

# Acute Dyspnea After Use of Non-Invasive Ventilation in COPD Patients: The Deventilation Syndrome

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## Research

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# Abstract

**Background:** In daily routine, many COPD patients lament early onset augmented dyspnea following use of NIV (Deventilation Syndrome, DVS) as a negative side-effect. This is the first study to this date to quantify and characterize DVS.

## Methods

This monocenter prospective observational study collected demographic, physiologic and symptomatic data from 67 in-patients with severe COPD Gold III-IV and chronic hypercapnic failure before, during and after use of an established NIV.

During their inpatient follow-up, we examined patients during the first hour after termination of nocturnal NIV. DVS was defined by the authors as an increase of  $\geq 2$  points on the Borg scale during the first 30 minutes. We monitored cardiovascular and respiratory data and measured diaphragm excursion. Subjective dyspnea was documented by use of the Borg scale and questionnaires. In addition, respirator and demographic data were collected.

## Results

DVS occurred in 58% of our COPD patients. Patients with DVS were more severely ill than non-DVS concerning bronchial obstruction (FEV1 0.6 vs 0.8l,  $p < 0.05$ ) and hypercapnia during spontaneous breathing (pre NIV pCO<sub>2</sub>: 54.5 vs 49.3mmHg,  $p < 0.02$ ). DVS patients showed significantly higher respiratory rates (RR) (20.1 vs 18.1/min  $p < 0.05$ ) after termination of NIV.

## Conclusions

This is the first trial quantifying and characterizing early onset augmented dyspnea after the use of NIV, referred to as DVS. It is now brought to attention as a frequent side effect of long-term home ventilation and possible pathophysiologic mechanisms are elucidated.

## Key Messages

Many patients with COPD and long-term non-invasive ventilation (NIV) suffer augmented dyspnea after use of therapy. To this date, frequency and cause of this side effect remained unnoted. This is the first study to document this negative side-effect, hereby labeled Deventilation Syndrome (DVS). In this study, 58% of the examined COPD patients suffered from DVS, defined as an acute increase of dyspnea  $\geq 2$  points via Borg scale after termination of NIV. A main key cause of DVS may be breath rate acceleration and dynamic hyperinflation after the use of NIV.

## Introduction

Non-invasive positive pressure ventilation (NPPV, NIV) is a widespread therapeutic option for patients with chronic hypercapnic failure due to COPD [1, 2] Effectively reducing hypercapnia by high-intensity ventilation can not only lead to improvement of health-related quality of life and lung function status, but has shown to reduce hospital re-admission and prolong long-term survival [1]. Persistent improvements of dyspnea in the daytime have also been documented [3, 4].

Aside many positive aspects, there are also negative side effects of NIV. Most commonly described are dryness of the upper airways, abdominal bloating or sleep fragmentation [5, 6], but also multifaceted fear of therapy [7].

This study now describes a further, highly burdening side effect: early onset acute dyspnea following the use of NIV – augmented in the morning, but also after use during the day.

During ongoing NIV, patients experience relief of dyspnea and can breathe without effort. In some patients, termination of NIV within minutes leads to increasing dyspnea and discomfort. This is accompanied by tachypnea with rapid, shallow breathing, increased heart rate, the need to sit upright (coachman's seat) and the feeling of restlessness, sometimes even leading to panic attacks and fear of use of NIV. This state is hereby defined as the Deventilation Syndrome (DVS).

The nomenclature “Deventilation Syndrome” is first found in a publication by Adler et al. [8], describing morning dyspnea mainly due to ventilator desynchronization in sleep medicine.

The novel use of this term has been adapted to describe augmented post-NIV dyspnea in an adequate and sufficient ventilatory situation.

COPD patients with long-term home ventilation (LT-NIV) were surveyed during a routine in-patient exam and additionally monitored in the first hour of post nocturnal use of NIV – thus establishing not only occurrence of DVS, but also possible physiological mechanisms.

This is the first study to this date to define and characterize DVS in patients with COPD and LT-NIV. Despite high prevalence and symptom burden, DVS so far remains widely unaddressed.

## **Methods**

### **Design**

In a monocenter prospective observational study demographic, physiological and subjective data was collected from in-patients with severe COPD III-IV and chronic hypercapnic failure before, during and after use of an already established NIV.

Extended routine examinations included cardio-respiratory monitoring during and one hour after the nocturnal use of NIV, including ultrasonic diaphragm measurements. Subjective dyspnea was documented before and after use of NIV by use of the Borg scale and questionnaires were supplemented.

Being an observational study to document the Deventilation Syndrome, no study endpoints were defined. The authors refrained from power calculation due to the observational character of the study.

## Patients

Between November 2016 and January 2019, 71 patients with severe COPD (Gold III<sup>o</sup>-IV<sup>o</sup>) and established long-term home NIV were included in the study. Sufficient data was collected from 67 patients. Inclusion criteria were: men and women with stable COPD disease, GOLD stage III-IV, regular use ( $\geq 4\text{h/d}$ ) of NIV (prescription  $\geq 1$  year) and age  $> 18$  years. Study participation required written consent and patients had to be able to follow the requirements of the project. The study protocol was granted permission by the ethics review board of the University of Heidelberg, Germany and all patients gave their written consent.

During the study any medically necessary concomitant therapy was allowed. Intercurrent diseases were treated according to the clinic standard.

Exclusion criteria were: Acute pulmonary impairment (e.g. pneumonia), other acute diseases such as acute pulmonary artery embolism, haemoptysis, internal bleeding, pneumothorax. In addition, serious neurological disorders (e.g. apoplex) or cardiovascular diseases with hemodynamic instability (e.g. heart failure NYHA  $\geq$  III, myocardial infarction  $< 1$  month ago) were excluded, as also newly occurring hypoxemia or worsening of hypercapnia  $\geq 20\%$  compared to previous values. In addition, alcohol/drug/drug abuse made participation in the study impossible.

## Deventilation Syndrome (DVS)

DVS is determined by dyspnea – a highly subjective symptom. Objectification is best done by use of the modified Borg scale [9] The minimal clinical importance difference for Borg is 1 point [10]. Being a novel syndrome, there is no definition of DVS to this date. For this study and further use of this terminology, DVS was defined by an increase of subjective dyspnea by  $\geq 2$  points on the Borg scale during the first 30 minutes after NIV termination – thus stressing the symptomatic and chronologic context after use of NIV.

## MEASUREMENTS

### Survey examination timeline

**Baseline (T0, day of admittance):** anamnesis, PE, questionnaires, BGA w/wo NIV, pulmonary function tests,  $\text{spO}_2$ , breath and heart rate, blood pressure, ultrasound measurement of diaphragm excursion

**Tn (following morning, with NIV):** dyspnea by Borg scale,  $\text{spO}_2$ ,  $\text{tCO}_2$ , breath and heart rate, blood pressure

**T1 (10 min post NIV):** dyspnea by Borg scale (and every 10 min for the following hour), BGA,  $\text{spO}_2$ ,  $\text{tCO}_2$ , breath and heart rate, blood pressure, ultrasound measurement of diaphragm excursion

**T2 (60 min post NIV):** dyspnea by Borg scale, BGA,  $\text{spO}_2$ ,  $\text{tCO}_2$ , breath and heart rate, blood pressure

## **Pulmonary Function Diagnostics**

These were carried out according to the internal standards of the lung function department of the University Thoraxklinik Heidelberg, using MasterScreenBody and PFT Body + Diff. by Care Fusion (Jaeger).

Body plethysmography:

Documentation of body plethysmography (functional residual capacity (FRC<sub>pleth</sub>), specific airway resistance (sRaw), total lung capacity (TLC) and residual volume (RV), airway resistance was calculated by use of sRaw and FRC(pleth)) and spirometric data (vital capacity (VC), forced vital capacity (FVC), forced expiratory volume (FEV1) and percentage value Tiffeneau index. Furthermore, measurement of diffusion capacity (TLC<sub>CO</sub>).

Reference values were calculated according to GLI for spirometric parameters and TLC<sub>CO</sub> [11, 12], while ECSC was referenced for body plethysmography [13].

Respiratory muscle strength:

Exhaustion of respiratory muscle function was measured non-invasively by maximal inspiratory mouth pressure (P<sub>imax</sub>), reflecting respiratory capacity. The respiratory load was documented by measurement of occlusion pressures (P<sub>0.1</sub>) [14].

## **Ultrasonic diaphragm measurement**

Measurements of diaphragm excursion were performed using the Philips Ultrasound Sparq with an abdominal transducer C 6-2. Patients were examined during spontaneous breathing on admission day (T<sub>0</sub>) and the following morning after termination of NIV (T<sub>1</sub>). This was done in a dorsal lying position, the torso elevated at approx. 45°. The right diaphragm was located in B-Mode and then excursion measured in M-Mode subcostal, mid clavicular line [15, 16].

## **Measurement of carbon dioxide values and blood gas analysis**

Carbon dioxide values were collected by two methods: continuous transcutaneous measurement and capillary blood draw (blood gas analysis, BGA), both examined on the earlobe.

BGA was assessed by arterialized capillary ear-lobe puncture earlobe skin [17]. The ABL 800 flex from Radiometer GmbH was used as blood gas analyzer. Transcutaneous CO<sub>2</sub> measurement was performed using TOSCA transcutaneous monitor TCM 4, Radiometer.

## **Monitoring**

Nightly monitoring of patients undergoing long term home NIV is an essential part of NIV surveillance, reflecting the respiratory situation and efficiency of ventilation during sleep. This standardized procedure

was performed during nocturnal use and extended one hour after termination of NIV on our ward using Philips IntelliVue MX550 monitors.

## **Questionnaires**

Borg perception of exertion CR10 Scale

Acquired by Modified Borg Scale (MBS) with 10-point dyspnea assessment [9]. An increase of  $\geq 2$  points after NIV termination was defined by the authors as relevant for DVS.

CAT: COPD Assessment Test

Cut off:  $< 10$  = low impairment to  $> 30$  = very high impairment [18].

mMRC: Modified Medical Research Council

Score from 0 ("never breathless, except during intense exertion") to 4 ("too short of breath to leave the house or to dress and undress alone") [19].

## **Statistical analysis**

Baseline characteristics are presented for the whole sample and stratified by group (DVS vs nDVS) by mean and standard deviation (SD) or median and interquartile range (IQR) or frequencies (n, %) as appropriate. Differences between groups were investigated by means of independent t-test, Mann-Whitney U test or chi-square test retrospectively. Continuous variables were explored graphically to justify parametric analysis.

Longitudinal models were applied to test for time x group effects for outcomes measured over time. Except for BORG (ordinal scale), a linear regression model with repeated measures statement was applied for each outcome with the explaining variables time, group, and interaction term. Group and time effects with confidence intervals and p-value were presented based on the contrast between groups at each visit and contrasts between the visits for each group.

For Borg, the total score was analyzed descriptively by median (IQR) at the four measurement points in time for each group (DVS and nDVS).

To analyze the relationship of Borg and FEV1, Spearman correlation coefficients were calculated.

This is an exploratory analysis so that p-values are interpreted descriptively. A p-value  $< 0.05$  was considered statistically significant. All analyses were performed in SAS version 9.4.

## **Results**

### **Baseline Characteristics**

Between November 2016 and January 2019, 71 patients were included in the study. One patient was excluded due to double enrollment, three patients did not complete the Borg scale, therefore 67 patients were further evaluated. 39 patients were retrospectively diagnosed with DVS, 28 did not present DVS symptoms.

Enrollment included overall 28 males and 39 females (corresponding to 42% and 58% respectively). The mean (SD) age of all patients was  $66.1 \pm 6.7$  years. Comorbidities were widespread, but severe and/or acute diseases were excluded according to the exclusion criteria of the study protocol.

No serious complications occurred during the study, e.g. acute exacerbation of the disease. All patients were compliant with both participation in the study and with their NIV therapy. However, 5 patients did not wish to perform lung function tests. In all, 13 patients were unable to undergo or complete body plethysmography due to their physical constitution and extremely high lung inflation, one further patient had non legible RV rates. Interestingly, 11 of these 13 patients were retrospectively diagnosed with DVS.

## Ventilatory setting

Ventilatory settings (VS) were documented (Table 1). The majority of patients was ventilated in ST mode (spontaneous/timed mode), 2 patients of the cohort used an aPCV mode (assisted pressure-controlled ventilation).

Table 1  
Ventilatory settings

	mean	n
IPAP, max, cm H <sub>2</sub> O	$21.2 \pm 3.2$	67
PEEP, cm H <sub>2</sub> O	$5.2 \pm 0.8$	67
RR, per minute	$10.9 \pm 2.1$	67
Ti_min, seconds	$0.9 \pm 0.1$	64*
Ti_max, seconds	$1.6 \pm 0.2$	64*
O <sub>2</sub> , l/min	$1.7 \pm 0.9$	61**
*I:E Setting		
**no oxygen		

## Subgroup Characteristics – DVS vs nDVS

Subgroup characteristics are presented in Table 2.

Table 2  
Subgroup Baseline Characteristics

	<b>n = 39</b>	<b>n = 28</b>	
	DVS	nDVS	p-value*
	mean ± SD	mean ± SD or n (%)	
Weight kg	67.3 ± 21.8	71 ± 20	0.485
Height cm	166.6 ± 9.8	165.6 ± 8.5	0.654
Age years	66.4 ± 6.6	65.9 ± 7	0.765
Male	18 (46.2%)	10 (35.7%)	0.39
Female	21 (53.8%)	18 (64.3%)	
Pack-years (packs/year)x years	52.9 ± 26.3	39.8 ± 20.2	0.031
BMI kg/m <sup>2</sup>	24.1 ± 7.2	25.8 ± 6.7	0.323
FEV1 liters	0.63 ± 0.3	0.81 ± 0.3	0.016
FEV1 %	25.2 ± 10.1	33.2 ± 13.5	0.009
Tiffeneau Index %	36.9 ± 9.5	40.8 ± 12.3	0.167
Pimax	4.0 ± 1.8	5.0 ± 2.1	0.064
RV liters	6.1 ± 1.6	5.4 ± 1.8	0.100
RV %	281.2 ± 78.2	246.1 ± 71.9	0.097
CAT points	25.5 ± 6.8	19.8 ± 7.5	0.002
MMRC	4.0 ± 1.2	3.0 ± 1.4	0.02
DM pre NIV (T0) mm	1258 ± 545	1284 ± 588	0.837
DM post NIV (T1) mm	1102 ± 485	1025 ± 417	0.549
Difference T0 – T1 mm	156 ± 500	259 ± 491	0.41
*p-value based on t-test for continuous variables and on chi-square test for categorial variables			

## Lung function analysis

Subgroup analysis of lung function measurements showed higher pulmonary impairment in patients with DVS and a clear trend to higher lung inflation. FEV1 was lower than in nDVS (0.6 vs 0.8l, p 0.016), corresponding to a mean FEV1 of 25% (GOLD IV) vs nDVS FEV1 mean 33% (GOLD III). Lung inflation was elevated in DVS, reflected by RV (6.1 vs 5.4l, p 0.10) and respiratory muscle strength via Pimax(RV) was

reduced in the DVS group compared to nDVS (4.0 vs 5.0 kPa, p 0.06, though both were not statistically significant due to a high drop-out rate in body plethysmography (insufficient maneuver).

## Carbon dioxide levels

When analyzing subgroup data, focus was placed on transcutaneous CO<sub>2</sub> measurements. As there was no transcutaneous T0 data, capillary CO<sub>2</sub> measurements were alternatively respected.

Patients with DVS had higher CO<sub>2</sub> levels than nDVS patients at all times of measurement (Table 3). Hypercapnia was decreased during NIV in both subgroups, but remained higher in DVS (49 vs 45mmHg, p 0.05). This effect was even clearer after NIV termination at T1 (54 vs 48mmHg p < 0.01) and T2 (53 vs 47mmHg, p < 0.01).

Table 3  
Subgroup tCO<sub>2</sub> levels at different points of time

	CO <sub>2</sub> Mean ± SD DVS	CO <sub>2</sub> Mean ± SD nDVS
T0 (p)	54.5 ± 11.1	49.4 ± 9.5
Tn (t)	49.1 ± 7.5	45.1 ± 7.3
T1 (t)	53.9 ± 9.2	47.8 ± 8.4
T2 (t)	53.4 ± 8.8	47.3 ± 7.4

*T0 baseline: no NIV Tn: with NIV (≥ 4h use) T1: 10 minutes after NIV T2: 60 minutes after NIV*

p: partial pressure, pCO<sub>2</sub> t: transcutaneous, tCO<sub>2</sub>

## Respiratory rate, subgroups

Respiratory rate (RR, breaths per minute (bpm)) was measured by continuous monitoring at four points of time (Table 4). It decreased significantly in the DVS group during use of NIV compared to spontaneous breathing (Tn 16.4 vs T0 18.9 bpm, p < 0.01). RR increase after termination of NIV was very clear (Tn 16.4 vs T1 20.1bpm, p < 0.01) and persisted up to one hour later (Tn 16.4 vs T2 20.4 p < 0.01). There was no significant difference in means between the RR at admission to after NIV termination.

Analysis in the nDVS group also showed a similar pattern with deceleration during NIV (Tn 15.3 vs T0 18 bpm, p < 0.01) and acceleration after use of NIV (Tn 15.3 vs T1 18.1 and T2 18.9 bpm, both p < 0.01).

Subgroup comparison (Fig. 1, Table 4) of RR on the day of admission (T0: 18.9 vs 18.0 bpm) and undergoing ventilation (Tn: 16.4 vs 15.3 bpm) showed no significant differences in means (p > 0.1), though a trend towards hyperventilation in the DVS group was documented.

Subgroup comparison after termination of NIV (T1) showed significant differences: mean RR in the DVS group was higher than nDVS (20.1 vs 18.1/minute, p 0.046). This effect did not persist at T2 (20.4 vs

18.9/minute, p 0.128), though further marked a trend.

Table 4  
Subgroup respiratory rates at  
different points of time

	AF DVS	AF nDVS
T0	18.9 ± 2.6	18.0 ± 1.9
Tn	16.4 ± 3.7	15.3 ± 3.5
T1	20.1 ± 5.3	18.1 ± 5.2
T2	20.4 ± 3.6	18.9 ± 4.8

*T0 baseline: no NIV Tn: with NIV (≥ 4h use) T1: 10 minutes after NIV T2: 60*

## Oxygen

There were no significant differences in oxygen saturation, both as independent variables at the different points in time and in a group as a dependent variable.

## Ultrasonic measurement of diaphragm excursion

The ultrasonic examination of the diaphragm was performed in all patients on day of admittance (T0) and the next morning after NIV termination (T1). In the overall group, T0 mean diaphragm excursion (± SD) was 1269 ± 559 mm, at T1 1069 ± 456 mm. Excursion difference between T0 and T1 (mean - 200mm) was statistically significant (p 0.03).

Inter-subgroup analysis showed a smaller difference of excursion rates between T0 and T1 in the DVS group compared to nDVS (DVS: mean - 157mm ± 499, nDVS: -260mm ± 491), though not statistically significant.

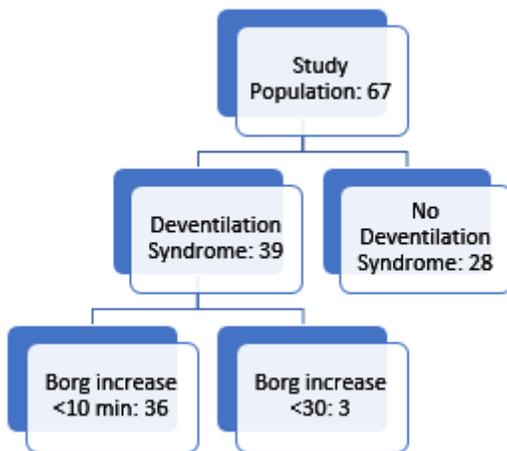
## Borg scale CR10

67 patients correctly filled out the Borg scale.

For this trial, an increase of ≥ 2 points on the Borg scale within 30 minutes after NIV termination was defined as Deventilation Syndrome, based on the patient's subjective dyspnea.

This criterion was met by 39 out of 67 patients (Table 5), corresponding to a share of 58.2%. The majority of patients (36/39) experienced dyspnea immediately after NIV termination (≤ 10minutes), only 3 patients showed symptoms between 10–30 minutes.

Table 5 Distribution of DVS and nDVS



In the DVS group, baseline (T0) median (IQR) Borg score was 3.0 (3.0) points and dropped to 1.0 (3.0) points undergoing NIV (Tn). After NIV termination, Borg value increased to median of 5.0 (4.0) points during the first 10 minutes, over 90% of the DVS patients experienced greater respiratory distress in this first time segment. Within the next hour, median Borg values dropped continuously and settled after 60 min at 3.0 (3.0) points – thus meeting baseline levels (Fig. 2).

In the nDVS group, baseline (T0) median (IQR) Borg score was 1.0 (3.5) points. During NIV (Tn) there was a decrease to 1.0 (2.0) points. Stopping the use of NIV led to a very slight increase to a median of 1.0 (3.0) points 10 minutes after, then rapidly sinking back to 1.0 (2.5) points. This value remained constant for the rest of the monitoring period. It is noteworthy that this decrease was much faster than in the DVS group and Borg even remained lower than spontaneous breathing on the day of admission (Fig. 2).

## Borg Scale and FEV1

As to be expected, there was a high correlation of Borg scale rankings and the severity of pulmonary impairment, measured by FEV1. Lower FEV1 levels were associated with more dyspnea ( $p < 0.01$ ).

## CAT

The CAT questionnaire documented a higher mean score in DVS patients than nDVS ( $25.5 \pm 6.8$  points vs  $19.8 \pm 7.5$  points, maximum score 40 points), reflecting lower FEV1 levels and higher disease burden. This effect was significant  $p < 0.01$ ).

## MMRC

The mMRC questionnaire revealed a significantly higher score in DVS than nDVS (median (IQR) 4.0 (2.0) vs 3.0 (3.0) points, maximum of 4 points (0–4),  $p 0.02$ ), reflecting higher respiratory distress in everyday life.

## Discussion

Acute dyspnea after the use of non-invasive ventilation (NIV) in a long-term setting is a common and stressful symptom in COPD patients. This is the first trial documenting prevalence and physiology of this symptom, hereby defined as Deventilation Syndrome (DVS). Despite an abundance of publications on NIV in COPD, many also addressing negative side-effects, DVS has remained widely unaddressed.

DVS was identified in 58% of COPD patients with chronic hypercapnic failure in a routine in-patient setting, thus emphasizing the relevance of the subject. Ventilator settings were effective in both groups (DVS and nDVS), leading to significant decrease of CO<sub>2</sub> levels and documented reduction of dyspnea per Borg scale undergoing NIV. Both groups were fully adapted to the regular use of NIV and showed no signs of discomfort or asynchronicity undergoing therapy. Nightly cardiovascular and pulmonary monitoring showed no signs of relevant sleep disordered breathing.

Dyspnea is a complex symptom and still not fully understood, though its role as a predictive marker in chronic lung diseases has been acknowledged [20–22]. It is highly subjective in perception and does not necessarily correlate with specific tests (e.g. spirometry, blood gas analysis), but dyspnea can – and should – be measured. Underlying mechanisms and qualities of dyspnea can be categorized in:

elevated work or effort in breathing (impaired respiratory muscles), tightness of the chest (bronchoconstriction) and intensity of air hunger (increased inspiratory drive, desensitized pulmonary mechanoreceptors) [22]. Following these main mechanisms can help understanding causes and thus provide therapeutic concepts in DVS.

Ultrasonic measurement of the diaphragm showed significant (pre NIV 1269mm, post-NIV 1069mm, p 0.03) movement impairment after the use of NIV in the overall group, possibly expressing transient reduction of diaphragm muscle strength. There was no significance between each subgroup, though the differences of diaphragm movement pre and post NIV do strike as noteworthy (nDVS 260mm vs DVS 157mm). Ventilator induced diaphragm dysfunction (VIDD) is a well-known entity that has not only been addressed in invasive-ventilator ICU settings [23–25], but also has been seen in NIV in COPD patients [26], though its role here is yet to be established.

Moreover, measurements of respiratory muscle strength via Pimax (from RV) were reduced in the DVS group compared to nDVS (4.0 vs 5.0 kPa, p 0.06).

While diaphragm impairment seems to be well tolerated in some patients, it could pose the fundament of DVS – especially in context of accelerated respiratory rates.

Changes of the respiratory rate (RR) provide a further, if not the main key in understanding DVS. Patients in both subgroups showed similar patterns of the RR: a significant drop from baseline to undergoing NIV – then picking up again back to baseline level (and exceeding baseline in DVS) after the use of NIV.

Remarkably, dyspnea by Borg scale and RR did not differ in both groups at baseline (afternoon) measurement on admission day or undergoing NIV, thus showing a similar initial patient situation.

DVS shows an impact after use of NIV: in DVS, RR was higher than nDVS patients ( $T_{10\text{min}}$ : 20.1 vs 18.1 bpm,  $p$  0.04) and remained elevated during the hour of monitoring ( $T_{60\text{min}}$ : 20.4 vs 18.9 bpm,  $p$  0.1, though most DVS patients were subjectively recovered by Borg scale 60 minutes after NIV termination in this study. RR after use of NIV in DVS patients was higher than at  $T_0$  (baseline) although not statistically significant, so time adjusted RR change should be acknowledged. During the short period of 10 minutes post NIV, DVS patients showed a mean RR increase of 4.3 bpm, in nDVS 2.8 bpm.

Potential reasons for acute RR increase could be reduced diaphragm strength or elevated inspiratory drive due to higher  $\text{CO}_2$  levels in the DVS group ( $t\text{CO}_2$   $T_{10\text{min postNIV}}$  54 vs 48 mmHg,  $p < 0.01$ ).

Also, higher overall bronchial obstruction in DVS (FEV1 25% vs 32.5% nDVS,  $p$  0.01), furthermore augmented obstruction in the early morning hours (circadian, vagal stimulation, decreased medication levels), increases breathing muscle activity and effort and can trigger dynamic hyperinflation in already severely inflated lungs (RV DVS 6.1 vs nDVS 5.4 liters,  $p$  0.1), thus circling into rapid shallow breathing (RSB). RSB and impaired diaphragm function have been identified as predictors for weaning failure [27], reflecting relevant breathing muscle exhaustion. A possible negative influence of DVS on long-term prognosis of COPD patients with NIV is yet to be surveyed.

It is also noteworthy that many DVS patients expressed fear of NIV termination in the morning due to experienced dyspnea in the past, posing a further possible cause for RR acceleration

Oxygen levels at any time also did not differ in both groups and thereby remain disregarded.

There are limitations in this trial to be discussed. First, this was a monocenter study of 67 patients, further measurements need to be done in a multicenter setting. Second, assessment of diaphragm function was performed only by ultrasonic diaphragm excursion (DE) and only in two examinations, showing high standard deviation. Initially, DE was only thought an addendum to other focus topics – it now evolved to possibly one of the key features in DVS. In the future, more detailed data (e.g. diaphragm thickening index, repeated measurements) will be needed. Third, there was no guideline in the protocol concerning medication intake. This was intentionally put in the hands of each patient to decide by need, hence heterogenous treatment patterns. Subsequent trials should standardize this procedure. And fourth, monitoring was only continued for one hour during which some patients did not return to baseline level in terms of dyspnea, respiratory rate and  $\text{CO}_2$  levels. So, full duration of DVS has not yet been captured.

## Conclusion

In conclusion, DVS is a frequent, but to this day insufficiently regarded side effect of LTH-NIV. The recognition of DVS is of high clinical relevance for health care givers and patients. This is the first trial documenting not only prevalence, but also relevant patient data leading to concepts of factors that presuppose DVS, by this stepping toward prevention and therapy of this often tormenting symptom. Further research is required to substantiate DVS and establish alleviating therapies.

# Abbreviations

BGA Blood gas analysis

BP Blood pressure

Bpm breaths per minute

CHRF Chronic hypercapnic respiratory failure

COPD Chronic obstructive pulmonary disease

DE Diaphragm excursion

DVS Deventilation Syndrome

EPAP Expiratory positive airway pressure Inspiratory/expiratory ratio

HR Heart rate

IPAP Inspiratory positive airway pressure

kHz Kilohertz

kPa Kilopascals

LTH-NIV Long term home non-invasive ventilation

Mbar Millibar

MmHg Millimeter of mercury

nDVS Non Deventilation Syndrome

NIV Non-invasive ventilation

NPPV Non-invasive positive pressure ventilation

pCO<sub>2</sub> Arterial partial pressure of carbon dioxide

PE Physical exam

PEEP Positive end-expiratory pressure

tCO<sub>2</sub> Transcutaneous measurement of arterial partial pressure of carbon dioxide

PVA Patient-ventilator asynchrony

RR Respiratory rate

RSB Rapid shallow breathing

SpO<sub>2</sub> Oxygen saturation of haemoglobin measured by pulse oximetry

TI<sub>MAX</sub> Maximal inspiratory time

VE Minute ventilation

$V_T$  Tidal volume

## Declarations

Ethics approval by Ethics Committee University of Heidelberg, S-484/2016

Consent for publication: not applicable

Availability of data: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests: the authors declare they have no competing interests

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First authorship is declared by the submitting author MS. MS conceived study design, acquired participants, collected and interpreted data. SI and GI collected and analyzed substantial data in COPD patients including questionnaires and diaphragm ultrasound. MK analyzed and statistically approved all collected data. FH and FT analyzed and interpreted lung function and demographic data. All authors read and approved the final manuscript.

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## Figures

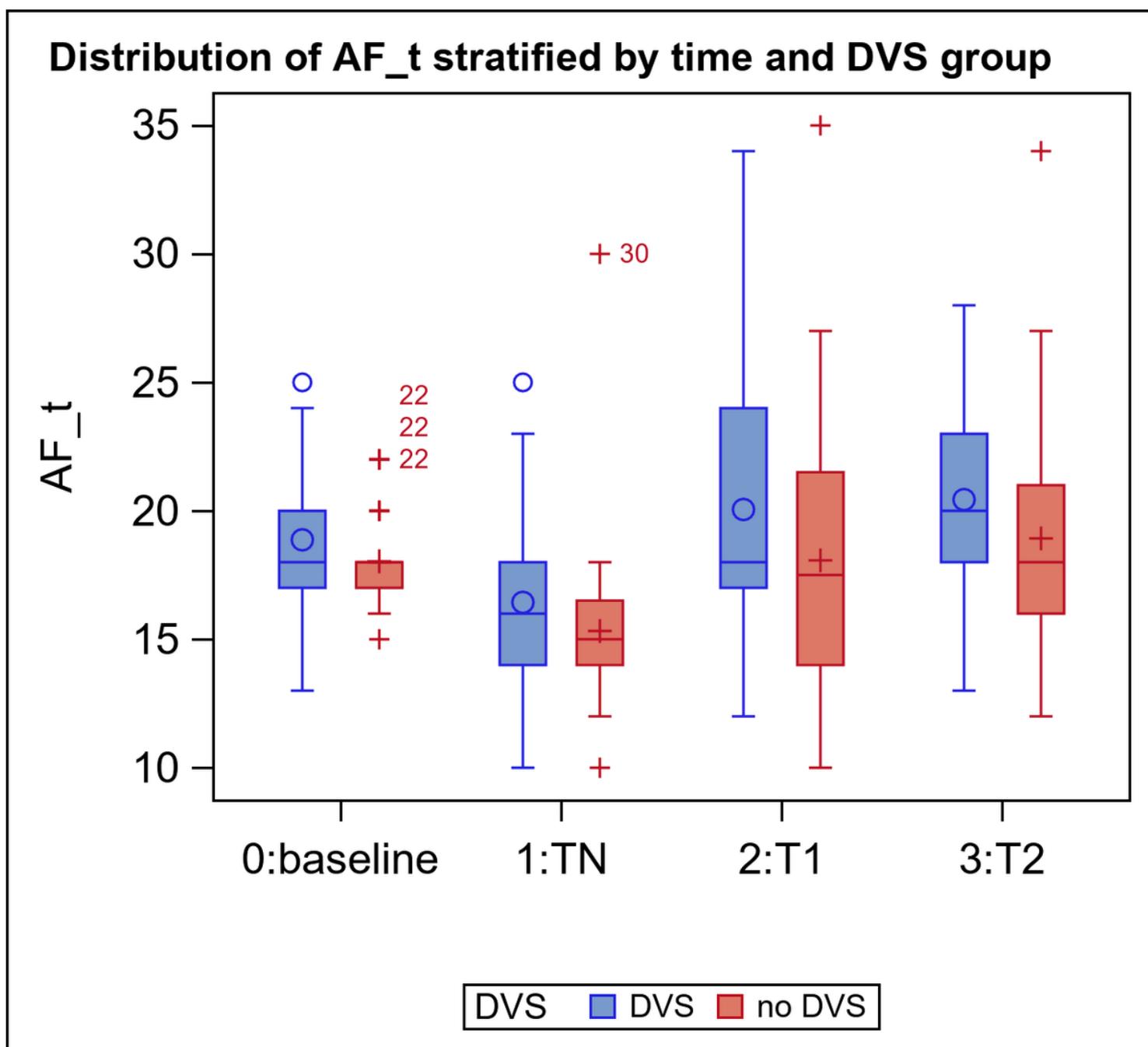


Figure 1

Respiratory Rate in subgroups DVS/nDVS stratified by time

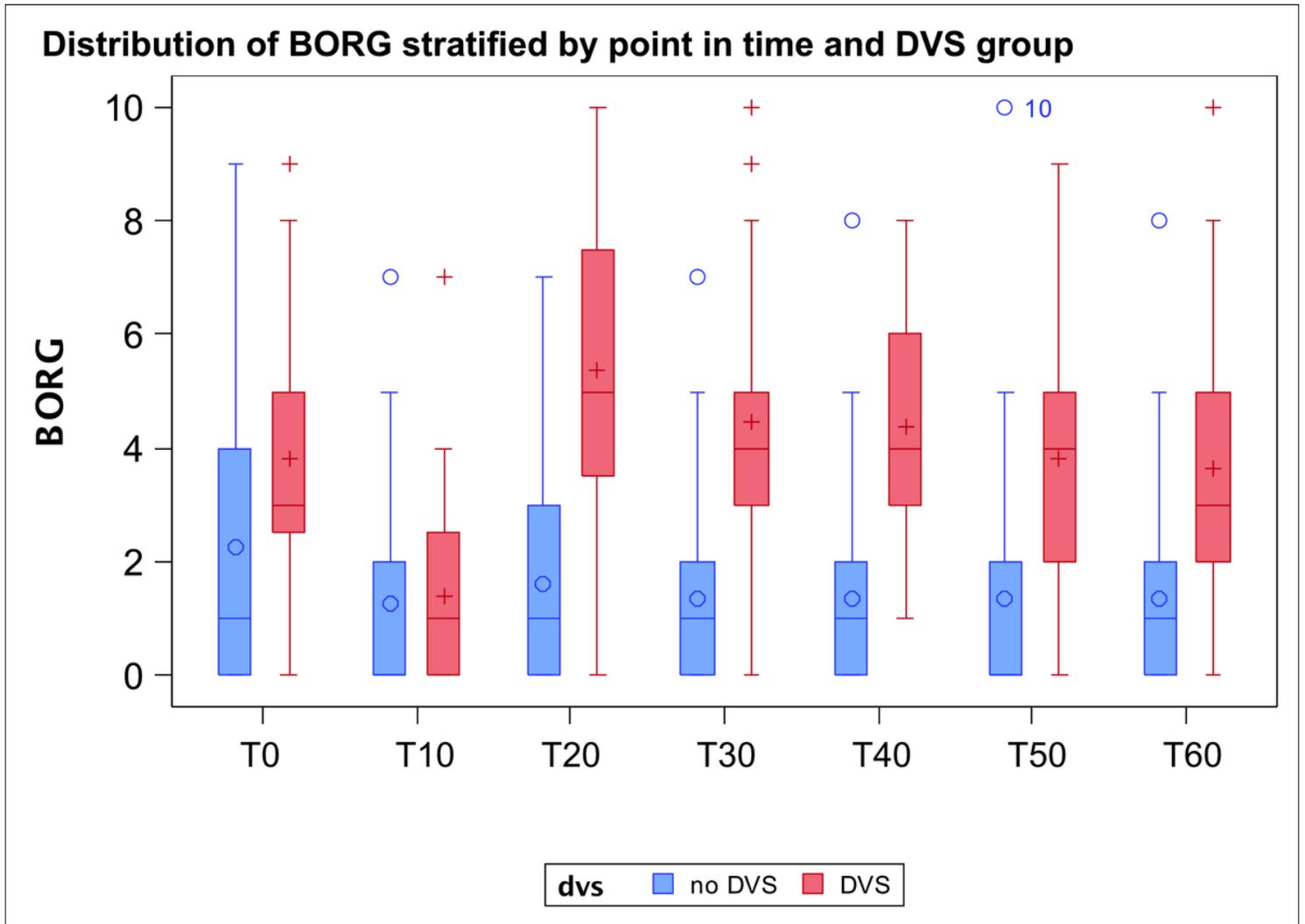


Figure 2

Borg stratified by point of time and subgroup