New data on noninvasive ventilation in stable chronic obstructive pulmonary disease: revolutionary or evolutionary?

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Noninvasive positive pressure ventilation (NPPV) reduces hypercarbic acidosis, dyspnea, need for intubation, and mortality when used to treat acute respiratory failure due to exacerbations of chronic obstructive pulmonary disease (COPD) in the acute care setting. In contrast, the role of routine NPPV with the aim of lowering partial pressure of carbon dioxide (PaCO₂) levels and improving other outcomes in hypercapnic outpatients has long been controversial, despite the findings of observational studies suggesting that patients with stable COPD and comorbid hypercapnia have an overall worse prognosis than nonhypercapnic patients.

One of the more recent larger randomized controlled trials (RCTs) is the Australian trial of Non-Invasive Ventilation in Chronic Airflow Limitation (AVCAL). In this multicentre, multiarm trial, 144 patients with stable COPD were randomized to NPPV or usual care. The primary end point was mortality, and the secondary end points included readmissions, hospital days, and quality of life. The NPPV group had a survival benefit (mean follow-up, 2.1 years; adjusted hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.40–0.99; P = 0.045) as well as improvements in sleep quality and sleep-related hypercapnia. Importantly, despite a signal for improved survival (in the adjusted analysis only), patients randomized to the NPPV arm in this study had a worse quality of life (QOL) in the domains of general and mental health as assessed by the SF-36 tool. In addition, based on the conflicting results of the numerous previous studies including the AVCAL study, a 2014 meta-analysis from the Cochrane collaboration, which included 7 studies of moderate-to-high quality (245 patients), concluded that NPPV has “no clinically or statistically significant effect on gas exchange, exercise tolerance, quality of life, lung function, respiratory muscle strength or sleep efficiency [and] should only be used in the context of a clinical trial.”

Within the past year, additional notable studies have been reported which were not included in the Cochrane review. Struik et al. attempted to address the question of whether NPPV applied at the time of discharge can lower the rate of readmissions following hospitalizations for acute hypercapnic respiratory failure in patients with COPD. The investigators randomized 201 patients with Global Obstructive Lung Disease (GOLD) stage 3 or 4 who remained persistently hypercapnic (PaCO₂ levels, 55–60 mmHg) at the time of hospital discharge to receive 1 year of nocturnal home NPPV vs. usual care. After a year, there were no differences in the rate of hospital readmissions, mortality, COPD exacerbations, or QOL indices. PaCO₂ levels fell significantly more in the NPPV group, but to similar levels in both the NPPV and usual-care groups despite average IPAPs of 21 cm H₂O, average EPAPs of 5 cm H₂O, backup rates of 16 per minute, and NPPV use of 6.3 hours per night. The authors concluded that NPPV was ineffective for reducing readmissions or mortality.

Within this context, the results of a study by Köhnlein et al. published earlier this year, are distinct. This prospective multicentre RCT addressed the utility of NPPV in patients with stable severe COPD and comorbid hypercarbia. The inclusion criteria were GOLD stage IV COPD and a baseline arterial PaCO₂ level exceeding 7 kPa (51.9 mmHg) at rest. Stability was judged based on no recent change in pharmacological...
management over the preceding 4 weeks. Patients were excluded if they had a body mass index greater than 35 kg/m², an alternate diagnosis contributing to hypercarbia, or comorbid heart failure.

All enrolled patients were admitted to the hospital at the time of randomization for a short stay to facilitate the initiation of study procedures. Patients randomized to usual care underwent optimization of their medications and were allowed to use NPPV only in the setting of an acute exacerbation with PaCO₂ levels exceeding 10 kPa (74 mmHg). The intervention group received usual care in addition to daily NPPV and were encouraged to use the NPPV for at least 6 hours per day. For those receiving NPPV, controlled ventilation using high backup rates was suggested with the target of reducing PaCO₂ levels by 20% from baseline or to less than 6.5 kPa (48.1 mmHg).

The results demonstrated an overall mean NPPV usage of 5.9 hours in the intervention group using an average IPAP of 21.6 cm H₂O, average EPAP of 4.8 cm H₂O, and a mean backup frequency of 16.1 per minute. One-year mortality significantly improved among those receiving daily NPPV (HR, 0.24; 95% CI, 0.11–0.49) compared with the usual care group based on the Kaplan–Meier survival analysis. Also, PaCO₂, pH, SaO₂, HCO₃⁻, forced expiratory ventilation in 1 second, and QOL as assessed by the St. George Respiratory Questionnaire significantly improved in the NPPV but not in the usual-care group. Minor skin rashes were reported in the NPPV group but resolved with the changing of a mask type.

A few theories have been presented as to why these results are so much more favorable than those reported previously. Köhnlein et al. used high inspiratory pressures and backup rates, with most patients receiving controlled ventilation while on NPPV with the specific target of achieving a significant decrease in PaCO₂ levels. These NPPV settings are much higher than those employed in most previous studies, although they are almost identical to those used by Struik et al. This latter study included a very different patient population than the Köhnlein study as NPPV was initiated upon discharge from the hospital after an admission for hypercarbic respiratory failure rather than after a period of clinical stability of at least 4 weeks. Furthermore, PaCO₂ levels dropped substantially in both NPPV and usual-care groups after hospital discharge in the Struik study, indicating less severe chronic CO₂ retention than was anticipated. It has long been held that COPD patients with more severe chronic CO₂ retention are the ones most likely to benefit from NPPV and that prognosis following hospitalization for hypercapnic respiratory failure marks a population with a substantially increased risk for rehospitalization and mortality during the subsequent year. Thus, once stability had been achieved, the greater chronic CO₂ retention in the Köhnlein study may explain the greater benefit of NPPV observed compared with the Struik study.

There are also several characteristics of the Köhnlein study that may have biased the study toward a favorable result. First, it was unblinded so that differential use of cointerventions may have predisposed to the dramatic improvement in mortality seen with NPPV. All patients were admitted to the hospital at the time of enrollment and subsequently readmitted at 3-month follow-up intervals. Clinicians, nurses, and respiratory therapists caring for those study patients were aware of group allocation, which might have influenced their provision of care in the 2 groups. Second, the generalizability of the results may be limited as it took study investigators nearly 7 years to screen 352 and enroll 201 patients from 36 study sites. This means that, on average, only slightly more than 1 patient was screened at each center per year, suggesting a high level of selectivity. Third, the restriction of NPPV for acute exacerbations to patients with PaCO₂ levels greater than 74 mmHg is much higher than the usual selection criterion of greater than 45 mmHg (with a pH of less than 7.35) and may have predisposed to a higher mortality rate in the usual-care group by delaying the initiation of acute NPPV.

Finally, no formal sleep study was required to exclude comorbid sleep apnea, which may have permitted the inclusion of patients with COPD and obstructive sleep apnea (the overlap syndrome), which also would have predisposed to favorable responses in the NPPV group.

Despite these concerns, the Köhnlein results demonstrate a dramatic improvement in survival and QOL. Considering the potential biases noted above and the discrepancy compared with the previous literature, further confirmatory trials are needed before routine nocturnal NPPV can be recommended for stable COPD with severe hypercapnia. Future research needs to clarify which patients are most apt to respond to NPPV and better differentiate the role of sleep apnea in observed favorable responses. In the meantime, domiciliary NPPV should be considered an option for COPD patients with stable but severe hypercapnia, although ideally initiated within the context of a clinical trial and coordinated through a center with appropriate expertise. If home NPPV is used, the Köhnlein study justifies the use of higher inspiratory pressures and backup rates compared with the earlier studies with the aim to reduce PaCO₂ levels. Based on the Struik results, home NPPV should not be employed immediately after hospitalization but should be reassessed on an outpatient basis some weeks after discharge. The bottom line is that higher inflation pressures and backup rates represent evolution in the use of NPPV for patients with stable hypercapnic COPD, but additional confirmatory data are needed before these can be considered truly revolutionary.
REFERENCES


2 Hill NS. Noninvasive ventilation has been shown to be ineffective in stable COPD. Am J Respir Crit Care Med. 2000; 161 (3 Pt 1): 689-690.


