What Are We Aiming for in Chronic Hypercapnic Respiratory Failure?

The wisdom of organizing illness into clinical syndromes—sepsis, ARDS, and the like—has been debated for at least 50 years, perhaps longer.[1,2] The utility comes from a syndrome's ability to facilitate the recognition or understanding of an important common element among the people who receive the label.[3] The "lumpers," being in favor of syndromes as a paradigm, note the promise of more reliable clinical recognition, efficient enrollment into studies, and optimization of care processes. The "splitters," taking the opposite position, emphasize the peril of grouping patients with different pathophysiology, different natural histories of disease, and differing responses to treatment. If the average outcome poorly represents how individuals will respond, both individual care and the efficiency of trials suffer.

Hypercapnic respiratory failure is the syndrome that occurs when alveolar ventilation is insufficient to match metabolic demand. Is the "syndrome paradigm" the right way for us to improve how we treat these patients? Or would efforts be better spent focusing on individual diseases? Comparison to where other syndrome-based research has excelled or struggled might provide guidance.

The heterogeneity of patients labeled as having ARDS or sepsis is one proposal for why few trials studying therapies for those conditions have shown replicable benefits.[4] A diverse range of pathologies can lead to hypercapnia. Permutations of physiologic derangements limiting the maximal sustainable ventilation (unfavorable respiratory system loads, muscle weakness, mechanical disadvantage, unstable ventilatory control) and those leading to a large ventilation requirement (ventilatory inefficiency, elevated metabolic rate) contribute to hypercapnia in differing degrees in different diseases.[5] Will most patients with hypercapnic respiratory failure respond similarly to a proposed management strategy? The demonstrated benefit of noninvasive ventilation (NIV) in COPD is contingent on selecting only spe
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with obesity hypoventilation syndrome appear to benefit from a wider variety of positive airway pressure modalities started whenever the condition is recognized.[9-11] This ought to give pause that individual treatment effects for people with the various specific diseases causing hypercapnia will be well represented by average treatment effects across the broad category of hypercapnic respiratory failure. The details may matter quite a lot.[12]

Conversely, few would dispute that organizing care around the umbrellas of ARDS and sepsis has facilitated understanding how processes of care should be organized and optimized. In sepsis, decompensation is recognized, blood cultures are drawn, and antibiotics are delivered faster.[13] Whereas significant unwanted variation continues to exist in the provision of lung-protective ventilation to patients with ARDS,[14] the goalposts are known. We have good estimates of how much mortality risk we can attribute to ARDS,[15] which lets us infer how big the societal burden is and how we should structure future studies.

A solid understanding of the corresponding elements of hypercapnic respiratory failure does not exist. The prognostic significance of hypercapnia has been underappreciated, so long as the kidneys were able to compensate, owing to it being relatively well tolerated in the short term. Now, accumulating evidence suggests that these patients face excessively high morbidity and mortality,[16] even if compensated.[17] Owing to the lack of routine assessment of CO_2, relatively little is known about how common hypercapnia is—though it may be very common[18] and very commonly missed.[19]

Even once patients with hypercapnic respiratory failure are identified and started on NIV, only sparse data inform care delivery. Table 1 summarizes the key guidance statements and guidelines pertaining to NIV management for chronic hypercapnic respiratory failure. All recommendations are based on expert opinion or low to very low levels of evidence because almost none of the recommendations been empirically tested.

short, the syndrome paradigm has a good track record dressing the types of evidence gaps that currently exist tients with hypercapnic respiratory failure. Thus, the investigation by Jimenez et al[20] in this issue of RESPIRATORY CARE is particularly timely.

The authors reviewed 337 subjects with chronic hypercapnic respiratory failure that were referred to a chronic ventilation clinic. Out-patients and in-patient referrals for domiciliary NIV initiation or optimization were included.

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Table 1. Recommendations From Key Guidelines or Guidance Statements Regarding the Management of Patients With Chronic Respiratory Failure Who Have Been Started on Noninvasive Ventilation: Methods, Treatment Goals, Follow-up, and Prognostication/Risk Stratification

Cause	Guideline	Key Recommendations on Management Parameters	Strength of Evidence
COPD	ERS 2019[8]	Suggest titration to normalize or reduce P_{aCO_2}	Conditional recommendation, very low certainty of evidence
		Suggest using a fixed, rather than titrating, mode of ventilation	Conditional recommendation, very low certainty of evidence
	ATS 2019[6]	Suggest NIV with targeted normalization of P_{aCO_2} in patients with hypercapnic COPD on long-term NIV	Conditional recommendation, low certainty
		Suggest not using in-lab polysomnography to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV	Conditional recommendation, very low certainty
	ONMAP 2021[7]	Monitoring by experienced personnel (such as RTs)	N/A
		Monitoring should be performed with ABGs, nocturnal oximetry, and adherence tracking targeting > 4 h nightly use	
OHS	ERS 2017[10]	NIV with pressure support or target volume ventilation are both effective	Grade B (supported by non-randomized evidence, or evidence extrapolated from randomized trials)
		Adherence > 4 h/d to NIV is crucial for improving hypercapnia	Grade B (supported by non-randomized evidence, or evidence extrapolated from randomized trials)
	ATS 2019[11]	Patients diagnosed during a hospitalization should be discharged on NIV therapy, then receive a titration polysomnogram within 3 mo of hospital discharge.	Conditional recommendation, very low certainty of evidence
		Patients with severe OSA (AHI > 30 events/h) who are stable clinically can be transitioned to CPAP	Conditional recommendation, very low certainty of evidence
	ONMAP 2021[9]	Patients diagnosed during hospitalization should be discharged on BPAP S/T or VAPS and receive a sleep study within 3 mo	N/A
		CPAP can be considered in patients who also have severe OSA after 2–3 mo of BPAP S/T or VAPS	
		Nocturnal $TcCO_2$ is an acceptable alternative for tracking hypoventilation at night.	
		Therapy failure is defined as persistent hypercapnia or symptoms following 3 mo of adequate adherence.	
Neuromuscular disease	ERS 2016[10]	24 h/d NIV is a treatment option when diurnal hypoventilation develops	Grade B (supported by non-randomized evidence, or evidence extrapolated from randomized trials)
	CHEST 2023[23]	Individualize NIV treatment to achieve ventilation goals	Conditional recommendation, very low certainty of evidence
		No strong evidence supports one mode of ventilation over another	Conditional recommendation, very low certainty of evidence
		Consider mouthpiece ventilation for daytime ventilatory support of bulbar function is maintained	Conditional recommendation, very low certainty of evidence
Restrictive lung disorders (includes neuromuscular)	ONMAP 2021[24]	Criteria to advance to a home mechanical ventilator from BPAP include VC < 30% of predicted, NIV needed 10+ h, severe breathlessness, worsening hypercapnia during the day, or daytime dyspnea requiring NIV	N/A

ERS = European Respiratory Society
ATS = American Thoracic Society
NIV = noninvasive ventilation
ONMAP = Optimal NIV Medicare Access Promotion Technical Expert Panel
RT = respiratory therapist
ABG = arterial blood gas
OHS = obesity-hypoventilation syndrome
OSA = obstructive sleep apnea
AHI = apnea-hypopnea index
BPAP = bi-level positive airway pressure
S/T = spontaneous/timed
VAPS = volume-assured pressure support
$TcCO_2$ = transcutaneous CO_2
VC = vital capacity
N/A = not applicable (generally because the ONMAP Technical Expert Panel was intended summarize evidence to inform insurance coverage criteria, rather than provide traditional guideline recommendations)

Subjects with a variety of causes of respiratory failure were represented, with the most common being subjects with non–amyotrophic lateral sclerosis (ALS) neuromuscular disease and restrictive disorders (41%) and the rest roughly split between ALS, obesity hypoventilation, spinal cord injury, and COPD.

All subjects were managed with NIV targeted toward normalization of blood CO_2 levels as assessed by transcutaneous CO_2 ($PtcCO_2$) monitors at clinic visits over 2 y of follow-up. The association of $PtcCO_2$ level and the risk of death was modeled using multivariable regression with $PtcCO_2$ level as a time-varying exposure. This approach allows the risk of death associated with an elevated $PtcCO_2$ level during days 0–180 to differ from days 180–365 and so on. The authors adjusted for baseline characteristics expected to influence the risk that PCO_2 would not be lowered and the risk of death, such as primary diagnosis, baseline PCO_2, body-mass index, Charlson comorbidity index, and demographics.

Roughly 25% of subjects died during follow-up. Failing to achieve the intended PCO_2 reduction markedly increased the risk of death, roughly proportionate to the degree of reduction from baseline (hazard ratio 0.08 for reductions $>$ 20% from baseline at 180–365 d, for example) and particularly at later time points (both 10.0–19.9% and 20% showing significant reductions when occurring after 365 d). The relationship held in important prespecified subgroups such as those who were referred for optimization of previously started NIV and those with ALS or COPD. Similar reductions in risk of death were seen if CO_2 exposure was dichotomized by whether patients achieved near normalization at $PtcCO_2$ of 50 mm Hg.

The most exciting interpretation of the data is that the reduction in mortality is *because* of the PCO_2 reduction. A variety of mechanisms make this a plausible explanation, and the trials showing benefits of high-intensity NIV in stable hypercapnic COPD offer the strongest empirical support.[6-8] As the trial experience in COPD would suggest, subjects with COPD in the cohort described by Jimenez et al were least likely to achieve reductions. However, when they did, they had a markedly reduced risk of death, also consistent with the cumulative trial evidence. The pattern of decreased mortality holds across the cohort, so perhaps the mechanism by which that risk is ameliorated does too.

However, it remains possible that a failure to normalize the PCO_2 is as an indicator of mortality risk rather than the cause of mortality per se. All subjects received NIV targeted toward normalization, but only some achieved it. Key prognostic indicators were controlled at baseline, but undoubtedly many of these potential confounders evolved over the 2 y of follow-up in ways not predictable at the time of study enrollment. Said differently, the confounders, in addition to the exposure, are time varying. Thus, failure to achieve or maintain normalization of PCO_2 might still indicate disease progression, waning engagement with health care, or shifting goals of care that associate with mortality through mechanisms not mediated by blood PCO_2 levels. Whereas theoretically possible to adjust for,[21] in practice it is hard to imagine better control of these factors in the absence of prospective data collection and, ideally, randomization between varying strategies.

However, the importance of these findings does not require that the reduction in risk of death is a causal effect of PCO_2 normalization. First, this work provides a robust validation of the ability of $PtcCO_2$ monitoring to distinguish between patients at low and high risk of adverse outcome, which could reduce the number of arterial blood gases required to manage these patients substantially. Second, even if, hypothetically, the persistent PCO_2 elevation is only a marker of increased risk of death, the current data still allow providers to give much better prognostic estimates to patients. The rate of death in this cohort was roughly half of what has been reported for unselected patients with hypercapnia,[17,22] suggesting that once patients have been diagnosed, established with a specialty clinic, and achieved improvements in PCO_2 level they are at a dramatically reduced risk of dying. Conversely, inability to achieve or maintain normalization of PCO_2 ought to trigger clinicians to consider interventions commensurate to the very high mortality risk these patients face.

Many uncertainties remain about how NIV should be delivered to patients with hypercapnic respiratory failure. However, both in the specific case of what PCO_2 we should target and when broadly considering how we should study these patients, the work of Jimenez et al moves us a bit closer to knowing what we should aim for.

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