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The Road Not Taken: Missed Opportunities in Managing Acute Exacerbations of Hypercapnic Respiratory Failure

What are the risk factors for recurrent exacerbations of hypercapnic respiratory failure, and how do we minimize them? Although there is frequently emphasis on controlling arterial blood gas tensions and reducing pulmonary infection, in this issue of the *Journal*, Adler and colleagues (pp. 200–207) have now shown the importance of systematic evaluation for comorbidities in both patients with chronic obstructive pulmonary disease (COPD) and patients without COPD who have experienced a severe hypercapnic exacerbation requiring intensive care unit (ICU) admission (1). Importantly, they have demonstrated that these comorbidities are not only underrecognized, despite patients being frequently hospitalized, but may be associated with poor outcome.

In a prospective, single-center study, the authors assessed pulmonary function, cardiac function using echocardiography, and the presence of sleep-disordered breathing using polysomnography in 78 consecutive chronic respiratory patients discharged from ICU after a hypercapnic exacerbation necessitating mechanical ventilation (invasive or noninvasive). Patients without COPD predominantly had obesity hypoventilation syndrome. Heart failure with preserved ejection fraction was found to be previously undiagnosed in 44% of patients, and hypertension had not been recognized before admission in 67%. The prevalence of severe obstructive sleep apnea (OSA) was surprisingly high in patients with COPD, at 51%, with an even greater prevalence in patients without COPD, at 81%.

Only a minority of patients with COPD had previously been diagnosed on spirometry, although a third of the total population had previously been hospitalized for respiratory failure. More than half of the patients studied had three or more morbidities (e.g., COPD, heart failure, obesity, and severe OSA). Multiple morbidities were associated with longer hospital admissions, and there was a trend to higher hospital-free survival in those with fewer comorbidities compared with those with a greater number of comorbidities.

How applicable are these results to general ICU practice and acute pulmonary care? As investigations for comorbidity were carried out after the index admission, only survivors could be studied, and it is not clear how representative they are of the total group admitted to ICU. Indeed, around 18% of the 197 patients screened for eligibility were not admitted to ICU, as the outcome was judged likely to be poor or futile (life expectancy estimated at $<$3 months), so coexisting problems are likely to be even more prevalent in this group with acute hypercapnic decompensation. Median pH on admission for the total patient cohort was 7.29 (interquartile range, 7.23–7.34), and in some centers, patients with a pH $>$7.26 would be managed with noninvasive ventilation (NIV) on acute pulmonary wards or high-dependency units, and not admitted to ICU (2, 3). There was no difference in outcome in patients treated with NIV or invasive ventilation, but only a minority required the latter.

Although pulmonary function tests were performed in all patients, 41 of 78 patients were unable to attend a sleep laboratory for polysomnography 3 months after discharge. The members of this group were older than those who did undergo polysomnography, which may have caused an underestimate of degree of sleep-disordered breathing. In a small subset of patents, simpler respiratory polygraphy was successfully performed, and as this may be sufficient for diagnosis of OSA, polygraphy rather than polysomnography may be a more practical and cost-effective solution to maximize the diagnosis of OSA. It is notable that only 29% of patients had previously been diagnosed with OSA, and less than a third with such a finding were being treated with continuous positive airway pressure or NIV before admission.

There was a preexisting diagnosis of heart failure in 21% of patients. In the 57/78 patients who underwent echocardiography postdischarge, the most notable finding was of heart failure with preserved ejection fraction in 44% (95% confidence interval, 31–58%). Right ventricular dilation was highly prevalent, at 42% in both COPD and non-COPD groups.

A limitation of the study is that the non-COPD group primarily consisted of obese patients, and other causes of hypercapnic respiratory failure such as neuromuscular disease were excluded. However, the prevalence of obesity in the Western world is increasing rapidly, and in many countries, obesity hypoventilation syndrome is now the prime indication for long-term NIV (4–6). The authors have extensive experience in home NIV and report that 67% of patients with multiple comorbidities were discharged with home NIV or continuous positive airway pressure, and a significant number of those with fewer comorbidities also received home ventilatory

support. This high use of home NIV may not be representative of ventilatory practice in other centers, but the use of home continuous positive airway pressure or NIV did not seem to decrease or prevent readmissions.

Until recently, the evidence that home NIV in COPD influences survival and readmissions has been mixed. Köhnlein and colleagues (7) showed that long-term NIV improved survival and health-related quality of life in chronically hypercapnic patients with COPD, but Struik and colleagues (8) found no advantage to discharging patients on home NIV after an acute hypercapnic exacerbation, probably because these individuals were still recovering with normalization of P_{CO_2} in the weeks postdischarge. Early results from a further trial (HOT-HMV UK [Home Oxygen Therapy–Home Mechanical Ventilation UK]) (9), in which patients were randomly assigned to NIV plus long-term oxygen therapy or long-term oxygen therapy alone after an acute hypercapnic exacerbation if hypercapnia persisted more than 2 weeks after discharge, have shown a considerable benefit in reducing admissions/death in the NIV group. This persistently hypercapnic COPD group seems to be a relatively small severe subgroup. Interestingly, arterial P_{CO_2} on discharge in both patients with COPD and patients without COPD in the current study by Adler and colleagues (1) was normal, but that is likely to be influenced by ongoing NIV use in many patients. In patients with obesity hypoventilation, as the authors point out, there is evidence from cohort series that patients receiving long-term NIV experience a correction of sleep-disordered breathing and arterial blood gas tensions. However, the role of comorbidities is evident, as cardiovascular risk remains high despite NIV (10), and in one series of patients with obesity hypoventilation with acute or chronic hypercapnic respiratory failure treated with NIV, use of cardiovascular medication was the only factor independently associated with a higher risk for mortality (11).

Although the authors convincingly demonstrate that comorbidities are significantly underdiagnosed, the data on whether treatment of these reduces readmission are less convincing, although a trend in reduction was seen, and crucially, symptom relief from optimizing the management of heart failure, chronic airflow obstruction, and sleep-disordered breathing is likely to improve quality of life. It remains clear, however, that a focus on simply correcting arterial blood gas tensions both acutely and long term, without understanding the contribution of comorbidities to current and future illness trajectory, is a missed opportunity. ■

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

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IPF: Moving from Idiopathic to Infectious Pulmonary Fibrosis?

Idiopathic pulmonary fibrosis (IPF) is, by definition, a disease without known cause. However, despite not having a precise, defined etiology, considerable advances in our understanding of, and ability to treat, IPF have been made in recent years. Indeed, it is somewhat ironic that there is less understanding and there are fewer treatment options in progressive fibrotic lung diseases with a "known" etiology, such as chronic hypersensitivity pneumonitis, connective tissue disease, or asbestosis. Central to the recent advances in understanding and treating IPF has been the description of a precise clinical phenotype associated with recognition of genetic and environmental risk factors for the development of disease.

Although the recognition of genetic risk factors for IPF, including mucin 5b, desmoplakin, as well as a surfactant protein and telomerase genes, is well documented, they explain only a

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

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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.

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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

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 Pa_{CO_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

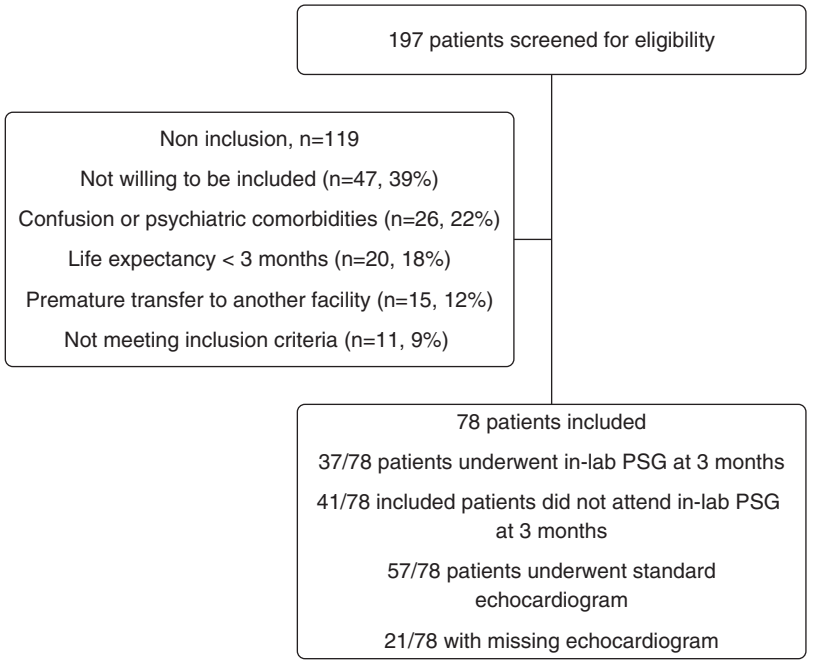

Figure 1. Study flow chart. PSG = polysomnography.

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 CO_2 partial pressure (Ptc_{CO_2}) 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 Ptc_{CO_2} 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 Ptc_{CO_2} 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 FEV_1 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, FEV_1/FVC, FEV_1, 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 FEV_1 compared with patients with COPD. Patients without COPD also presented with decreased total lung capacity and no hyperinflation compared with patients with COPD (Table 2). For the entire study population, FEV_1 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_{O_2}/FI_{O_2}, median (IQR)				0.504
kPa	33.1 (24.3–38.8)	34.3 (25.6–42.1)	32.7 (24.1–37.3)	
mm Hg	248 (182–291)	257 (192–316)	245 (180–280)	
Pa_{CO_2} 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_{CO_2} 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_{CO_2} 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_{CO_2} 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_{CO_2} during sleep compared with an awake supine Ptc_{CO_2} value was less frequent (32%) in patients with COPD compared with patients without COPD (58%).

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
D_{LCO}, % 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; D_{LCO} = diffusion capacity of the lung for carbon monoxide; RV = residual volume; TLC = total lung capacity.
Data are given as mean ± SD.

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

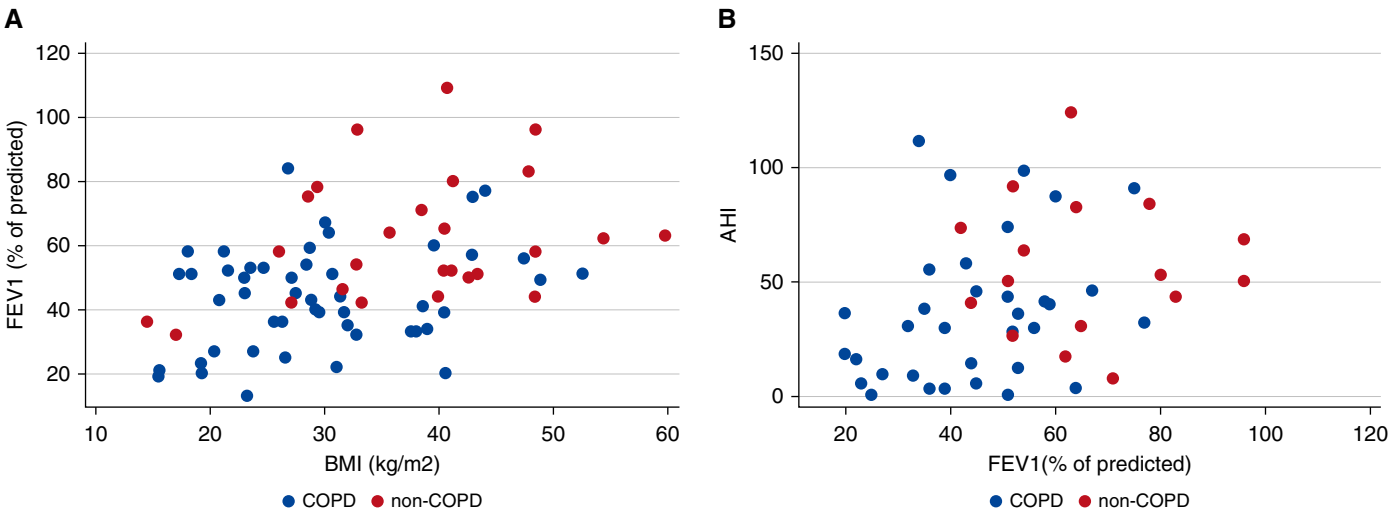

Figure 2. Positive correlation between body mass index and FEV_1 (*A*) and apnea–hypopnea index (*B*). AHI = apnea–hypopnea index; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

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.

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_{CO_2} during sleep, kPa	6.6 (5.9–7.0)	6.6 (6.2–7.0)	0.783
Maximum Pt_{CO_2} during sleep, kPa	7.2 (6.7–7.6)	7.3 (7.0–7.7)	0.515
Increase in Pt_{CO_2} 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).

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

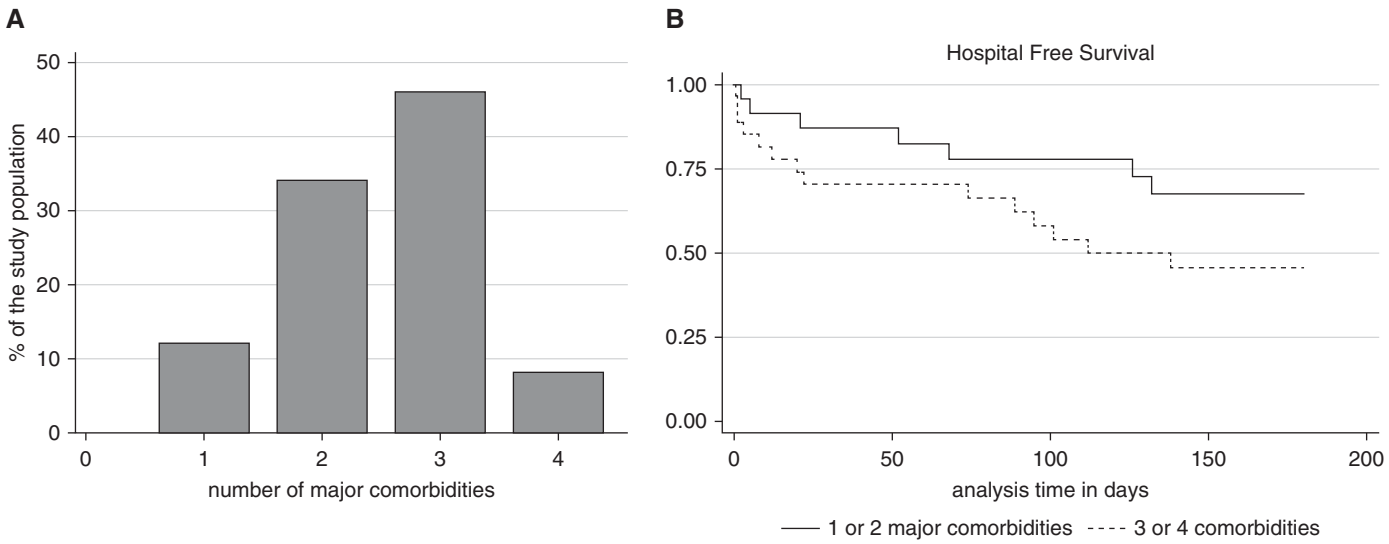

Figure 3. (*A*) Number of objectively identified comorbidities. (*B*) Kaplan-Meier survival curves according to hospital-free survival in higher and lesser comorbid patients ($P = 0.127$).

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 ± 10.1 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.

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