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Over the past two decades, noninvasive ventilation (NIV) has assumed an increasingly important role in the management of hypercapnic respiratory failure in both the acute and chronic setting. While the benefits of this therapy are well documented, a proportion of patients will not tolerate treatment or fail to benefit from it. The following articles raise some of the issues around who benefits from therapy and what strategies could be employed to maximise clinical outcomes.
I. Noninvasive ventilation (NIV) in acute respiratory failure


Authors: Chandra D, et al
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3297087/

Using data from more than 7.5 million inpatient COPD admissions collected by the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, these authors assessed the pattern and outcomes of NIV use for acute exacerbations of COPD over a 10 year period (1998-2008) in the US. A significant shift toward NIV for the treatment of respiratory failure was found over this time period accompanied by a reduction in the need for invasive ventilation (IMV). In addition, a decline in in-hospital mortality was also observed. However, the subgroup of patients failing initial NIV and subsequently managed with IMV showed a worsening mortality such that by 2008 these patients had a 61% (95% CI 24-109%) higher odds of death compared with those placed directly on IMV, and a 677% (95% CI 475-948%) greater odds of death compared with patients successfully managed with NIV alone. Not only did this subgroup have the highest in-hospital mortality, they also generated the most expensive and longest hospitalisations. While the nature of this study does not permit analysis of the reasons for the high mortality in the NIV- to- IMV group, it does highlight the need for clinicians to identify early patients likely to fail NIV and to carefully consider the appropriateness of escalating therapy for that individual. Furthermore this study demonstrates the increasingly important role of NIV as initial therapy for acute hypercapnic exacerbations of COPD in routine clinical practice and the need for respiratory and critical care clinicians to develop and expand expertise with this therapy.

Rescue therapy by switching to total face mask after failure of face mask-delivered noninvasive ventilation in Do-Not-Intubate patients in acute respiratory failure

Authors: Lemyze M, et al
URL: http://journals.lww.com/ccmjournal/pages/articleviewer.aspx?year=2013&issue=02000&article=00013&type=abstract

Despite the effectiveness and benefits of using NIV as first line therapy for the management of acute on chronic respiratory failure, it is not universally successful, and 30-40% of patients commenced on therapy are likely to fail. Mortality rates are high in this NIV failure group, especially where NIV have been introduced as a ceiling of care. The interface used and the patient’s tolerance of this are seen as key aspects in the success of therapy. Oronasal (ON) masks are the most commonly used interface in the acute setting. However, total face masks are a newer option for NIV delivery, although their role in the management of respiratory failure is still being evaluated. This prospective observational study evaluated consecutive patients with do-not-intubate (DNI) orders treated with NIV for acute respiratory failure. NIV was commenced using an ON mask and switched to a total face mask if there was i) failure with ON mask to reverse clinical signs of ARF ii) failure to improve gas exchange or iii) major discomfort or severe skin damage from the ON mask. Changing the interface during the first 12 hours of NIV was considered an “early switch” and after this time, a “late switch”. Seventy-four patients with DNI orders
were managed with NIV over the 12-month study period. In 36 of these patients (48.6%), the interface was switched due to failure of NIV while using the ON mask. This failure group required a longer period of NIV during the first 48 hrs, had longer stays in ICU and needed higher IPAP and EPAP pressures. Twenty-three of the 36 ON mask failures survived to hospital discharge after the change in interface to the total face mask. The most common reason for switching masks was failure to reverse hypercapnic respiratory failure (67%), and this mostly led to an “early” switch. In 31% the mask was switched due to skin breakdown or mask intolerance, and this most frequently was a “late” switch. It was unclear why gas exchange improved with the total face mask, but it is possible that the ability to deliver higher pressures with fewer leaks was a factor. This study suggests that the total face mask can be considered as an alternative to ON masks. If NIV fails to improve acute respiratory failure initially using an ON mask, changing to the total face mask may improve gas exchange and if switched early can reduce the likelihood of developing facial pressure sores, permitting a more prolonged period of NIV to be tolerated.

**Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease.**

**Authors:** Carrillo A, et al  
**Reference:** Am J Respir Crit Care Med 2012; 186:1279-1285  

The use and benefits of NIV are well established for patients presenting with acute exacerbations of COPD and hypercapnia. However, the evidence for its efficacy in other patient groups presenting with acute hypercapnic respiratory failure (AHRF) is lacking due to an absence of well designed trials. Using the same NIV protocol, Carrillo and colleagues prospectively studied 716 consecutive patients in AHRF with either a diagnosis of Obesity hypoventilation Syndrome (OHS -173 subjects) or COPD (543 subjects). Both groups presented with the same severity of acidosis (pH 7.22±0.08) and hypercapnia (OHS:84±18mmHg vs COPD: 86±22mmHg, p=0.34), had similar Charlson indexes and almost 30% in each group had “Do not Intubate” orders. Similar physiological responses after one hour of NIV were seen in both groups. Patients with OHS had lower rates of late NIV failure, readmission to ICU, as well as in-hospital mortality, with no difference between the groups in the rate of NIV failure (OHS 6% vs COPD 11%, p=0.11). Readmission rates and adjusted survival over the next 12 months were similar between the two groups. Although this was not a randomised trial, it does illustrate the efficacy of NPPV in the acute setting for patients with OHS, even those presenting with significant respiratory acidosis. It also raises a number of questions about the overall recognition and management of OHS. Thirty nine percent of these OHS patients had been prescribed home oxygen but only 9% nocturnal non-invasive ventilation, a more definitive long term therapy for this condition. It was not possible from this study to identify reasons why PAP therapy had not been previously offered. However, as 65% had previously been admitted to ICU and a third had been hospitalised in the previous year it suggests the patients may have been diagnosed with another respiratory condition (COPD or asthma) or the diagnosis of OHS was just overlooked; in either case, there was a delay in introducing more appropriate therapy. This would be in keeping with findings of other studies and highlights the need for clinicians to consider the possibility of hypoventilation in morbidly obese hospitalised patients to ensure early and appropriate intervention is offered.
The failure of NIV to reverse respiratory failure even amongst well selected patients has been attributed to a number of factors including timing of intervention and clinician expertise. However, data concerning the most effective method of initiating and guiding settings to provide effective ventilator support are limited. ICU-dedicated ventilators as well as many of the newer generation simpler NIV-specific devices provide graphical real time flow and pressure waveforms that can be used to detect patient/ventilator asynchrony, a factor which has been shown to affect clinical outcome in intubated patients. Whether recognition and titration of settings to minimise these asynchronies has any impact on clinical outcomes during acute NIV has not been evaluated previously. In this randomised trial, the authors were able to demonstrate that using ventilator graphics of flow and pressure to monitor and improve patient-ventilator interactions produced a more rapid normalisation of pH and fall in CO2 during the first 2 hours of therapy than simply monitoring and adjusting settings based on the numeric data such as tidal volume, leak and respiratory rate alone. Tolerance to ventilation at 2 hours was also significantly higher in the graphics driven titration group. However, no difference in NIV success rate (86% for the graphics driven group vs 80% for standard titration group) or overall 30 day survival rates were seen, although it should be noted that the study was not sufficiently powered to detect differences in these outcomes. Since NIV failure most commonly occurs within the first few hours of commencing therapy, more rapid identification of suboptimal patient-ventilation interaction and adjustment of settings accordingly may improve physiological and patient-centred outcomes, although this hypothesis needs further evaluation. The analysis of waveforms during NIV is a skill set that respiratory clinicians involved in initiating NIV need to develop further.

Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomized controlled trial

Authors: Di Marco F, et al
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3388700/

The occurrence of patient-ventilator asynchrony (PVA) during NIV and the potential for negative outcomes arising from this is not limited to the acute setting. In recent years, awareness of the frequency and consequences of PVA during nocturnal ventilatory support has increased. Despite the widespread use of NIV for hypercapnic patients with severe stable COPD, strong evidence of significant benefit in this group is still lacking. In some patients, severe morning dyspnea when ceasing nocturnal NIV can arise that may impact on the quality of life for these individuals. These symptoms may arise from inappropriate machine settings leading to asynchrony and worsening of pulmonary mechanics. In this study, Adler and colleagues identified 9 out of 32 patients with severe COPD using long term nocturnal NIV who reported morning dyspnoea (ie a Borg score >4 when coming off the ventilator), of whom 8 underwent two full night polysomnograms (PSG). During the first night, patients were studied on their usual home settings to detect and quantify the presence of PVA. This was followed by a second PSG where

Polysomnography in stable COPD under non-invasive ventilation to reduce patient-ventilator asynchrony and morning breathlessness

Authors: Adler D, et al
Reference: Sleep Breath 2012;16(4):1081-90
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3497941/
ventilator settings were adjusted to reduce sleep disordered breathing and patient-ventilator asynchrony. The most common PVA identified in this study was unrewarded inspiratory efforts which had not been clinically suspected until identified on the PSG. By identifying these events and adjusting ventilator settings appropriately, patient-ventilator synchrony was markedly improved and morning dyspnoea was diminished, although sleep quality and gas exchange were not significantly altered. As this was not a physiological study, the mechanisms underlying this improvement in dyspnoea could not be established. However, the authors speculated that excessive pressure support could produce dynamic hyperinflation and an increase in intrinsic PEEP which would lead to unrewarded efforts, increased work of breathing and consequently morning dyspnoea when ceasing NPPV. Unfortunately, whether PVAs were present and to what degree in those COPD patients not reporting morning dyspnoea was not investigated.

While the limitations of this small, non-blinded short term observational trial are obvious, it does serve to confirm findings from previous studies regarding the potential for significant PVA to arise during nocturnal NIV and the impact this could have on clinical outcomes. These events are not easily identified from nocturnal gas exchange monitoring or daytime clinical review. Prospective, longer term trials are required to determine whether overnight adjustment of ventilator settings targeted at reducing PVA produces improvements in compliance, symptoms or quality of life, particularly in those patients who experience difficulty tolerating therapy or who fail to benefit from it.

III. Titrating settings for nocturnal noninvasive ventilation in stable patients with COPD and hypercapnic respiratory failure

High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial

Authors: Murphy P, et al
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526870/

The limited benefits of nocturnal NPPV so far demonstrated in patients with stable hypercapnic COPD have been thought by some to be attributable at least in part to the low level of pressure support and back up rates used in the majority of the long term trials. High intensity NIV (ie high inspiratory pressures >25cmH2O and high back up rates) are currently advocated by some centres for this group in order to achieve improvements in nocturnal and awake gas exchange. However, the extent to which it is the high pressure or high rate that plays the most significant role in achieving improved clinical outcomes compared to more standard lower settings has not been investigated. In this 12 week, two treatment cross over trial, 12 patients were recruited to receive high pressure/high back up rate (high intensity) or high pressure/low back up rate (high pressure) NIV in a randomised fashion for a 6 week period. Mean baseline PaCO2 of the group was 61±12mmHg with an FEV1 % predicted of 32±12%. Only 7 patients completed the trial, with 3 of the 5 withdrawals claustrophobic or intolerant of therapy. This small study found no difference in ventilator adherence between the high intensity and high pressure NPPV strategies in this population (6:37±1:45 hrs vs 6:33±2:14 hrs; p=0.85). There were also no between group differences in the change in PaCO2, health-related quality of life (HRQoL) or sleep quality seen. Both strategies achieved similar overnight control of transcutaneous CO2. In interpreting their data, the authors suggested that in stable COPD, high pressure was the major factor modifying the improvement in awake CO2.
rather than the high back up rate. In addition, the study results support the notion that high pressures during sleep are acceptable and tolerated by patients with stable COPD, with good adherence to therapy and no evidence of this strategy adversely affecting sleep quality. Of interest, although similar improvements in HRQoL were achieved with both protocols, the respiratory complaints domain of the Severe Respiratory Insufficiency questionnaire used showed a greater improvement during the high pressure period. The authors suggested that greater patient-ventilator asynchrony during the high intensity strategy may have been responsible for this by imposing a higher mandatory back up rate which may have affected patient-ventilator synchrony. However, only limited nocturnal monitoring was performed which was unable to confirm this proposal. While there are many limitations of this study including low patient numbers, a limited study period and lack of data on changes in pulmonary mechanics or functional capacity, the results add further support to the growing evidence which suggests the need to use at least a high pressure strategy in stable hypercapnic COPD patients if significant gas exchange and clinical outcomes are to be achieved. However, the high drop out rate also raises the importance of identifying barriers and limitations to this NIV strategy.

**Physiological changes during low- and high-intensity noninvasive ventilation.**

**Authors:** Lukácsovits J, et al

**Reference:** Eur Respir J. 2012 Apr;39(4):869-75.

**URL:** [http://erj.ersjournals.com/content/39/4/869.long](http://erj.ersjournals.com/content/39/4/869.long)

To date most trials evaluating NIV in patients with COPD and chronic respiratory failure have used inspiratory pressure (IPAP) settings of around 14-17cmH2O and back up respiratory rates of 12-14bpm. This has been referred to as low intensity (Li-) NIV. More recently a strategy of using inspiratory pressures around 28cmH2O with higher back up rates of 20-21bpm (High intensity (Hi-)) NIV has been proposed with the aim of achieving a maximal reduction in PaCO2 during sleep. The longer term clinical benefits and tolerability of this high intensity approach have yet to be established in large well designed trials. Furthermore, the impact on lung mechanics and cardiac output has not been studied. This physiological investigation evaluated the short term effects (30 minutes) of these two setting strategies in 15 stable COPD patients with hypercapnia (FEV1 24±8% predicted; PaCO2 59±7mmHg). Hi-NIV significantly improved PaCO2 over levels achieved with Li-NIV, with larger increases in VT and VE and reduced inspiratory effort observed. However, cardiac output and stroke volume reduced significantly more with Hi-NIV, impacting on oxygen transport. Unfortunately, because Hi-NIV almost completely abolished inspiratory muscle activity, dynamic intrinsic PEEP measurements could not be made so the impact of this strategy on lung hyperinflation could not be estimated. The findings of this study provide a cautionary reminder of the important heart-lung interactions, and while the Hi-NIV strategy is an attractive one for achieving greater gas exchange improvements, this study highlights the need to ensure these are not offset by impairments in cardiac performance and oxygen delivery capacity. Careful monitoring during initiation of Hi-NIV should be undertaken in patients with pre-existing cardiac disease, those with severe hypoxemia or if significant anemia is present. Higher pressures may need to be applied slowly over a period of days, with attention to minimizing asynchrony between patient and the ventilator especially during sleep, as this could worsen dynamic hyperinflation and reduced cardiovascular performance.
Obesity hypoventilation syndrome (OHS) is characterised by significant obesity, raised daytime CO2 and sleep disordered breathing, and has become the most common indication for home ventilation in many countries. Two features of this disorder, upper airway obstruction and severe nocturnal hypoxemia, are also factors associated with increased cardiovascular and metabolic risk. Compared to eucapnic obese individuals those with OHS are more likely to have cardiovascular disease and diabetes, and have higher mortality rates. Although NIV is used widely to manage this condition, no study has previously looked specifically at the impact of therapy on cardiovascular risk in OHS. In this trial, 35 patients with mild OHS (mean PaCO2 46±4mmHg) were randomised to either NIV or lifestyle counselling for a 4 week period. There were significant improvements in diurnal PaCO2, sleep architecture and reduced respiratory events with NIV compared to the lifestyle group. However, cardiovascular, metabolic and inflammatory parameters remained unchanged despite significant improvements in sleep hypoxemia in the NIV group. Adherence to therapy was not an issue, with a mean nightly use of 5.6±2.2hrs. Although it could be argued 4 weeks was too short a period for improvements in biological markers of inflammation or metabolic function to occur, studies in eucapnic OSA have reported changes in these parameters within days or weeks of commencing CPAP. These findings have several implications. Firstly, early detection and intervention in patients with OHS is important to minimise the development and progression of co-morbid conditions. Secondly, simply treating sleep disordered breathing is not sufficient to reduce the cardiovascular and metabolic risk profile of these individuals. Use of NIV needs to be accompanied by other measures to reduce weight and increase physical activity.

Impact of different back-up respiratory rates on the efficacy of non-invasive positive pressure ventilation in obesity hypoventilation syndrome: a randomized trial

Authors: Contal O, et al
URL: http://journal.publications.chestnet.org/article.aspx?articleid=1216043

Although OHS is now a major indication for home ventilation, the most effective mode of therapy to use has not been established. Bilevel support can be set with a backup rate (Spontaneous timed mode) or without one (Spontaneous mode -ST). Furthermore, the backup respiratory rate (BURR) may be set low (just below the average sleeping rate) or high (set to capture and “control” the patient’s rate). The impact of different rate settings on ventilation and sleep has not been evaluated. In this crossover trial, 10 stable patients with OHS established on home NIV underwent 3 consecutive nights randomised to the three different rate settings (spontaneous mode, Low BURR - 11bpm; High BURR – 21bpm). During the spon-
taneous mode, the apnea-hypopnea index was significantly higher than in the ST mode with either a low or high BURR, with a high number of central and obstructive events seen. Patients perceived little difference in sleep quality or ventilator comfort between the three conditions. Based on their findings, the authors questioned the use of the Spontaneous mode in patients with OHS. However, the data needs to be interpreted in light of the study protocol. The IPAP and EPAP levels were unaltered during the study period and had not been initially determined during PSG. Therefore the pressure settings used in the study may have been inappropriate, and would have favoured the Low BURR condition given that the back up rate used during this condition was closest to that used for home ventilation in these patients. With the pressure settings used, both the mean tidal volume and variability of this measurement was higher in the spontaneous mode, which would have favoured the development of central events if CO2 levels were lowered. Although mean transcutaneous CO2 was not statistically different over the 3 nights, it was 3mmHg lower during the spontaneous mode night possibly reflecting transient episodes of hypocapnia which would have promoted central events. The significant residual obstruction seen during the Spontaneous mode may have contributed to more arousals and breathing instability. While it would appear that the use of a back up rate is advantageous in this disorder, the study highlights the importance of monitoring and titrating pressure settings specifically during sleep to minimise ongoing respiratory abnormalities irrespective of the mode used.

Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial

Authors: Murphy P, et al
URL: http://thorax.bmj.com/content/67/8/727.long

Fifty consecutive patients with OHS (BMI 50+7kg.m2; CO2 49+6mmHg) were randomised to either standard fixed pressure bilevel therapy set in the spontaneous timed mode or to a hybrid bilevel mode known as average volume assured pressure support (AVAPS) for a 3-month period. This latter mode allows the targeting of a set tidal volume through the automatic adjustment of the pressure support. In this study, both modes were similarly effective in reducing daytime CO2 levels. The degree to which health related quality of life, daytime vigilance and weight loss occurred also showed no difference between modes. The use of NPPV ≥4hr per night irrespective of the mode used was associated with improved symptoms and physical activity as well as weight loss. The findings from this study, along with the study by Contal and colleagues summarised above, suggest that adjusting settings to best control nocturnal hypoventilation appears to be the key element in effective ventilatory support. This is more likely to be achieved with nocturnal monitoring. The results confirm earlier, smaller short term trials finding no significant clinical advantage in the routine use of AVAPS in patients with OHS. However, this does not preclude this mode of ventilatory support being indicated on an individual basis for patients failing fixed pressure bilevel support.
The 18th Congress of the Asian Pacific Society of Respirology

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Congress Venue: Pacifico Yokohama

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