10)				
VAS-dyspnea now**	–19.2 [–26.7: –11.8]	–8.2 [–17.2: 0.7]	–11.0 [–22.8: 8]	0.067
VAS-Dyspnea 3 days	–56.5 [–77: –18.5]	–27 [–57: –2]	–29	0.013*

**Notes:** \*p-Value<0.05 is considered statistically significant. \*\*Estimates reported as mean with 95% confidence intervals and p-values from t-test.

**Table 4** Reflection of Patients' Answers to the SQ Descriptor Choice Shown in Figure 2: The Construct, Dimensions, and Domains of the Multidimensional Dyspnea Profile

Sensory Item that Most Accurately Describes Your Sensation of Dyspnea	Intervention Group Baseline (n)	Control Group Baseline (n)	Intervention Group End of Intervention (n)	Control Group by End of Intervention (n)
My breathing requires muscle work or effort	1	1	4	5
I am not getting enough air or I am smothering or I feel a hunger for air	26	28	6	20
My chest and lungs feel tight or constricted	7	9	8	13
My breathing requires mental effort or concentration	6	7	10	5
I am breathing a lot	9	9	14	9

**Notes:** Total number of answers (n) in Table 4 does not add up to n=127 at baseline nor by end of intervention, since many patients had a hard time choosing a descriptor.

Moreover, AOA reduced patients' perception of anxiety by 2 units in the intervention group as opposed to 0.5 units in the control group on the MDP. We found no reports on the MCIDs on item level for the MDP except from the A1 scale.<sup>31</sup> However, the MCIDs are reported on domain level by Ekström et al, and are given by a mean (95% CI) 3.02 (0.06: 5.99) for the "sensory domain" and 2.07 (−0.71: 4.86) for the "emotional domain",<sup>31</sup> making the effect of the AOA on the sensory domain not only significant but also clinically relevant. Given that the item scales have identical rating scales, with ranges from 0 to 10, the reduction of 2 units on the anxiety item, could potentially be considered clinically important, but psychometric evidence lacks. We also found a trend towards a reduction in as-needed use of opioids and benzodiazepines, however this was not significant.

Our results on patients' perceptions of dyspnea showed the five items within the sensory dimension on MDP to have higher intensity by admission and a greater sensitivity to AOA, than the five items within the emotional dimension. Our study also reports that "Air hunger" was the descriptor that most accurately describes how patients hospitalized with AECOPD's breathing feel at admission. A finding consistent with a study that assessed dyspnea in 156 hospitalized patients of mixed diagnoses via MDP, which found that "air hunger" was the most predominant and intense component of severe dyspnea.<sup>44</sup> Furthermore, our study shows that the choice of "Air hunger" as the most accurate descriptor was reduced by 20 patient choices in the intervention group as opposed to 8 patient choices the control group, indicating an effect of AOA on sensations of "Air hunger".

Air hunger is known to be unpleasant and to induce a more intense emotion of anxiety than eg work effort, which may explain why the anxiety item was the only item within the emotional domain that was also reduced by the AOA intervention.<sup>45</sup> A laboratory study, on healthy subjects, showed that hypoxic and hypercapnic drives to breath generate sensations of "air hunger".<sup>16</sup> The semantic structure of the MDP, that makes single items responsive to specific exposures, provides an option to relate the measures to literature. A trial including patients hospitalized with AECOPD from the same wards as our study found the fraction of time with SpO<sub>2</sub><89% to be 42.9%, whereas the fraction of time with SpO<sub>2</sub>>92% was 10.5% when oxygen was administered by a nurse.<sup>5</sup> Therefore, we believe that hypoxemia and oxygen under-treatment may be the main contributor to the intensity of breathing discomfort, the sensory predominance of air hunger, and the emotional response of anxiety, in hospitalized patients with AECOPD. The results from Hansen et al in combination with our results indicates a limited impact of hyperoxemia on dyspnea and anxiety. We believe this to be an important point, since hyperoxemia must be considered a therapeutic consequence of oxygen supplementation. A "side effect" identified across settings by several observational studies, showing a severe tendency of hyperoxygenation in patients hospitalized with AECOPD, increasing their risk of hypercapnic respiratory failure.<sup>46–49</sup> The association between the fraction of time with hypoxemia or hyperoxemia and specific items on the MDP in patients admitted with AECOPD needs to be investigated further.

Dyspnea is a cardinal symptom of COPD, with a severe and debilitating impact on patients' quality of life. The symptom is one of the main reasons for patients seeking hospital emergency units, and getting hospitalized, and it

remains a major limit for discharging patients and it is a contributing cause of readmission. During admission the high intensity of dyspnea often requires nurse attention, interventions, and time. Alleviating dyspnea by AOA may therefore not only impact the patients' quality of life, the length of hospital stays, and nurse resources, but may also be a potential palliative intervention across different etiologies.

## Strength and Limitations

A main strength of our study is the multicenter RCT design. Further, the treatment groups were fairly balanced on key predictors of outcomes in patients with COPD reflecting a valid method of randomization, and we had a reasonable degree of follow-up. Patients recruited in our study were very ill and might have been excluded from participating in other randomized trials, and we find it a strength that we hereby contribute to solid data in a rigid design on these severely ill patients.

We prioritized to collect our data through individual interviews, not self-administration, and thereby we believe we have provided the study with data of high quality and completeness. To ensure this, some end-of intervention data were collected while the patient were still receiving the intervention (if the patients were back on the usual LTOT dose or if the patient had a need for supplemental oxygen throughout the intervention), while some were collected without the patient being connected to the device (if the patient had become normoxic and had weaned from oxygen, then the ward nurses would have disconnected the device) and the different procedures must be considered when interpreting the results. However, despite the different procedures for data collection, we do not think this procedure to have had an effect on our results, since our focus period is short, the risk of recall bias equally split between the two groups due to the randomized design, and the patients, although severely sick, were cognitive capable to provide clinically relevant PROMS. By describing both the physical and emotional dimensions of dyspnea, as an outcome of AOA, the study has provided a wide description of the impact of the intervention, which must be considered a strength.

Despite the strengths, some limitations deserve careful consideration. First, the open-labeled design may have been a limitation, as it may have biased the patients' subjective experiences of the sensory and emotional aspects of dyspnea. Thus, the reduction seen on the anxiety item could be explained by this mechanism, but this remains speculative as the design does not provide further arguments to prove or disprove this assumption. It should be mentioned that dyspnea is by definition subjective and cannot be consistently measured, and that subjective data are more sensitive to open label originated biases. Also, the first author both enrolled patients in the study and collected the data, a combination that may have generated social-desirability bias. Our inclusion was somewhat slow, partly due to COVID-19 and partly due to NIV as an exclusion criteria. Nonetheless, we believe the risk of NIV therapy is generalizable across advance stages of COPD. Because we included a population of severely ill patients in an acute phase of their disease, fatigue, delirium, breathlessness, and terminal stage of disease were the main reasons for non-participation and loss to follow up, although this was at a reasonable level. Excluding the sickest and expectedly the population with the most severe symptoms may introduce selection bias and must be evaluated as a limitation of the study. Nonetheless, we consider these circumstances to be an unavoidable condition in any acute setting and a reflection of the reality we seek to mirror, and our results needs to be interpreted considering these limitations.

In conclusion, AOA reduces the overall breathing discomfort and the sensory dimension of dyspnea significantly, but not the emotional response or consumption of as-needed opioids or benzodiazepines, in patients hospitalized with AECOPD and hypoxemia.

The high intensity of dyspnea during admission often requires intense nurse interventions and time. Alleviating dyspnea by AOA may not only increase the patients' quality of life, but may also reduce the length of hospital stays and the use of nurse resources.

## Data Sharing Statement

The authors will share all study data. However, we must comply to national and international data regulations to protect patient's right to own data. Thus, scientists can approach the corresponding author with a plan, and we will do every effort to help formulating the request within legislative frames.

## Ethics Approval and Informed Consent

All patients involved in the study signed an informed consent approved by the Capital Regions' Committee on Health Research Ethics (H-17040114).

## Consent for Publication

All authors involved in the study gave consent for publication.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

O2matic Ltd has not been involved in the study. EFH is the main inventor of O2matic Ltd and a shareholder but has not been involved in data collection or analysis. The authors report no conflicts of interest in this work.

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