NIPPV FOR THE HYPERCAPNIC COPD AND OBSESITY HYPOVENTILATION PATIENT

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Gaurav Singh, MD, completed all of his medical education and training locally. He attended UC Berkeley for undergraduate studies and UCSF for medical school. He also went on to complete a Masters of Public Health at UC Berkeley. He completed residency training in Internal Medicine at Stanford University, followed by Pulmonary and Critical Care fellowship as well as Sleep Medicine fellowship at Stanford University. He joined the Stanford faculty in Pulmonary, Critical Care, and Sleep Medicine after his medical training. He has recently transitioned his career to VA Palo Alto Healthcare System.

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Disclosures

- No conflicts of interest

Learning Objectives

1. Recognize when to consider NIPPV over CPAP for hypercapnic COPD and obesity hypoventilation syndrome
2. Identify the appropriate NIPPV modality and settings to select for hypercapnic COPD and obesity hypoventilation syndrome
3. Understand the health outcomes associated with NIPPV use among patients with hypercapnic COPD and obesity hypoventilation syndrome

Outline

- Relevant pathophysiology
- Rationale and mechanism of NIPPV
- Clinical evidence supporting use of NIPPV
- Patient selection for NIPPV
- NIPPV initiation and titration
- Qualification criteria for NIPPV

Review Question: COPD

1. Which non-invasive ventilation modality has been demonstrated to prolong the time to hospital readmission or death in patients with hypercapnic COPD?

A) Bilevel

B) Bilevel-S/T

C) Volume Assured Pressure Support

D) Adaptive Servo Ventilation

Review Question: OHS

2. What clinical outcome has demonstrated improvement with bilevel compared to continuous positive airway pressure in patients with obesity hypoventilation syndrome?

A) Daytime hypercapnia

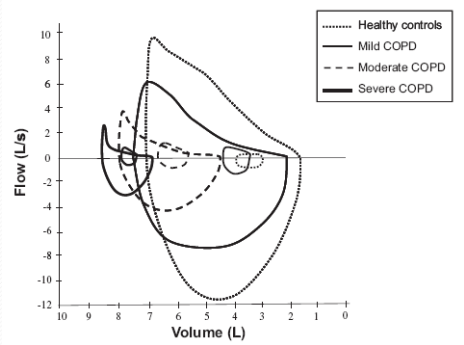
B) Quality of life

C) Daytime sleepiness

D) Pulmonary hypertension

Hypercapnic COPD: Definitions

- GOLD definition of COPD: post-bronchodilator $FEV_1/FVC < 70\%$
- Hypercapnia: $PaCO_2 > 45$ mmHg



www.goldcopd.org

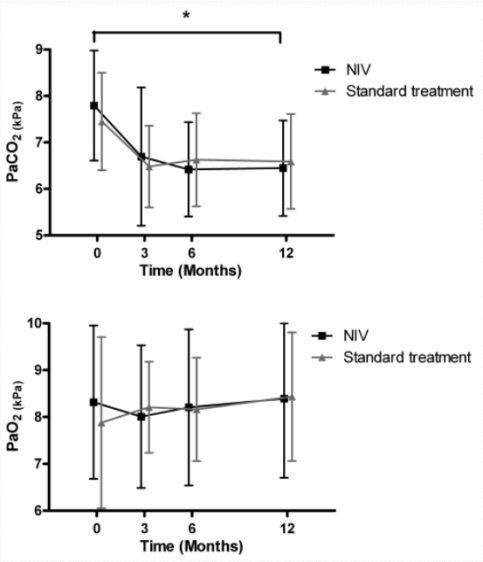
Hypercapnic COPD: Pathophysiology

- Lung parenchyma and airway destruction
  - Poor matching of ventilation to perfusion (i.e., V/Q mismatch or dead space ventilation)
- Imbalance between inspiratory muscle capacity and load placed on respiratory system
  - Hyperinflation changes configuration of diaphragm and shortens inspiratory muscles (mechanical disadvantage, atrophy, respiratory muscle weakness)
  - Excessive resistive load on respiratory muscles due to increased airway resistance and intrinsic positive end-expiratory pressure (iPEEP), inspiratory threshold

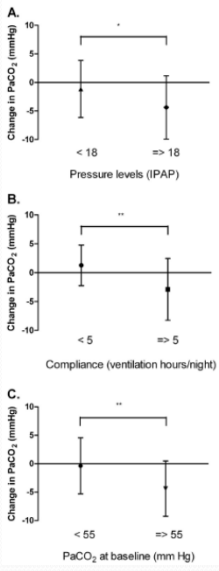
NIPPV Rationale/Mechanism in COPD

- Relief of ventilatory muscle fatigue
- Reduction in respiratory load
  - Decrease in lung hyperinflation with improvement in lung volumes
  - Decrease in iPEEP
- Augment alveolar ventilation
- Correcting CO_2 responsiveness (i.e., change in central chemosensitivity)
- Treating sleep-disordered breathing
- Benefits: improvements in dyspnea, nocturnal and daytime respiratory function, gas exchange, sleep quality, and functional status

Effective NIPPV Reduces PaCO2



Struik et al. Thorax. 2014;69:826-34

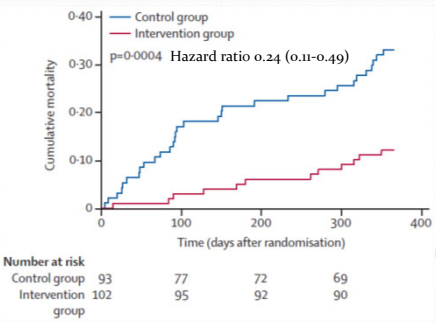


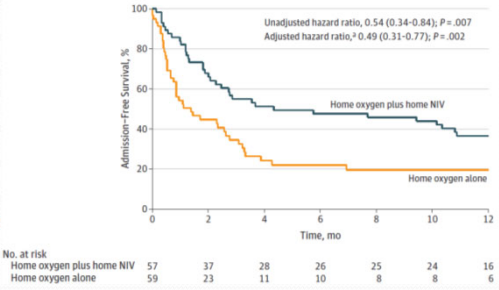
Struik et al. Respir Med. 2014;108:329-37

Factors that augment reduction in $PaCO_2$

- Higher IPAP
- Better adherence
- Higher baseline $PaCO_2$

NIPPV Improves Mortality/Readmission





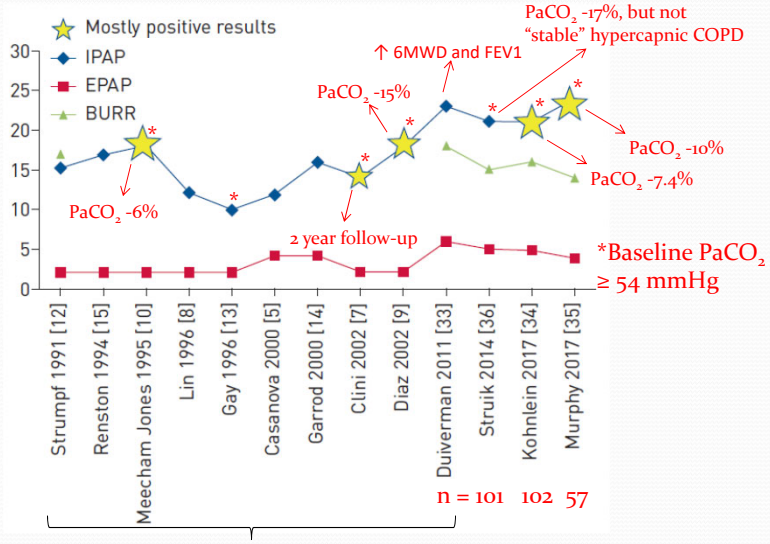
- Baseline $PaCO_2$ ≥ 51.9 mmHg (mean 58.5 mmHg)
- No exacerbation within 4 weeks
- NIPPV targeted to reduce $PaCO_2$ by at least 20% or < 48 mmHg
- Mean IPAP 21.6 cmH_2O, EPAP 4.8 cmH_2O, backup rate 16.1 breaths/min
- 1-year mortality 12% in NIPPV group vs 33% in control group

Kohnlein Lancet Respir Med. 2014;2:698-705

- Baseline $PaCO_2$ > 53 mmHg (mean 59.0 mmHg)
- Persistent hypercapnia after acute COPD exacerbation (2-4 weeks after resolution of respiratory acidemia)
- NIPPV targeted to reduce $PaCO_2$ by 3.75 – 7.5 mmHg overnight
- mMean IPAP 24 cmH_2O, EPAP 4 cmH_2O, backup rate 14 breaths/min
- Mean time to readmission or death 4.3 months in NIPPV group vs 1.4 months in control group

Murphy et al. JAMA. 2017;317:2177-2186

Overview of Randomized Controlled Trials

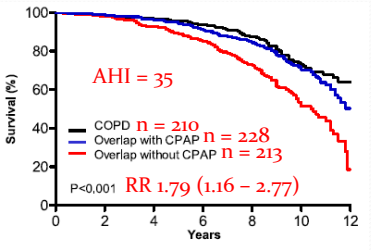


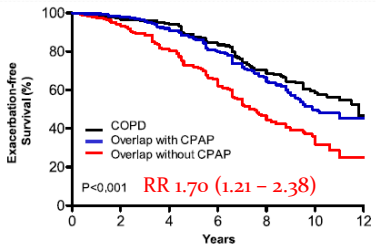
Duiverman. ERJ Open Res. 2018;4

Reasons for Heterogeneity

- Underpowered studies
- Patient selection and poorly characterized patient populations
  - Severity of COPD and degree of baseline hypercapnia
- NIPPV pressures capable of achieving adequate ventilation and reduction in $PaCO_2$
- Adherence with NIPPV therapy
- Duration of therapy and follow-up
- Underlying OSA

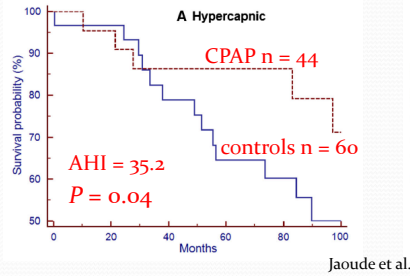
The Overlap Syndrome

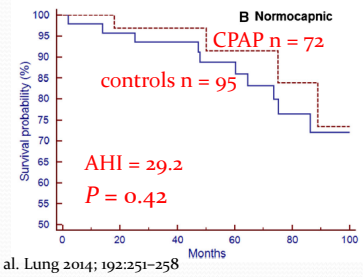




Adjust for age, sex, BMI, smoking, EtOH, comorbidities, COPD severity, AHI, daytime sleepiness

Marin et al. Am J Respir Crit Care Med 2010; 182:325-31





$PaCO_2 \geq 45$ mmHg (average 51.6 mmHg)

Jaoude et al. Lung 2014; 192:251–258

Selecting COPD Patients for NIPPV

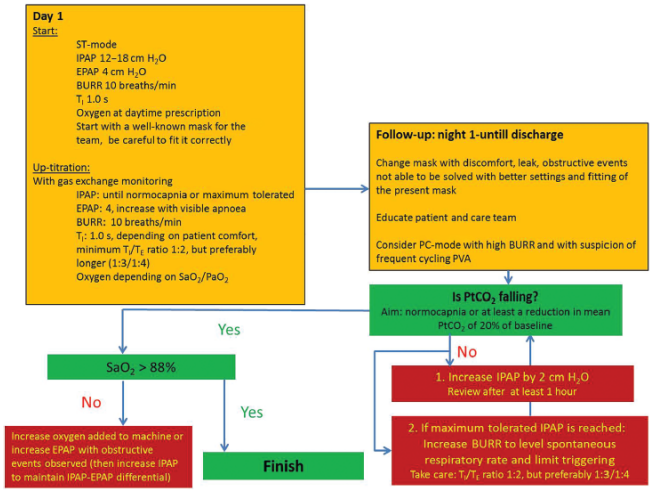
- Patients most likely to derive a benefit are those with most severe and advanced disease
- Daytime $PaCO_2$ ≥ 52 mmHg and O2 desaturation during sleep (i.e., SpO_2 ≤ 88% for ≥ 5 minutes) despite use of supplemental O_2 at ≥ 2 L/min
- History of hospitalization for acute respiratory failure with persistent, severe hypercapnia
- Others recovering from acute exacerbation that necessitated use of continuous NIPPV during hospitalization

Initiation of NIPPV for COPD

- Optimal approach has not been determined
- Typically start bilevel with EPAP of 5 cmH_2O and IPAP of 10 cmH_2O and gradually increase
  - Final IPAP near 15 cmH_2O (range 12-20 cmH_2O)
    - Adjust IPAP for pressure support (PS) that achieves goal tidal volume (~8 ml/kg ideal body weight), as tolerated
  - Final EPAP at least 5 cmH_2O below IPAP
    - Adjust EPAP to eliminate obstructive apneas
    - If ineffective trigger, adjust EPAP to overcome high iPEEP

"High Intensity" NIPPV

- Specific NIPPV settings to achieve normocapnia or lowest $PaCO_2$ levels possible
- Often requires high IPAP ± backup rate



van der Leest and Duiverman. Respirology. 2018 Nov 30

Other NIPPV Options for COPD

- AVAPS/iVAPS
  - Volume-assured pressure support
    - No proven clinical benefit of switching from high intensity NIPPV; possible physiological advantages in breathing pattern
- AVAPS AE
  - Includes auto-titrating EPAP
    - Optimize EPAP to maintain airway patency
- Mouth Piece Ventilation (MPV)
  - Prevents deterioration of gas exchange as well as NIPPV in COPD exacerbations with mild to moderate acidosis, and it is better tolerated
- Ventilation before oxygenation

Challenges

- Patient comfort and tolerance of high pressures
  - Concern for hyperinflation with high backup rate
  - Important to titrate stepwise (usually over several days)
- Cardiovascular side effects
  - High IPAP may reduce cardiac output in patients with cardiac failure
- Initiation of NIPPV in the hospital or ventilator facility
  - Not mandatory for success
- Reimbursement for devices with backup rate
  - Standard bilevel devices only allow for PS of 10 cmH_2o

Qualifying for NIPPV: COPD

ABG with $PaCO_2$ ≥ 52 mmHg (awake and on prescribed FiO_2)

AND

Sleep oximetry with oxygen saturation ≤ 88% for ≥ 5 cumulative minutes on 2 L/min O_2 or prescribed FiO_2 (whichever is higher)

AND

OSA and CPAP treatment have been considered and ruled out (formal sleep testing not required)

E470 = Bilevel S

Conversion from S to ST

Situation 1 (after period of initial use of E0470):

ABG with $PaCO_2$ worsening ≥ 7 mmHg vs original ABG (awake and on prescribed FiO_2)

AND

Facility-based PSG on E470 with oxygen saturation ≤ 88% for ≥ 5 cumulative minutes (not caused by OSA – AHI < 5)

E471 = Bilevel ST

Situation 2 (no sooner than 61 days after initial use of E0470):

ABG with $PaCO_2$ ≥ 52 mmHg (awake and on prescribed FiO_2)

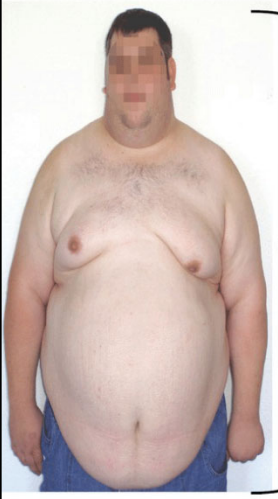
AND

Sleep oximetry on E470 with oxygen saturation ≤ 88% for ≥ 5 cumulative minutes on 2 L/min O_2 or prescribed FiO_2 (whichever is higher)

OHS: Definition and Consequences

- OHS definition: awake alveolar hypoventilation ($PaCO_2$ > 45 mmHg) in obese (BMI > 30 mg/kg^2) patients which cannot be attributed to other causes (i.e., neuromuscular, metabolic, lung, or chest wall diseases)
- OHS will progress if not treated with PAP, and it is associated with significantly worse cardiovascular morbidity, mortality, and healthcare utilization vs eucapnic OSA and eucapnic obese patients
- Can lead to pulmonary hypertension, right heart failure, and increased risk of hospitalization due to acute-on-chronic hypercapnic respiratory failure

OHS: Pathophysiology



Altered upper airway mechanics; ↑ upper-airway resistance, OSA

Impaired respiratory mechanics; ↓FRC, ↓ ERV, ↓ compliance, ↑ resistance, ↑ mechanical load

Gas exchange deterioration; V/Q mismatch, ↑VD/VT

Respiratory muscles weakness

Neurohumoral influences leptin resistance

↑ Sleep $PaCO_2$, ↓ sleep PaO_2, ↑ serum bicarbonate

↑ Work of breathing

Blunted ventilatory drive; ↓ CO_2 response

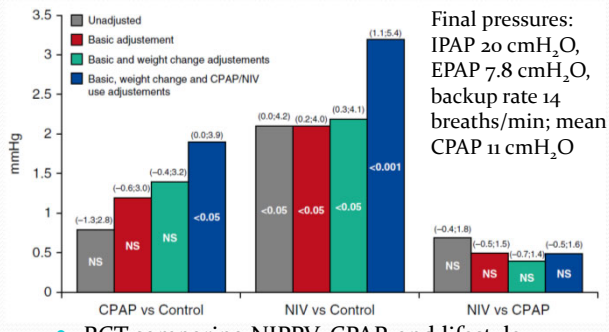
Chronic daytime hypercapnia

Boing et al. J Thorac Dis. 2015;7:1273-85

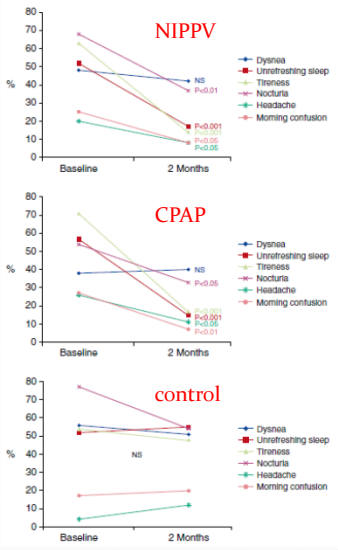
NIPPV Rationale/Mechanism in OHS

- Controversy remains as to the preferred modality of positive airway therapy
- Conceptually, NIPPV should be more effective than CPAP, as it addresses the various complex pathophysiological disturbances that result in OHS:
  - EPAP for upper airway resistance, chest wall and abdominal resistance, and atelectasis
  - IPAP for altered ventilatory drive, worsened hypoventilation during sleep, and rest of respiratory muscles

Pickwick Study



Final pressures: IPAP 20 cmH_2O, EPAP 7.8 cmH_2O, backup rate 14 breaths/min; mean CPAP 11 cmH_2O

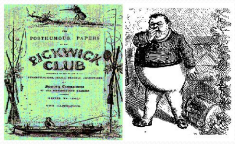


- RCT comparing NIPPV, CPAP, and lifestyle modification in OHS patients with severe OSA
- Main outcome: daytime $PaCO_2$
- Total n = 221, follow-up = 2 months
- Greatest reduction in $PaCO_2$ and bicarbonate in NIPPV group, but not significant vs CPAP
- FEV_1 and 6MWD improved more with NIPPV than CPAP

Masa et al. Am J Respir Crit Care Med. 2015;192:86-95

Pickwick Study: Update

- RCT of CPAP vs NIPPV for OHS with severe OSA
- Primary outcome: hospitalization days
- Secondary outcomes: hospital resource utilization, mortality, cardiovascular events, compliance, side effects
- Total n = 215
- Median follow-up = 5.42 years
- Hospital days/yr was 2.19 ± 5.65 for CPAP and 1.44 ± 3.07 for NIV (adjusted P = 0.12)
- No difference in secondary outcomes



Quiroga et al. European Respiratory Journal 2018 52: Suppl. 62, OA5414

Cardiovascular Effects of NIPPV

- Secondary analysis of Pickwick Study
- Conventional transthoracic 2D and doppler echo performed at baseline and after 2 months
- At baseline 55% of patients had pulmonary hypertension (PH), 51% with left ventricular hypertrophy (LVH)
- NIPPV lowered systolic pulmonary artery pressure, but CPAP did not (–3.4 mmHg, –5.3 to –1.5; adjusted P = 0.025 vs control and P = 0.033 vs CPAP)
  - Greater reduction with NIPPV in those with PH at baseline (–6.4 mm Hg, –9 to –3.8)
- NIPPV reduced left ventricular mass and improved 6MWD (32 m; 19 to 46)

Corral et al. Thorax. 2018;73:361-368

Selecting OHS Patients for NIPPV

- ~90% of patients with OHS have coexisting OSA → CPAP is appropriate initial modality
- Bilevel is appropriate for patients with OHS and sleep-related hypoventilation (i.e., few obstructive events during sleep)
  - Patients with OHS and OSA who fail or do not tolerate CPAP should be treated with bilevel
  - Patients who fail or do not tolerate bilevel should be treated with average volume-assured pressure support
- Features that suggest bilevel may be more appropriate than CPAP:
  - Lower AHI on PSG
  - More restrictive physiology on PFTs
  - More severe and persistent O_2 desaturation during PSG

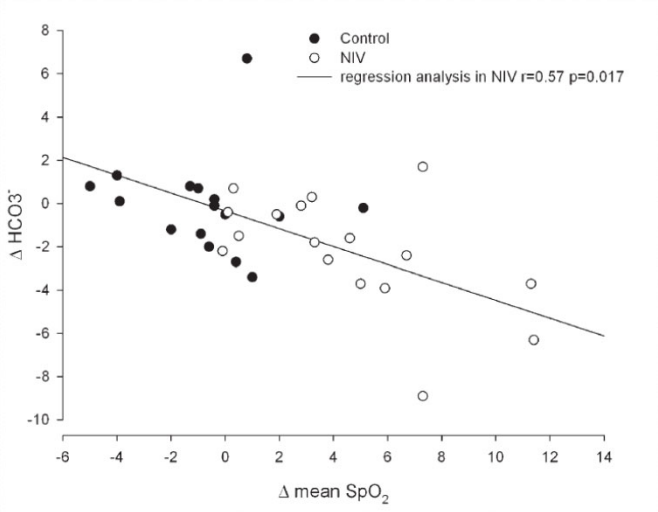
Initiation of NIPPV for OHS

- At a minimum, set EPAP at 4 cmH_2O and IPAP at 8 cmH_2O
- EPAP should be adjusted for obstructive apneas
  - Some studies have adjusted EPAP for all obstructive events (obstructive apneas, hypopneas, flow limitation, and snoring) → results in higher EPAP
  - Increase IPAP simultaneously to maintain pressure difference between EPAP and IPAP
- IPAP should be adjusted for hypoventilation (which may be manifested by persistent O_2 desaturation unrelated to obstructive events) and hypopneas

Monitoring/Goals of NIPPV in OHS

- Normalize $PaCO_2$ (< 45 mmHg) during wakefulness and sleep
- Eliminate O_2 desaturation during wakefulness and sleep
- Treat sleep disordered breathing (obstructive apneas, hypopneas, and hypoventilation)
- Improve sleep architecture and quality
- Relieve symptoms (daytime hypersomnolence, morning headache)
- Prevent complications (erythrocytosis, pulmonary hypertension, right heart failure, mortality)

NIPPV Improvement in SpO_2 During Sleep Correlates with Reduction in Bicarbonate



- Total n = 35
- 1-month follow-up
- Mean IPAP 18 cmH_2O, EPAP 11 cmH_2O, backup rate 13 breaths/min

Borel et al. Chest. 2012;141:692-702

Other NIPPV Options for OHS

- AVAPS/iVAPS
  - Residual airway obstruction on bilevel (but EPAP fixed)
  - Sufficient alveolar ventilation cannot be achieved with bilevel (due to decreased respiratory system compliance)
  - Can achieve higher PS vs bilevel (which has maximum of 10 cmH_2O) and higher overall pressure (30 vs 25 cmH_2O)
  - Similar improvement in daytime $PaCO_2$ as bilevel
- AVAPS AE
  - Likely better for obstructive events and maintaining airway patency
  - Can achieve even higher maximal pressures (i.e., 50 cmH_2O)

Qualifying for NIPPV: OHS

ABG with $PaCO_2$ ≥ 45 mmHg (awake and on prescribed FiO_2)

AND

Spirometry with FEV_1/FVC ≥ 70%

AND

ABG with $PaCO_2$ worsening ≥ 7 mmHg vs original ABG (done during sleep or immediately upon awakening on prescribed FiO_2)

OR

PSG or HST with oxygen saturation ≤ 88% for ≥ 5 minutes (not caused by OSA – AHI < 5)

E470 = Bilevel S

Conversion from S to ST

Covered E0470 is being used

AND

Spirometry with FEV_1/FVC ≥ 70%

AND

ABG with $PaCO_2$ worsening ≥ 7 mmHg vs ABG used to qualify for E0470 (done during sleep or immediately upon awakening on prescribed FiO_2)

OR

PSG or HST on E0470 with oxygen saturation ≤ 88% for ≥ 5 minutes (not caused by OSA – AHI < 5)

E471 = Bilevel ST

TABLE 5] Matching NIV Settings to Patient's Respiratory Mechanics

Pathophysiology/ Device Settings	Chronic OHS (Compensated)	Chronic COPD (Compensated)	Chronic NMD (Compensated)
Respiratory mechanics	↑ Muscle load (↑ UA resistance, 90% OHS) Increased resistance from chest and abdominal wall ↓ FRC due to obesity (expiratory flow limitation, airway closure, V/Q mismatch) ↓ Respiratory drive (leptin resistance, 10% OHS)	↑ Muscle load (↑ Lower airway resistance in COPD) ↓ Muscle capacity (diaphragm atrophy, mechanical disadvantage)	↓ Muscle capacity ↑ Chest wall resistance
Target volume (cc)	Target tidal volume 8 cc/kg ideal body weight	Target tidal volume 8 cc/kg ideal body weight	Target tidal volume 8 cc/kg ideal body weight
	To adjust PS (BPAP-ST), expiratory tidal volume (AVAPS), or Va (iVAPS) based on ABG (pH, $Paco_2$), $TcCO_2$, or a combination		
IPAP (cm H_2O)	High IPAP BPAP-ST: adjust IPAP to a PS for goal tidal volume (average PS, 8-10 cm H_2O) VAPS: allow a large IPAP max/IPAP min difference to reach target expiratory tidal volume or Va	High IPAP (or best tolerated) BPAP: adjust IPAP to a PS for goal tidal volume (or best tolerated) Allow large IPAP max/IPAP min difference to reach target expiratory tidal volume or Va as tolerated	Intermediate IPAP (or best tolerated) Adjust IPAP to a PS for tidal volume goal in BPAP-ST. (average PS, 6 cm H_2O) Allow IPAP min at a higher baseline
EPAP (cm H_2O)	High EPAP in OHS/OSA Adjust to eliminate obstructive apneas (average 8-12 cm H_2O) or snoring	Adjust to eliminate obstructive apneas if present If ineffective trigger, increase EPAP to overcome high iPEEP (first-line therapy)	Low EPAP to reduce work of breathing and improve triggering
Respiration rate (bpm)	To adjust to goal minute ventilation based on ABGs or $TcCO_2$, or both		
Trigger sensitivity[a]	Respironics: Auto-Trak or flow trigger 2-3 L/min ResMed: trigger from medium to low	Respironics: Auto-Trak or flow trigger 4-5 L/min ResMed: trigger medium	High trigger sensitivity to support a weak respiratory muscular effort Respironics: flow trigger at 1-3 L/min ResMed: trigger high or very high
Rise time (ms)	Default or slow rise time Respironics: 3 (300 ms)-6 (600 ms) ResMed: 500-900 ms	Fast rise time	Default or slow rise time Respironics: 3 (300 ms)-6 (600 ms) ResMed: 500-900 ms
Ti (ms)	Long Ti or long Ti min to maximize tidal volume and gas exchange by (↑ I:E) Ti/Ttot 50%	Short Ti or short Ti max to increase expiratory time and minimize iPEEP (↓ I:E) Ti/Ttot 25% in patients with BMI > 30	Long Ti or long Ti min to maximize tidal volume and gas exchange (↑I:E) Ti/Ttot 50%
Cycle Sensitivity[a]	Default or low cycle sensitivity Respironics: Auto-Trak or manual at 10%-15% of peak flow ResMed: Cycle medium to low	Default or high cycle sensitivity (early cycle) to provide a longer exhalation time (↓ I:E) Respironics: Auto-Trak or manual at 30%-50% of peak flow ResMed: Cycle sensitivity medium to high	Default or low cycle sensitivity (late cycle) to provide a longer inhalation time (maximize tidal volume and gas exchange by high I:E) Respironics: Auto-Trak or manual at 10%-15% of peak flow ResMed: Cycle low

Selim et al. Chest. 2018;153:251-265

Key Points

- NIPPV addresses the underlying pathophysiology of hypercapnic COPD and OHS, manifest as reduction in $PaCO_2$
- High intensity NIPPV has demonstrated physiological and clinical benefit in hypercapnic COPD (reduction in mortality and readmissions)
- NIPPV improves lung function, exercise capacity, pulmonary hypertension, and left ventricular hypertrophy vs CPAP in OHS patients
- Appropriate patient selection for NIPPV is essential

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Thank You!

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