

Comorbidities and Subgroups of Patients Surviving Severe Acute Hypercapnic Respiratory Failure in the Intensive Care Unit

Dan Adler¹, Jean-Louis Pépin², Elise Dupuis-Lozeron^{1,3}, Katerina Espa-Cervena¹, Roselyne Merlet-Violet³, Hajo Muller⁴, Jean-Paul Janssens¹, and Laurent Brochard^{5,6}

¹Division of Pulmonary Diseases, ³Division of Clinical Epidemiology, and ⁴Division of Cardiology, Geneva University Hospitals, Geneva, Switzerland; ²Université Grenoble Alpes, Hypoxie Physiopathologie, Institut National de la Santé et de la Recherche Médicale, U1042, CHU de Grenoble, Laboratoire Exploration Fonctionnelle Cardiorespiratoire, Pôle Thorax et Vaisseaux, Grenoble, France; ⁵Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada; and ⁶Keenan Research Centre and Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada

Abstract

Rationale: No methodical assessment of the lung, cardiac, and sleep function of patients surviving an acute hypercapnic respiratory failure episode requiring admission to the intensive care unit (ICU) has been reported in the literature.

Objectives: To prospectively investigate the prevalence and impact of comorbidities in patients treated by mechanical ventilator support (invasive or noninvasive) for acute hypercapnic respiratory failure in the ICU.

Methods: Seventy-eight consecutive patients admitted for an episode of acute hypercapnic respiratory failure underwent an assessment of lung, cardiac, and sleep function by pulmonary function tests, transthoracic echocardiography, and polysomnography 3 months after ICU discharge.

Measurements and Main Results: Sixty-seven percent (52 of 78) of patients exhibited chronic obstructive pulmonary disease (COPD), although only 19 had been previously diagnosed. Patients without COPD were primarily obese. Prevalence of

severe obstructive sleep apnea was 51% (95% confidence interval, 34–69) in patients with COPD and 81% (95% confidence interval, 54–96) in patients without COPD. Previously undiagnosed cardiac dysfunction with preserved ejection fraction was highly prevalent (44%), as was hypertension (67%). More than half of the population demonstrated at least three major comorbidities known to precipitate acute hypercapnic respiratory failure. Multimorbidity was associated with longer time to hospital discharge. Hospital readmission or death occurred in 46% of patients over an average of 3.5 months after discharge.

Conclusions: Severe hypercapnic respiratory failure requiring ICU admission resulted primarily from COPD or obesity. Major comorbidities are highly prevalent in both cases and most often ignored. Surviving acute hypercapnic respiratory failure should be an opportunity to systematically evaluate lung, heart, and sleep functions to improve poor outcomes.

Clinical trial registered with www.clinicaltrials.gov (NCT 02111876).

Keywords: acute hypercapnic respiratory failure; COPD; intensive care

Patients with an episode of severe acute hypercapnic respiratory failure (AHRF) suggestive of an acute exacerbation of chronic obstructive pulmonary disease (COPD) or an obesity hypoventilation

syndrome are admitted to the intensive care unit (ICU) to receive noninvasive ventilation (NIV). In most patients, NIV is successful (1), and ICU mortality is now consistently reported to be as low as 5–10%.

However, hospital and ICU readmissions are frequently observed (1–3) in specific at-risk COPD phenotypes (4) or because of the underdiagnosis and lack of integrated care for associated comorbidities in other

(Received in original form August 18, 2016; accepted in final form December 14, 2016)

Supported in part by the Ligue Pulmonaire Genevoise and by the research fund of the Department of Internal Medicine, Geneva University Hospitals and Faculty of Medicine. This fund received an unrestricted educational grant from AstraZeneca Switzerland.

Author Contributions: D.A., J.-P.J., and L.B. designed the study. D.A. coordinated the study. D.A. and R.M.-V. were in charge of patient screening, enrollment, and follow-up. R.M.-V., H.M., and K.E.-C. acquired the data. D.A. and E.D.-L. performed statistical analysis. D.A., J.-L.P., J.-P.J., and L.B. analyzed the data and wrote the first version of the manuscript. All authors read and approved the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Dan Adler, M.D., Division of Pulmonary Diseases, Geneva University Hospitals, 4 Rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland. E-mail: dan.adler@hcuge.ch

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 196, Iss 2, pp 200–207, Jul 15, 2017

Copyright © 2017 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201608-1666OC on December 14, 2016

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

Subject: No methodical assessment of the lung, cardiac, and sleep functions of patients surviving an acute hypercapnic respiratory failure episode treated by noninvasive ventilation in the intensive care unit has been reported in the literature. However, a methodical assessment of comorbidities to improve long-term care of these patients needs to be better defined.

What This Study Adds to the

Field: This study provides for the first time an objective and methodical assessment of the lung, cardiac, and sleep function of patients surviving acute hypercapnic respiratory failure and suggests that multimorbidity is common, most often unrecognized, and may be associated with poor outcome.

patient categories. The correct assessment of comorbidities following AHRF needs to be better defined to improve the long-term care of these patients. In addition, the benefits of pursuing NIV after AHRF in unselected patients with COPD remains a subject of debate (5).

Improved outcomes can be expected in obese comorbid patients with COPD and in patients with COPD with coexistent obstructive sleep apnea (OSA), the so-called “overlap syndrome” (6–8). Obesity hypoventilation syndrome patients exhibit a poor prognosis when untreated (9), although this seems to be reversed by appropriate ventilator support (10–12). In these patients treated with NIV, comorbidities become the major predictors of mortality (13), as is the case in OSA (14). Multimorbidity is now increasingly reported as a key feature in chronic diseases, including COPD (15–17), and requires the validation of specific clinical pathways.

Comorbidities have rarely been systematically and objectively studied in patients discharged from an ICU admission for AHRF (18, 19). Moreover, there is poor agreement between chart-based and objectively identified comorbidities in COPD (20). We hypothesized that the

coexistence of COPD, obesity, OSA, and/or cardiac failure may be highly prevalent in patients surviving AHRF and could contribute to their poor prognosis and frequent readmissions. The primary objective of this prospective cohort study was to objectively capture the prevalence of these comorbidities and their impact on outcome in patients surviving AHRF in the ICU.

Methods

Study Design and Setting

We conducted a prospective single-center cohort study at the pulmonary division of Geneva University Hospitals (Geneva, Switzerland) between January 2012 and May 2015. Patients who had survived AHRF were consecutively recruited at ICU discharge. Inclusion criterion was the occurrence of AHRF as the primary reason for admission, defined as P_{aCO_2} greater than 6.3 kPa, requiring invasive or noninvasive mechanical ventilation in the ICU. Exclusion criteria were as follows: less than 18 years old, known or suspected neuromuscular disease, pregnancy, iatrogenic respiratory failure, life expectancy of less than 3 months, confusion despite total/partial blood gas normalization, or a major psychiatric disease.

Demographic data were collected at ICU discharge. We also used electronic medical files to collect past medical history and some variables not specifically measured in our study protocol. Complete pulmonary function tests (including spirometry, lung volumes, and diffusion capacity) were systematically performed according to American Thoracic Society/European Respiratory Society Pulmonary Function Tests Task Force Standardization guidelines 15 days after ICU discharge. On the same day, transthoracic echocardiography was also performed. An in-laboratory polysomnographic study was proposed to patients 3 months after hospital discharge. A subset of 14 patients who did not return home after their stay in the ICU were proposed ambulatory cardiorespiratory polygraphy in their long-term facility (Figure 1). All patients provided written informed consent, and the study was approved by the institutional review board (CER11-28) and registered at www.clinicaltrials.gov (identifier NCT02111876).

Assessment of Pulmonary Function

Obstruction was defined as FEV_1/FVC less than fifth percentile of the predicted value to prevent spirometric overdiagnosis of COPD in an elderly population, as

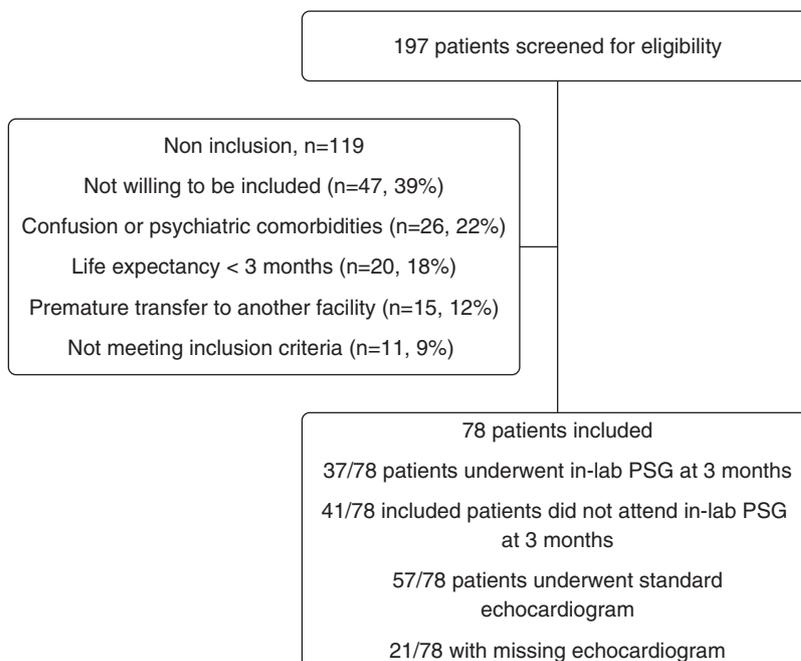


Figure 1. Study flow chart. PSG = polysomnography.

proposed by the Global Initiative for Chronic Obstructive Lung Disease (21).

Assessment of Cardiac Function

Standard echocardiograms were performed according to current guidelines (22) and the analysis was centralized by a single expert investigator (H.M.) using the same equipment (acquisition with IE33 or CX-50; off-line analysis using Xcelera; Philips Medical Systems, Amsterdam, the Netherlands). Systolic left ventricular (LV) dysfunction was defined as LV ejection fraction less than 55%. Diastolic LV function was categorized as follows: normal, mildly impaired, impaired relaxation without increased filling pressures, moderately impaired, impaired relaxation with elevation of filling pressures or pseudonormal filling pattern, and severely impaired (i.e., advanced reduction in compliance or a reversible or fixed restrictive filling pattern) (23). Right ventricular (RV) dilation was assessed in comparison with LV size in the apical and subcostal four-chamber views and defined as RV midcavity diameter or an area equal or greater than the LV. Pulmonary hypertension was categorized as unlikely, possible, or likely according to the European Society of Cardiology 2009 guidelines (24).

Sleep Studies

Overnight polysomnography (Embla N7000; Embla Systems, Broomfield, CO) was recorded 3 months after ICU discharge and 2 days after noninvasive support (continuous positive airway pressure or NIV) withdrawal for patients treated at home with positive pressure ventilation, according to the American Academy of Sleep Medicine 2012 recommendations (25). Clinical stability was confirmed after assessment by a study nurse before admitting patients to the sleep laboratory. Nasal pressure transducer, oral thermistors, and thoracic/abdominal strain gauges were used to record breathing. Oxygen saturation as measured by pulse oximetry and nocturnal transcutaneous CO₂ partial pressure (PtcCO₂) were simultaneously and continuously monitored using a transcutaneous capnograph with an ear probe heated at 43°C (Tosca 500; Radiometer, St Gall, Switzerland).

Sleep stages and arousals were scored according to the American Academy of Sleep Medicine guidelines (26). Apnea was

scored if a drop of more than 90% in the peak flow signal excursion was noted for greater than or equal to 10 seconds using an oronasal thermal sensor. It was then categorized as obstructive, central, or mixed based on respiratory efforts. Hypopnea was defined as a nasal pressure signal drop of greater than or equal to 30% lasting at least 10 seconds and associated with either a greater than 3% oxygen desaturation or an arousal. Nocturnal hypoventilation was defined as an increase in PtcCO₂ to a value greater than 7.3 kPa for more than or equal to 10 minutes, or an increase greater than or equal to 1.33 kPa in PtcCO₂ during sleep (compared with an awake supine value) to a value exceeding 6.7 kPa (26).

Clinical Outcomes

After ICU discharge, all patients were followed up for 1 year or until death. Hospital and ICU readmission and death were recorded at 1, 3, 6, and 12 months by reviewing hospital medical records or through telephone calls to patients or family members.

Statistical Analysis

Descriptive statistics are reported as counts and percentages for categorical data and means and SD or the median and interquartile range (IQR) for continuous variables. When comparing subgroups, we used the Mann-Whitney-Wilcoxon test for continuous variables or Fisher exact test for categorical variables. We assessed the relation between FEV₁ and the body mass index (BMI) by a linear regression model. The log-rank test was used to test if survival was different for patients with more than two of the following comorbidities: obesity, COPD, severe apnea, and heart failure. To evaluate the impact of missing values for severe apnea and heart failure in this analysis, we performed multiple imputation by chained equations using the R package mice (27). Imputations were drawn from a logistic regression model. Variables used for imputation were age, sex, BMI, FEV₁/FVC, FEV₁, the Simplified Acute Physiology Score II, presence of dyspnea, respiratory muscle strength, ICU length of stay, COPD, neck circumference, Mallampati score, survival time, and survival status. We generated 35 data sets corresponding to the proportion of missing values for severe apnea. For each of these, the effect of the number of comorbidities

was estimated by a univariate Cox proportional hazards model. The results for each imputed dataset was combined using Rubin's rules (28).

Results

Patients

Between January 2012 and May 2015, a total of 185 patients were assessed for eligibility at ICU discharge and 78 patients were enrolled. The study flow chart is shown in Figure 1. Causes for noninclusion were unwillingness to be enrolled in a clinical trial (39%), confusion or severe psychiatric disease (22%), life expectancy of less than 3 months (18%), premature transfer to another care facility (12%), and not meeting the inclusion criterion (9%). Baseline characteristics of the 78 patients included are presented in Table 1.

Pulmonary Function Tests

Only 19 of 78 (24%) patients had a past history of COPD, including spirometric evaluation. Twenty-eight of 78 (36%) participants had already been hospitalized for respiratory failure, 16 of 78 (21%) within the preceding year. Pulmonary function tests revealed that 52 of 78 (67%) patients actually had COPD. Patients without COPD were primarily obese (21 of 26; 81%) with a higher BMI and FEV₁ compared with patients with COPD. Patients without COPD also presented with no decreased total lung capacity and no hyperinflation compared with patients with COPD (Table 2). For the entire study population, FEV₁ increased linearly with BMI ($P < 0.001$), thus probably reflecting the mirror influence of severe COPD and morbid obesity as an explanation for an episode of AHRF requiring ICU admission (Figure 2A; see Figure E1 in the online supplement).

Prevalence of Sleep-disordered Breathing

Twenty-three of 78 (29%) patients had a known history of OSA, but only 7 of 23 (30%) were treated by continuous positive airway pressure or NIV at study inclusion (Table 2, Figure 2). A significant proportion of patients (41 of 78; 53%) did not attend the sleep laboratory recording 3 months after ICU discharge. These patients were older (71 yr [IQR, 65–78] vs. 66 yr [IQR, 60–73], respectively), but other

Table 1. Demographic and Clinical Characteristics of the Study Population

	Study Population (n = 78)	COPD (n = 52)	Non-COPD (n = 26)	P Value
Age, yr, mean ± SD	68.6 ± 9.6	69.2 ± 9.4	67.5 ± 10.2	0.327
Male sex, n (%)	41 (53)	28 (54)	13 (50)	0.813
Current smoker, n (%)	42 (53.8)	29 (55.8)	13 (50)	0.473
Obesity, n (%)	44 (56)	23 (44)	21 (81)	0.003
BMI, kg/m ² , mean ± SD	32.8 ± 10.3	29.8 ± 8.8	38.8 ± 10.6	<0.001
Diabetes, n (%)	27 (34.6)	14 (26.9)	13 (50.0)	0.073
Chronic kidney disease, n (%)	9 (11.5)	6 (11.5)	3 (11.5)	1.000
Gastroesophageal reflux, n (%)	15 (19.2)	12 (23.1)	3 (11.5)	0.246
Hospitalization in the previous year, n (%)	28 (35.9)	21 (40.4)	7 (26.9)	0.319
SAPS II, mean ± SD	37.5 ± 13.6	39.4 ± 13.4	33.6 ± 13.3	0.109
Orotracheal intubation, n (%)	16 (20.5)	13 (16.7)	3 (3.8)	0.237
ICU LoS, d, median (IQR)	3 (2–4)	3 (1–4)	2.5 (2–4)	0.771
pH at ICU admission, median (IQR)	7.29 (7.23–7.34)	7.29 (7.23–7.33)	7.29 (7.19–7.37)	0.867
Pa _{O₂} /Fi _{O₂} , median (IQR) kPa	33.1 (24.3–38.8)	34.3 (25.6–42.1)	32.7 (24.1–37.3)	0.504
mm Hg	248 (182–291)	257 (192–316)	245 (180–280)	
Pa _{CO₂} at ICU admission, kPa, median (IQR)	8.5 (7.6–9.8)	8.4 (7.6–9.8)	8.6 (7.3–9.4)	0.652
Pa _{CO₂} at ICU discharge, kPa, median (IQR)	6.0 ± 0.9	6.1 ± 0.9	5.9 ± 0.9	0.346

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IQR = interquartile range; LoS = length of stay; SAPS II = Simplified Acute Physiology Score II.

baseline characteristics (sex, BMI, diagnosis of COPD, Pa_{CO₂} at ICU admission, Simplified Acute Physiology Score II, ICU length of stay) did not differ from participants attending the sleep study. However, patients who did not attend the in-laboratory sleep study (n = 24 of 41; 59%) were readmitted more often to the ward or ICU, or died within the first 3 months of follow-up after ICU discharge (*P* < 0.001).

Sleep variables according to COPD status are presented in Table 3. Prevalence of moderate or severe sleep apnea (apnea–hypopnea index, ≥15/h of sleep) was 66% (95% confidence interval [CI], 48–81) in patients with COPD and 94% (95% CI, 70–100%) in patients

without COPD. Prevalence of severe sleep apnea (apnea–hypopnea index, >30/h of sleep) was 51% (95% CI, 34–69%) in patients with COPD and 81% (95% CI, 54–96%) in patients without COPD. Using multiple imputation for missing sleep study variables did not affect significantly OSA prevalence. Sleep hypoventilation, defined as a Ptc_{CO₂} value of more than 7.3 kPa for more than 10 minutes, was observed in 48% and 58% of patients with and without COPD, respectively. An increase greater than 1.33 kPa in Ptc_{CO₂} during sleep compared with an awake supine Ptc_{CO₂} value was less frequent (32%) in patients with COPD compared with patients without COPD (58%).

Cardiovascular Comorbidity and Echocardiographic Findings

Before ICU admission, 52 of 78 patients (67%; 95% CI, 55–77) were already treated for hypertension and 16 of 78 (21%) patients had a diagnosis of heart failure. Fifty-seven of 78 (73%) patients underwent echocardiographic evaluation according to the study protocol. Heart failure with reduced ejection fraction was infrequent in our study population (9%; 95% CI, 3–19%). Median LV ejection fraction was 65% (IQR, 60–65%) with no significant difference between patients with COPD and patients without COPD. Heart failure with preserved ejection fraction was highly prevalent (44%; 95% CI, 31–58%). Pulmonary hypertension was unlikely in 18% (95% CI, 9–30%), possible in 39% (95% CI, 26–53%), and likely in 16% (95% CI, 8–28%) of patients. In 27% (95% CI, 16–40%) of cases, it could not be evaluated by echocardiography. RV dilatation was highly prevalent (42%; 95% CI, 29–57%) in both COPD and non-COPD groups (*P* = 0.548).

Impact of Comorbidities

All patients had one or more comorbidities and more than half had at least three comorbidities potentially contributing to their acute respiratory failure (i.e., COPD, obesity, heart failure, and severe OSA) (Figure 3). Combinations of major

Table 2. Pulmonary Function Test Data

	Study Population (n = 78)	COPD (n = 52)	Non-COPD (n = 26)	P Value
FEV ₁ , % of predicted	50.0 ± 18.9	43.5 ± 15.3	62.9 ± 19.2	<0.001
Residual volume, % of predicted	123.5 ± 55.9	140 ± 60.4	91 ± 24.8	<0.001
TLC, % of predicted	87.6 ± 28.0	95.9 ± 29.7	72.1 ± 15.5	<0.001
RV/TLC, % of predicted	132.8 ± 24.7	140.2 ± 24.8	118.9 ± 17.7	<0.001
DL _{CO} , % of predicted	60.2 ± 23.1	56.9 ± 22.1	66.6 ± 24.2	0.062
K _{CO} , % of predicted	92.8 ± 28.0	88.9 ± 30.1	99.8 ± 22.8	0.062

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DL_{CO} = diffusion capacity of the lung for carbon monoxide; RV = residual volume; TLC = total lung capacity.

Data are given as mean ± SD.

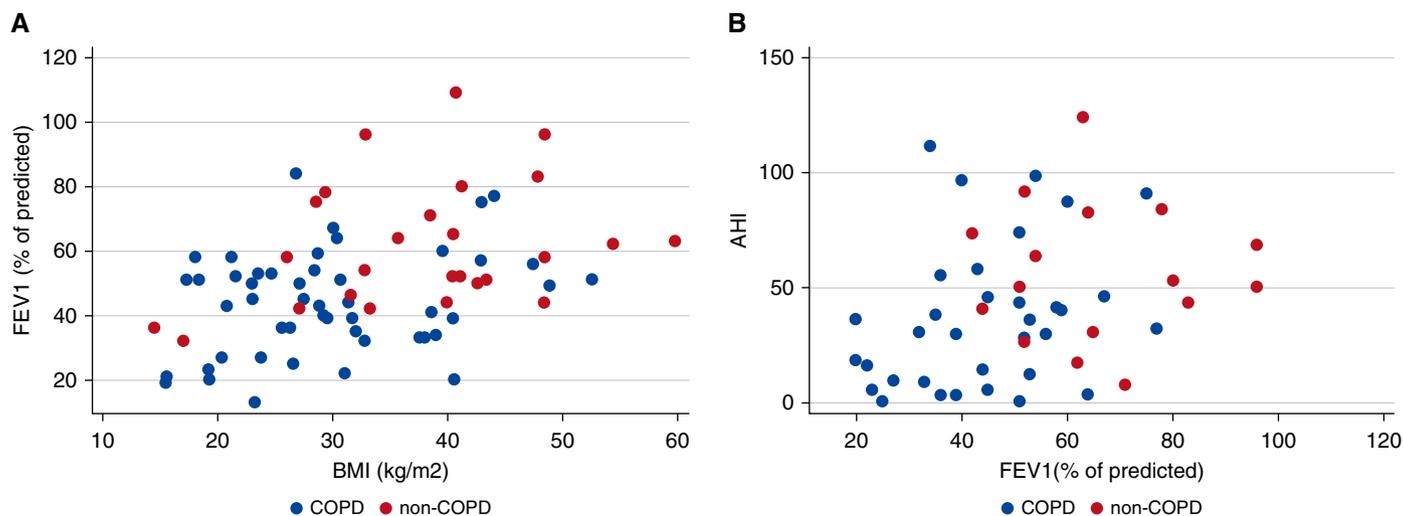


Figure 2. Positive correlation between body mass index and FEV₁ (A) and apnea-hypopnea index (B). AHI = apnea-hypopnea index; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

comorbidities were highly prevalent: 18 of 50 (36%; 95% CI, 23–51) patients assessed for sleep breathing disorders had an overlap syndrome (COPD and OSA with an apnea-hypopnea index >30/h); 61% (95% CI, 42–78%) had severe OSA and heart failure; and 54% of COPD (95% CI, 39–68%) cases had heart failure. For patients who experienced more than one event during 6 months after ICU discharge, only the first event was included in the combined endpoint. There was no association between initial orotracheal intubation and outcome at 6 months. Hospital readmission occurred in 36 patients (46%) over a median follow-up of 3.5 months (IQR, 1.0–5.9). ICU readmission occurred in 18 (23%) patients

and three participants died during the same observation period. The Kaplan-Meier analysis for nonmissing data showed that less comorbid patients had a trend toward higher hospital-free survival compared with more comorbid individuals ($P = 0.127$ on the log-rank test). Multiple imputation for missing data for severe sleep apnea and heart failure had no effect on hospital-free survival between groups ($P = 0.314$).

Hospital length of stay outside the ICU was 21 days (IQR, 15.5–25.5) for patients with greater than or equal to three major comorbidities compared with 15 days (IQR, 9.0–18.5) in less comorbid patients ($P = 0.007$). As a group, comorbid individuals were more likely to be discharged home on continuous positive

airway pressure or NIV treatment compared with less comorbid individuals (63% vs. 27%; $P = 0.021$); however, this seemed not to prevent death or readmission. For the whole study population, the death rate was 9 of 78 (11.5%) at 6 months and 13 of 78 (16.7%) at 1 year.

Discussion

In this prospective cohort study, consecutive patients surviving a severe AHRF episode treated with NIV in the ICU were assessed to describe the burden of comorbidities contributing to acute respiratory failure. We voluntarily did not restrict inclusion criteria to a specific group of patients with a preestablished diagnosis of COPD, obesity hypoventilation syndrome, or heart failure but tried to stick to a pragmatic study describing all AHRF survivors after index admission in the ICU because this is where acute ventilator support was mostly performed in our institution. Our results show the high prevalence of multimorbidity that contributed to the occurrence of severe hypercapnic respiratory failure, which was most often undetected and untreated before the AHRF episode in our population.

As expected, acute exacerbation of COPD was the main reason for ICU admission and multimorbidity was highly prevalent in patients with COPD. Many studies have shown that comorbid chronic conditions are frequent in patients with

Table 3. Polysomnographic Data of the Study Population

	COPD (n = 25)	No COPD (n = 12)	P Value
N1 + N2 sleep stage, %	69.1 (58.6–83.4)	78.7 (72.6–96.4)	0.211
N3 stage sleep stage, %	18.3 (6.4–24.5)	12.1 (0.2–21.7)	0.397
REM sleep stage, %	12.2 (2.5–17.4)	6 (0.1–10.2)	0.090
Total sleep time, min	365 (259–441)	393 (343.2–406.5)	0.746
Sleep efficiency, %	74.0 (54.8–83.8)	75.6 (60.8–80.0)	0.910
AHI, h ⁻¹	31.9 (14.3–45.6)	66.0 (48.0–83.8)	0.014
HI, h ⁻¹	27.6 (11.9–39.9)	44.7 (21.7–64.3)	0.101
MA, h ⁻¹	45 (31–55)	54.0 (48.0–74.8)	0.060
Mean Pt _{CO₂} during sleep, kPa	6.6 (5.9–7.0)	6.6 (6.2–7.0)	0.783
Maximum Pt _{CO₂} during sleep, kPa	7.2 (6.7–7.6)	7.3 (7.0–7.7)	0.515
Increase in Pt _{CO₂} during sleep, kPa	0.4 (0.3–0.6)	0.5 (0.3–0.7)	0.537

Definition of abbreviations: AHI = apnea-hypopnea index; COPD = chronic obstructive pulmonary disease; HI = hypopnea index; MA = microarousals; N1 = non-REM stage 1; N2 = non-REM stage 2; N3 = non-REM stage 3. Data are given as median (interquartile range).

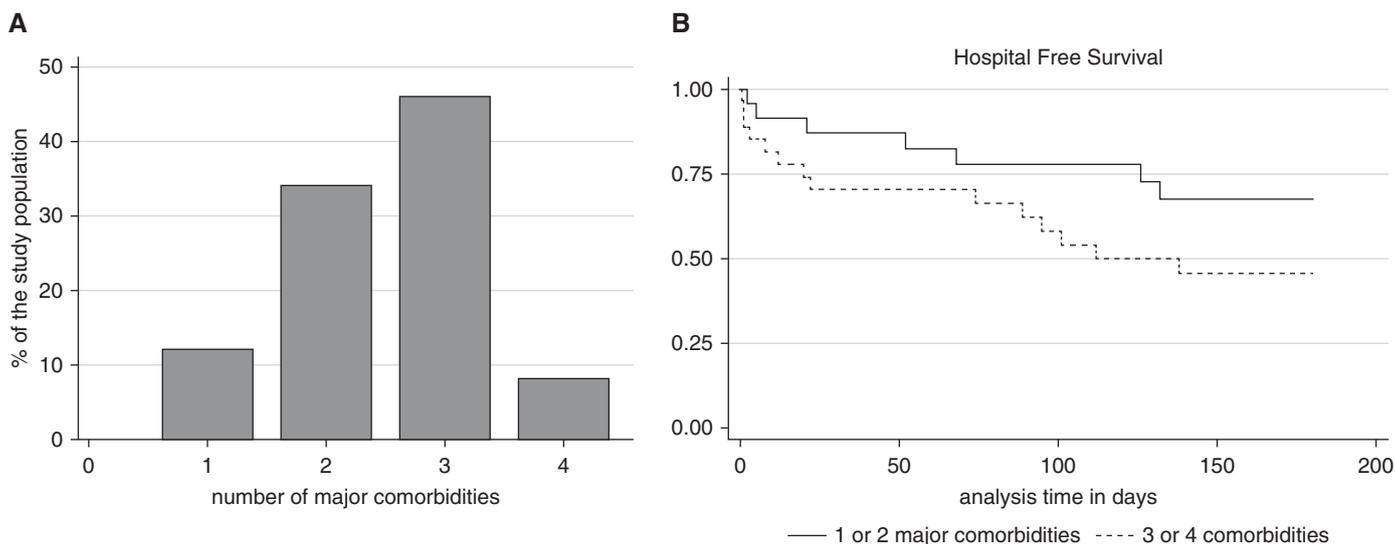


Figure 3. (A) Number of objectively identified comorbidities. (B) Kaplan-Meier survival curves according to hospital-free survival in higher and lesser comorbid patients ($P = 0.127$).

COPD and contribute to poor outcome (15, 29, 30). However, most studies relied on self-reported questionnaires or health care databases, thus probably underestimating the true prevalence of comorbidities (31). Only one prospective study used validated objective measurements to illustrate the high prevalence of comorbidities, but it did not assess patients with OSA with a sleep study or those with cardiac failure with echocardiography (16). However, it is recommended to actively seek and treat important comorbid conditions, including cardiovascular disease and metabolic syndromes to reduce COPD hospitalizations and mortality (21).

To our knowledge, our study is the first to objectively assess the prevalence and severity of OSA in patients surviving AHRF in the ICU by sleep studies using the most recent recording techniques and scoring criteria. We observed a much higher than expected prevalence of moderate to severe OSA and severe OSA for both COPD and non-COPD groups. Our data extend the recent knowledge that the prevalence of sleep-disordered breathing is continuously increasing among older adults and in high-risk groups to the ICU context (32). In a large population-based sample in Switzerland, a recent direct assessment of sleep-disordered breathing using home polysomnography suggests that the prevalence of moderate to severe sleep-disordered breathing is high (49.7%; 95% CI, 46.6–52.8 in men) (23.4%; 95% CI,

20.9–26.0% in women) (33). The mean BMI in our study was $32.3 \pm 10.1 \text{ kg/m}^2$ and more than half of our population was obese, thus accounting partly for the high prevalence of severe OSA.

In the study by Marin and coworkers (7) addressing overlap syndromes (OSA plus COPD), continuous positive airway pressure treatment improved survival and reduced exacerbations. Combining OSA with other comorbidities may be associated with an effect on the impact of hospital-free survival, although our study was underpowered to demonstrate this effect. This is in line with a recent retrospective observation designed to identify novel risk factors associated with readmission after hospitalization for acute exacerbation of COPD. Using the Medicare 41 Hospital Readmission Reduction Program variables, Glaser and El-Haddad (34) identified sleep apnea among other comorbid conditions, as a novel risk factor for readmission. Our data reflect the clinical spectrum of patients with COPD admitted to the ICU (i.e., from cachectic patients with a low FEV_1 and severe emphysema to highly comorbid, metabolic patients with chronic inflammation and a lower impairment in pulmonary function tests), with both subgroups being recognized as reproducible across different studies (4, 16, 17).

Previous reports in patients with COPD have estimated the prevalence of cardiac failure as between 9% and 52% (35). However, the various definitions used were

not based on current recommendations and standardized echocardiographic assessments (31). In a cohort of stable patients with COPD over 60 years old undergoing systematic echocardiographic measurement, the prevalence of cardiac failure was 17% and increased the risk of mortality (36). In our study, systolic heart failure was in the range of previously published studies. However, heart failure with preserved ejection fraction was highly prevalent (44%; 95% CI, 31–58%) and often unrecognized. The low awareness of cardiac failure by treating physicians is surprising in a study population with a long history of tobacco use and multiple risk factors for cardiovascular disease. This is of importance because COPD is associated with increased mortality in heart failure with preserved ejection fraction (37). Thus, the integrated management of comorbidities could have a major impact on AHRF survivors and this needs to be tested in a future trial of a postdischarge care bundle to reduce readmissions after index ICU admission for AHRF.

This study was monocentric and this has several implications. The strength was the homogeneity of practices and assessment of comorbidities. The first limitation is that our findings need to be replicated in other centers to allow generalization. Second, the starting point of our study was “being discharged alive from the ICU after AHRF” and the main variables were measured after ICU

discharge during a period of clinical stability. Our results should therefore not be extrapolated to the subgroup of patients referred for AHRF and who subsequently died in the ICU. Third, we can only report on the high prevalence of comorbidities and their impact on outcomes during follow-up and our data preclude any causal inference related to initial ICU admission. Fourth, we did not include lung imaging (computed tomography) in the objective post-ICU characterization of patients. Using pulmonary imaging to phenotype lung disease has been applied to large-scale COPD cohorts. The phenotyping potential of computed tomography has, however, not yet been identified in a way that can

change patient treatment or outcomes after admission for AHRF. Finally, a significant number of patients did not attend the sleep laboratory for the follow-up sleep study. Indeed, AHRF survivors as a group are frail and reluctant to participate in a systematic follow-up requiring coming back to a sleep laboratory. As a result of a smaller sample size and nonrandom selection of patients not attending their sleep study, estimation of OSA prevalence might have been subjected to some bias.

Conclusions

Relying on a prospective and objective evaluation, our data suggest that multimorbidity in patients surviving AHRF

is common, most often unrecognized, and may be associated with poor outcome. Surviving AHRF in the ICU should be an opportunity for clinicians to evaluate lung and heart functions, and sleep-disordered breathing, because treatment of such important comorbidities may positively impact on hospital readmissions and mortality. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Rosemary Sudan for editorial assistance. The authors acknowledge the contributions of the Clinical Research Center, University of Geneva Faculty of Medicine.

References

- Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, Capilla L, Torres A. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:1279–1285.
- Chu C-M, Chan VL, Lin AWN, Wong IWY, Leung W-S, Lai CKW. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004;59:1020–1025.
- Adler D, Dupuis-Lozeron E, Richard J-C, Janssens J-P, Brochard L. Does inspiratory muscle dysfunction predict readmission after intensive care unit discharge? *Am J Respir Crit Care Med* 2014;190:347–350.
- Rennard SI, Locantore N, Delafont B, Tal-Singer R, Silverman EK, Vestbo J, Miller BE, Bakke P, Celli B, Calverley PMA, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. Identification of five chronic obstructive pulmonary disease subgroups with different prognoses in the ECLIPSE cohort using cluster analysis. *Ann Am Thorac Soc* 2015;12:303–312.
- Struik FM, Sprooten RTM, Kerstjens HAM, Bladder G, Zijnen M, Asin J, Cobben NAM, Vonk JM, Wijkstra PJ. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014;69:826–834.
- Borel J-C, Pépin JL, Pison C, Vesin A, Gonzalez-Bermejo J, Court-Fortune I, Timsit J-F. Long-term adherence with non-invasive ventilation improves prognosis in obese COPD patients. *Respirology* 2014;19:857–865.
- Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010;182:325–331.
- O'Donoghue FJ, Howard ME. Obesity, COPD, NIV and reverse epidemiology. *Respirology* 2014;19:777–779.
- Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MRG, Zwillich CW. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004;116:1–7.
- Budweiser S, Hitzl AP, Jörres RA, Schmidbauer K, Heinemann F, Pfeifer M. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. *Respir Res* 2007;8:92.
- Pérez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vázquez Caruncho M, Caballero Muinelos O, Alvarez Carro C. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128:587–594.
- Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, Gagnadoux F. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010;138:84–90.
- Borel J-C, Burel B, Tamisier R, Dias-Domingos S, Bague J-P, Levy P, Pépin JL. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS One* 2013;8:e52006.
- Kendzierska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS Med* 2014;11:e1001599.
- Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, et al.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–161.
- Vanfleteren LEGW, Spruit MA, Groenen M, Gaffron S, van Empel VPM, Bruijnzeel PLB, Rutten EPA, Op 't Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:728–735.
- Vanfleteren LEGW, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. *Lancet Respir Med* 2016;4:911–924.
- Pacilli AMG, Valentini I, Carbonara P, Marchetti A, Nava S. Determinants of noninvasive ventilation outcomes during an episode of acute hypercapnic respiratory failure in chronic obstructive pulmonary disease: the effects of comorbidities and causes of respiratory failure. *Biomed Res Int* 2014;2014:976783.
- Scala R, Bartolucci S, Naldi M, Rossi M, Elliott MW. Co-morbidity and acute decompensations of COPD requiring non-invasive positive-pressure ventilation. *Intensive Care Med* 2004;30:1747–1754.
- Triest FJJ, Franssen FME, Spruit MA, Groenen MTJ, Wouters EFM, Vanfleteren LEGW. Poor agreement between chart-based and objectively identified comorbidities of COPD. *Eur Respir J* 2015;46:1492–1495.
- Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–365.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, et al.; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography,

- European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79–108.
23. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiography* 2009;22:107–133.
 24. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, *et al.*; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
 25. Kohler M, Stoewhas A-C, Ayers L, Senn O, Bloch KE, Russi EW, Stradling JR. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2011;184:1192–1199.
 26. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, *et al.* Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *Clin Sleep Med* 2012;8:597–619.
 27. Buuren SV, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011;45:1–67.
 28. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons; 2004.
 29. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2794–2800.
 30. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;65:956–962.
 31. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016;4:138–148.
 32. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–1014.
 33. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310–318.
 34. Glaser JB, El-Haddad H. Exploring novel Medicare readmission risk variables in chronic obstructive pulmonary disease patients at high risk of readmission within 30 days of hospital discharge. *Ann Am Thorac Soc* 2015;12:1288–1293.
 35. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJV. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;11:130–139.
 36. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, Comignani PD, Gimeno G, Arakaki D, Laffaye N, Fuselli JJ, Massolin HP, Gambarte J, *et al.* Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012;39:51–58.
 37. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XHT, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012;59:998–1005.