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Inside this issue: Non-Invasive Ventilation

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Effect of home Noninvasive Ventilation with Oxygen Therapy vs Oxygen Therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial.

Authors: Murphy PB, et al.

Reference: JAMA 2017;317(21):2177-2186.

URL: https://doi.org/10.1001/jama.2017.4451

The value of NIV in acute exacerbations of COPD in reversing respiratory acidosis, avoiding intubation and improving in-hospital mortality is well established. Nevertheless, readmission and mortality rates during the subsequent 12 months remain high. Only one previous large-scale randomised trial has been able to demonstrate convincingly the value of home NIV in stable hypercapnic COPD patients, lowering awake CO2 levels and reducing mortality. The authors of this current randomised study allocated 116 patients with COPD and persistent hypercapnia 2-4 weeks following an exacerbation of lung disease requiring in-patient NIV to either home oxygen therapy alone or home NIV plus oxygen therapy. The median time to readmission or death (primary end point) was significantly lower in the home NIV group (4.3 vs 1.4 months) with a 12-month absolute risk reduction of meeting this primary end point of 17% (95%CI, 0.1%-34%). A beneficial effect of home NIV on HRQOL up to 3 months was also seen, while the median exacerbation rate per year was also significantly reduced. It is likely that the longer term, secondary outcomes favouring NIV were underestimated in this study, as 17 of the 57 patients allocated to home oxygen alone crossed over to the NIV group after meeting the primary end point, with the data analysed as intention to treat. This study provides several key pieces of data regarding the use of home NIV in this population. Foremost, it demonstrates the high pressure ventilation strategy is effective in reducing nocturnal CO2 levels and is well tolerated by patients, even those with severe lung disease. By effectively ventilating patients during sleep, as evidenced by significantly reduced nocturnal CO2 levels in the NIV group, a reduced exacerbation rate and prolonged duration to readmission is achievable. However, home NIV in this severe patient group did not improve 12-month mortality compared to the oxygen alone group. These results suggest there is significant clinical value in offering home NIV to patients with persisting hypercapnia several weeks following an exacerbation of lung disease, through reductions in subsequent exacerbations and increasing the time to the next hospital admission. These benefits appear to be achieved without adversely impacting on the patient's quality of life.

Impact of High-Intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study

Authors: Duiverman M et al.

Reference: Respir Res. 2017 May 2;18(1):76.

URL: https://doi.org/10.1186/s12931-017-0542-9

Two recent large randomised trials have demonstrated important clinical benefits are achievable with home NIV in hypercapnic COPD patients if sufficiently high inspiratory pressures to produce a significant fall in CO2 are used. With the high intensity NIV (HI-NIV) approach, a back up rate (BURR) above spontaneous breathing frequency is also added. Such an approach to home ventilation requires more time for the patient to acclimate to therapy with implications for resource utilisation and costs. Given that many patients with severe COPD also have

coexistent heart disease, HI-NIV could have detrimental effects on the heart. This randomised, crossover pilot study evaluated changes in cardiac output and NTproBNP in stable COPD after 6 weeks each of low intensity (mean IPAP 15cmH2O, BURR 12bpm) and high intensity (mean IPAP 23cmH2O, BURR 15bpm). Overall, 6 weeks of NIV did not affect cardiac output during spontaneous breathing with either approach. Furthermore, no significant acute changes in cardiac output occurred with the application of NIV in either mode. However, the authors reported inter-individual differences in response, with HI-NIV reducing cardiac output in two patients with heart failure, and when very high IPAP was used. However, no adverse cardiac events occurred over the study period. Only HI-NIV significantly improved awake CO2 levels, although LI-NIV was sufficient to improve health-related quality of life and lung function in this group. These results, while limited by the small number of patients studied, serves to illustrate the need to monitor cardiac performance in COPD patients with comorbid heart failure undergoing NIV, particularly when high IPAP is used. The study also highlights the importance of individualising NIV titration and settings in order to achieve optimal therapy for that particular patient. Finally, additional research into the longer term impact of both respiratory and non-respiratory outcomes of HI-NIV is needed.

Discontinuing noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations: a randomised controlled trial.

Authors: Sellares J, et al

Reference: Eur Respir J 2017; 50: 1601448

URL: https://doi.org/10.1183/13993003.01448-2016

The benefits of NIV as first line therapy in exacerbations of COPD with acute respiratory acidosis are firmly established. However, there has been far less attention paid to determining the most effective and safest approach to NIV weaning in these patients. It has also been shown that prognosis is very poor in patients where a second episode of acute hypercapnic respiratory failure (AHRF) occurs during NIV therapy. Recent BTS guidelines recommend tapering daytime ventilation first before discontinuing nocturnal therapy. A previous study addressing this question found no difference between NIV weaning approaches, but was likely underpowered. In this current study, 120 patients were allocated to direct discontinuations of NIV after recovery of AHRF or maintaining NIV for an additional 3 nights following resolution of AHRF. The primary outcome of interest was the difference in the incidence of AHRF relapse within 8 days after NIV discontinuation. NIV was able to be discontinued after the first attempt in 106 (88%) patients. The rate of AHRF relapse was not different between groups, with 10 (17%) patients in the direct withdrawal group and eight (13%) in the nocturnal NIV group needing to restart NIV (p=0.56). Although the length of stay in the intermediate respiratory care unit was longer in the nocturnal NIV group, overall hospital stay was not significantly different between groups. Similarly, the rate of hospital mortality, long-term dependency on NIV, 6-month hospital readmission and survival did not differ between groups. Hence, it seems that extending NIV 2-3 nights after recovery from acute respiratory exacerbation does not influence the likelihood of a subsequent relapse of AHRF nor does it alter other aspects of clinical outcome. A reduction in high dependency length of stay has implications for resource utilisation and health care costs.

The comparative effectiveness of noninvasive and invasive ventilation in patients with pneumonia

Authors: Stefan MS, et al.

Reference: J Crit Care 2018;43:190-196

URL: https://doi.org/10.1016/j.jcrc.2017.05.023

The use of NIV in pneumonia remains controversial, with high treatment failure rates compared to its use for other causes of acute respiratory failure. Nevertheless, pneumonia remains a common reason for commencing NIV in many centres. In this retrospective study, the authors used a large, multihospital electronic database to compare outcomes of patients hospitalised with pneumonia and treated initially with NIV to those in whom invasive ventilation (IMV) was initially used. Of the 3971 patients included in the analysis, 27.9% were initially managed with NIV. Overall, 45.2% presented with community acquired pneumonia, with the remainder diagnosed as hospital-acquired pneumonia. Those treated with NIV tended to have a lower severity of illness at admission and more frequently had comorbid COPD or heart failure. In a propensity-matched cohort analysis, NIV was associated with a 29% relative reduction of in-hospital mortality compared with IMV. Additionally, hospital stay and likelihood of home discharge was higher in the NIV group, with no significant difference in 30-day readmission rate between groups. However, further analysis found that this survival benefit was limited to those with a history of COPD or heart failure. NIV failure was significantly more common in patients without prior cardiopulmonary conditions compared to those with these conditions (21.3% versus 13.8%, p = 0.002). While the recently published ERS/ATS guidelines for NIV were unable to offer a recommendation on the use of NIV for de novo acute respiratory failure, the findings of this study confirms previous data highlighting the high likelihood of NIV failure and lack of benefit in terms of reducing intubation or improving survival when NIV is used in patients with pneumonia in the absence of underlying cardiopulmonary disease. This study reinforces the need for careful patient selection when considering NIV for initial management of pneumonia. The role, benefits and timing of high flow nasal therapy in this population requires further investigation, but may be a more appropriate therapy choice for patients without comorbid respiratory or heart disease for managing de novo respiratory failure secondary to pneumonia.

Prognostic value of nocturnal hypoventilation in neuromuscular disease

Authors: Orlikowski D, et al.

Reference: Neuromuscul Disord. 2017 Apr;27(4):326-330.

URL: https://doi.org/10.1016/j.nmd.2016.12.006

The timing of home non-invasive ventilation (NIV) for adults with neuromuscular disorders is well established for those with symptomatic awake hypercapnia. However, there is increasing interest in the use of transcutaneous carbon dioxide monitoring to identify early those with nocturnal hypoventilation in order to commence NIV prior to the development of awake hypercapnia and potentially life-threatening acute respiratory decompensation. Unfortunately, there is a scarcity of data to inform clinicians what degree of nocturnal hypoventilation constitutes a significant respiratory risk, signifying the need for nocturnal NIV. The authors of this study compared the prognostic value of different published definitions of nocturnal hypoventilation and applied them to 124 individuals

with slowly progressive neuromuscular disorders, with a follow up period of up to 6.5 years. Depending on the definition used, the prevalence of nocturnal hypoventilation ranged from 3 to 44%, with a cumulative incidence of home ventilation of 33% at 2 years and 72% at 5 years. A peak TcCO2 ≥49 mmHg was found by the authors to be a more sensitive, albeit less specific, criteria identifying those at risk of requiring subsequent home ventilation than the definition of nocturnal hypoventilation put forward by the American Academy of Sleep Medicine: increase in the arterial PaCO2 (or surrogate) to > 55 mm Hg for ≥ 10 minutes or ≥ 10 mm Hg increase in PaCO2 (or surrogate) during sleep, in comparison to an awake supine value, to a value exceeding 50 mm Hg for ≥ 10 minutes. While this was a retrospective study and did not include patients with more rapidly progressive disorders such as ALS, the results highlight several important issues including the value of transcutaneous carbon dioxide monitoring during sleep; the accuracy of methods and measures to identify hypoventilation during sleep; and the potential clinical consequences of the timing of nocturnal ventilation in different neuromuscular disorders.

Treating chronic hypoventilation with automatic adjustable versus fixed EPAP Intelligent Volume-Assured Positive Airway Pressure Support (iVAPS): a randomized controlled trial.

Authors: McArdle N, et al.

Reference: Sleep 2017 Oct 1;40(10), zsx136

URL: https://doi.org/10.1093/sleep/zsx136

Newer modes of ventilation which use algorithms to automatically adjust pressure settings to deliver effective ventilation despite changes in ventilatory demand are now incorporated into many home ventilators. A number of studies have investigated the efficacy of devices offering automatic adjustment of pressure support (volume targeted pressure support – VtPS) in people with chronic respiratory failure requiring non-invasive ventilation (NIV), but the ability of automatically adjusting end positive airway pressure (autoEPAP) to maintain upper airway patency in those with co-existent OSA has not been previously evaluated. This study, designed as a non-inferiority, randomised double blind cross over study, evaluated VtPS with either AutoEPAP or FixedEPAP in 25 patients diagnosed with chronic hypoventilation. For the whole group, there was no difference in AHI between EPAP modes, nor were objective sleep quality, subjective comfort or sleep quality different. Nevertheless, inter-individual differences in AHI between modes were seen in some patients, without any obvious predictors to explain this difference. There was some suggestion from the data that leaks with AutoEPAP could impact on the control of OSA in some individuals. Conversely, other patients showed a lower AHI with AutoEPAP, suggesting there may be a subgroup of patients in whom the AutoEPAP mode may be advantageous. The results of this study are limited by subjects using each mode for a single night only, so any longer term benefits remain unknown. In addition, these were stable patients already established on home NIV, so the efficacy of AutoEPAP in treatment naïve patients or those who are clinically unstable is yet to be established. Finally, as this study evaluated a single brand of device with a proprietary algorithm, these results cannot be generalised to all autoadjusting bilevel devices with AutoEPAP. Nevertheless, these early data suggest the newer algorithms for automatic titration of ventilatory support may be as efficacious as poysomnographically-guided manual titration of therapy, potentially reducing time and resources needed to provide effective nocturnal ventilation for patients with chronic hypoventilation syndromes, particularly those in whom upper airway instability is also an issue.

NIV prolongs survival in some ALS patients with severe bulbar impairment at NIV indication.

Authors: Sancho J, et al.

Reference: ERJ Open Res 2018; 4: 00159-2017

URL: https://doi.org/10.1183/23120541.00159-2017

The value of noninvasive ventilation (NIV) in relieving symptoms and extending survival in patient with ALS and no to moderate bulbar impairment is well recognised. However, the benefits of therapy in those with more severe bulbar dysfunction (BD) have been questioned. This prospective study sought to determine the effect of bulbar impairment on survival in ALS patients with NIV, following 140 patients in whom NIV was indicated: 120 underwent NIV and 20 refused therapy. Confirming findings from other controlled and observational studies, survival was significantly longer in the NIV-treated group compared to those not undergoing NIV (median 18.5 months vs 3 months, p<0.0001). In those with severe BD, NIV use was associated with a median 13 month survival versus 3 months in the non-NIV group (p=0.001). NIV was able to relieve hypoventilation symptoms in >80% of patients, irrespective of the degree of bulbar dysfunction. Compliance with NIV did not differ between groups. It should be noted that volume rather than pressure-preset ventilation was used in this study. Of clinical importance, the authors found severity of bulbar dysfunction at NIV initiation (measured by the Norris scale bulbar score) and percent of sleep with SpO2 <90% on NIV were predictive of NIV failure in ALS. These finding confirm previous studies showing ALS patients with severe BD can benefit from NIV if they are able to tolerate therapy. Consequently efforts need to be made to minimise problems associated with severe BD such as secretion management, to reduce barriers to patient comfort and adherence to NIV. Additionally, once on therapy patients need to be monitored to ensure effective ventilation is achieved, obstructive events related to BD are corrected as much as possible and sleep time with SpO2 below 90% is kept to a minimum in order to extend survival.

Laryngeal responses to mechanically assisted cough in progressing amyotrophic lateral sclerosis.

Authors: Andersen TM, et al.

Reference: Respiratory Care 2018; 63:(5) 538-549

URL: https://doi.org/10.4187/respcare.05924

Respiratory complications including hypoventilation, secretion retention and pneumonia are major causes of mortality in patients with ALS. Mechanical insufflation-exsufflation (MI-E) to assist with secretion clearance is widely advocated for this patient group both in the home and during acute respiratory infections. These devices are designed to deliver positive pressure to assist the depth of inhalation followed by the creation of negative pressure to increase expiratory flow rates and cough effectiveness. However, therapy is not always effective, especially in those with bulbar dysfunction. Over the past few years, these authors have conducted a series of investigations evaluating the impact of MIE in ALS patients using laryngoscopy. They have previously demonstrated laryngeal adduction during both insufflation and exsufflation can occur, compromising airflow and consequently the effectiveness of therapy. In this latest study, the authors looked at longitudinal changes in the laryngeal responses to MI-E with the progression of ALS. Thirteen subjects were followed for a median of 17 months. In most

patients, adverse laryngeal responses to externally applied pressures during MI-E were found to be present before the onset of other bulbar symptoms. Initially, laryngeal adduction occurred at the highest insufflation pressures only but with disease progression this occurred at lower pressures. The findings of this study provide some important insights into the mechanisms for the variability in response to MI-E in ALS, and emphasise the need for a different and more tailored approach to pressure setting in this patient group compared to other neuromuscular disorders. In patients with ALS, higher inspiratory pressures and flows may be counterproductive, especially as disease progresses.

Switch of noninvasive ventilation (NIV) to continuous positive airway pressure (CPAP) in patients with obesity hypoventilation syndrome: a pilot study.

Authors: Orfanos S, et al.

Reference: BMC Pulmonary Medicine 2017;17:50

URL: https://doi.org/10.1186/s12890-017-0391-9

The most severe respiratory disorder stemming from obesity and sleep disordered breathing is the Obesity Hypoventilation Syndrome (OHS). A number of randomised studies comparing various positive airway pressure (PAP) therapies for this condition have recently been published, demonstrating similar improvements in sleep disordered breathing and correction of daytime respiratory failure irrespective of the mode of PAP used. Some small differences in clinical parameters such as six minute walk distance and pulmonary hypertension favouring bilevel PAP have been reported in short-term trials, but the longer term impact of these differences on hospital readmission, subsequent cardiovascular events or survival have not been determined. Furthermore, a significant proportion of individuals with OHS are diagnosed and commenced on bilevel PAP in the acute setting, and continue on this therapy long term. The costs of bilevel PAP, particularly the more complex modes of therapy, are substantially high than continuous PAP (CPAP) therapy. This prospective study of stable OHS patients with coexistent OSA (AHI>15/hr) established on bilevel PAP for at least 2 months, found no differences in mean AHI, diurnal or nocturnal gas exchange, leaks or compliance after one month on CPAP compared to bilevel PAP. Quality of life and sleep quality measures did not differ between therapies, although the Epworth Sleepiness score was lower on CPAP compared to bilevel PAP (4.2 vs 8.2, p=0.004). Twelve of the 15 patients studied reported a preference for CPAP over bilevel PAP. Although the sample size is small, the authors used this study to illustrate the feasibility and safety of switching stable OHS patients from bilevel to CPAP using home monitoring and device-derived measures. It should be noted that 12 of the 15 patients were commenced on bilevel therapy during an acute episode of respiratory decompensation requiring hospitalisation. The potential to switch to longer term CPAP results in significant reductions in equipment costs and appears to be well accepted by most patients. However, we are still awaiting data to confirm whether cardiovascular outcomes are equivalent between therapies, recognising that most deaths in OHS arise from cardiovascular events rather than respiratory failure.

Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF.

Authors: Cowie MR, et al.

Reference: Eur J Heart Fail. 2018;20(3):536-544.

URL: https://doi.org/10.1002/ejhf.1048

In patients with heart failure and reduced ejection fraction, sleep disordered breathing is common and adversely affects prognosis. Treatment with CPAP therapy is highly recommended for those with predominately OSA. However, treatment of central sleep apnea (CSA) with PAP therapy in this patient group is less clear cut. Adaptive servoventilation (ASV) was designed to stabilise breathing in patients with CSA by automatically increasing pressure support in response to apneic or hypopneic events, while reducing support during episodes of hyperpnea and normal tidal breathing. The SERVE-HF trial was a large multinational randomised trial that compared ASV to medical therapy alone in patients with predominately CSA and left ventricular ejection fraction (LVEF) ≤45%. Based on previous work, it was believed ASV would diminish central events and improve LVEF. Despite effectively controlling CSA, ASV was associated with an increased risk of cardiovascular death compared with medical therapy. These were very unexpected findings and led to significant speculation regarding possible underlying mechanisms for the higher mortality with ASV. The current study from the same authors reports a preplanned substudy from the SERVE-HF trial looking at more detailed measures from 312 subjects to better understand the mechanistic changes occurring with ASV. After 12 months, echographically measured LVEF did not differ between the ASV and control groups. Likewise, other measures of cardiac structure and function including left ventricular dimensions, wall thickness, diastolic function and right ventricular dimensions and ejection fraction did not differ between groups at follow up. ASV also had no effect on cardiac biomarkers, renal function or systemic inflammation over the 12 month period. Hence the increased mortality in the ASV group does not appear to be associated with adverse remodelling or worsening of heart failure. However, these findings also do not explain the increased risk of sudden (presumably cardiac) death seen in the SERVE-HF study. Results from any further analyses of the SERVE-HF trial as well as the eagerly awaited ADVENT-HF study will hopefully shed some much needed light on the issue of PAP therapy and its consequences for patients with heart failure with reduced LVEF.

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