Acute noninvasive ventilation – what’s the evidence?

Respiratory Medicine Update: Royal College of Physicians & BTS
Thu 28th January 2016

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Consultant in Respiratory Medicine, Sleep & Ventilation and Lung Function Leads

Oxford Centre for Respiratory Medicine, Churchill Hospital Site, OUH NHS Foundation Trust
Department of Physiology, Anatomy and Genetics, University of Oxford
NIV helps restore the balance between load, capacity and drive

**Load**
- Increased airways resistance
- Airway secretions and hyperinflation
- Obesity
- Kyphoscoliosis

**Drive**
- Renal compensation blunting ventilatory responses
- Oxygen supplementation
- Opiates

**Capacity**
- Functional or actual diaphragmatic weakness

Cardiac impairment & Metabolic factors
How does NIV work?

**IPAP**
- Increases alveolar ventilation by increasing tidal volume
- Decreases PaCO$_2$ (and also bicarbonate, so restoring ventilatory sensitivity)
- Decreases work of breathing

**EPAP**
- Increases oxygenation by increasing FRC
- Recruits under-ventilated lung units
- Offsets intrinsic PEEP
- Reduces CO$_2$ rebreathing (favourable RR: $V_T$)
- Splints upper airway
The Copenhagen poliomyelitis epidemic, 1952

The renaissance in clinical physiology!


Bjorn Ibsen – Danish anaesthesist

Manual positive pressure ventilation

Poul Astrup – father of modern acid-base physiology
Non-Invasive Negative Pressure Ventilation
Early NIV

Negative pressure

Cumbersome

Poor mobility

Upper airway obstruction

Positive pressure – driven by CPAP treatment from 80s

Used for long-term ventilation first, then acute

Progressive comfort of masks & ventilator synchrony
NIV initially used in the home setting

Respiratory failure due to heterogenous causes
N = 180
Followed for 5 years

Simonds and Elliott
NIV use in AE COPD
Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease


Lancet 1993; 341: 1555-57

n=60
PCO₂ > 6 kPa
PO₂ < 7.5 kPa

Reduced 30 day mortality:
1/26 cf 9/30...
(excluded those NIV intol)

Breathlessness
NONINVASIVE VENTILATION FOR ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

LAURENT BROCHARD, M.D., JORDI MANCEBO, M.D., MARC WYSOCKI, M.D., FRÉDÉRIC LOFASSO, M.D.,
GIORGIO CONTI, M.D., ALAIN RAUSS, M.D., GÉRALD SIMONNEAU, M.D., SALVADOR BENITO, M.D.,
ALESSANDRO GASPERETTO, M.D., FRANÇOIS LEMAIRE, M.D., DANIEL ISABEY, PH.D., AND ALAIN HARF, M.D.

Time at which intubation was performed

n=85 pt AE COPD
In ICU

Patients intubated:
11/43 NIV
31/42 standard care

Mortality:
4/43 NIV (9%)
12/ 42 standard (29%)
• UK multi-centre (13), ward based; delivered by clinical staff
  22 of 25 wards had no experience of NIV
  Nurse: patient = 1:11
• Acute exacerbations COPD (n = 236)
  – RR > 23
  – pH 7.25 – 7.35
  – PaCO₂ > 6kPa
• Usual medical care v NIV + usual medical care
  Simple bi-level devise + written protocol
  – EPAP 4 cmH₂O
  – IPAP 10 ↑ to 20 cmH₂O or max tolerated in 1hr
Plant et al, Lancet 2000

Results

• ‘Need for intubation’
  - BSC: 32/118 (27%)
  - NIV: 18/118 (15%)  (p<0.05)

• Mortality
  - BSC: 24/118 (20%)
  - NIV: 12/118 (10%)  (p<0.05)

• Staff workload
  - ↑ by 26 mins in 1st 8 hrs

• Training
  - 7.6 hrs/ 3M + 0.9 hrs/ M ongoing
Overall benefit of NIV:

But no significant benefit of acute NIV if pre-NIV pH < 7.30:
Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis
JVJ Lightowler, JA Wedzicha, MW Elliott and FSF Ram
BMJ 326, Jan 2003

Objective
To determine the effectiveness of NPPV in the management of patients with respiratory failure due to an acute exacerbation of COPD
## Results

### Treatment Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>NPPV n/N</th>
<th>UMC n/N</th>
<th>RR (95%CI Fixed)</th>
<th>Weight %</th>
<th>RR (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avdeev 1998</td>
<td>7 / 29</td>
<td>12 / 29</td>
<td></td>
<td>11.2</td>
<td>0.58[0.27,1.27]</td>
</tr>
<tr>
<td>Barbe 1996</td>
<td>4 / 14</td>
<td>0 / 10</td>
<td></td>
<td>0.5</td>
<td>6.60[0.39,110.32]</td>
</tr>
<tr>
<td>Bott 1993</td>
<td>5 / 30</td>
<td>13 / 30</td>
<td></td>
<td>12.1</td>
<td>0.38[0.16,0.94]</td>
</tr>
<tr>
<td>Brochard 1995</td>
<td>12 / 43</td>
<td>33 / 42</td>
<td></td>
<td>31.1</td>
<td>0.36[0.21,0.59]</td>
</tr>
<tr>
<td>Celikel 1998</td>
<td>1 / 15</td>
<td>6 / 15</td>
<td></td>
<td>5.6</td>
<td>0.17[0.02,1.22]</td>
</tr>
<tr>
<td>Dikensoy 2002</td>
<td>4 / 19</td>
<td>7 / 17</td>
<td></td>
<td>6.9</td>
<td>0.51[0.18,1.45]</td>
</tr>
<tr>
<td>Plant 2000</td>
<td>22 / 118</td>
<td>35 / 118</td>
<td></td>
<td>32.6</td>
<td>0.63[0.39,1.00]</td>
</tr>
</tbody>
</table>

Total (95%CI)

55 / 268 106 / 261 100.0 0.51[0.38,0.67]

Test for heterogeneity chi-square=7.59 df=6  p=0.27
Test for overall effect  z=-4.82 p<0.00001

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![Favours NPPV vs UMC](image-url)
Results

Endotracheal Intubation

<table>
<thead>
<tr>
<th>Study</th>
<th>NPPV n/N</th>
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<tr>
<td>Avdeev 1998</td>
<td>5 / 29</td>
<td>8 / 29</td>
<td></td>
<td>8.8</td>
<td>0.62[0.23,1.68]</td>
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<tr>
<td>Barbe 1996</td>
<td>0 / 10</td>
<td>0 / 10</td>
<td></td>
<td></td>
<td>Not Estimable</td>
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<tr>
<td>Bott 1993</td>
<td>0 / 30</td>
<td>2 / 30</td>
<td></td>
<td>2.8</td>
<td>0.20[0.01,4.00]</td>
</tr>
<tr>
<td>Brochard 1995</td>
<td>11 / 43</td>
<td>31 / 42</td>
<td></td>
<td>34.7</td>
<td>0.35[0.20,0.60]</td>
</tr>
<tr>
<td>Celikel 1998</td>
<td>1 / 15</td>
<td>2 / 15</td>
<td></td>
<td>2.2</td>
<td>0.50[0.05,4.94]</td>
</tr>
<tr>
<td>Dikensoy 2002</td>
<td>2 / 17</td>
<td>7 / 17</td>
<td></td>
<td>7.7</td>
<td>0.29[0.07,1.18]</td>
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<tr>
<td>Kramer 1995</td>
<td>1 / 11</td>
<td>8 / 12</td>
<td></td>
<td>8.5</td>
<td>0.14[0.02,0.92]</td>
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<tr>
<td>Plant 2000</td>
<td>18 / 118</td>
<td>32 / 118</td>
<td></td>
<td>35.4</td>
<td>0.56[0.34,0.94]</td>
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<tr>
<td>Total(95%CI)</td>
<td>38 / 273</td>
<td>90 / 273</td>
<td></td>
<td>100.0</td>
<td>0.42[0.31,0.59]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=4.18 df=6 p=0.65
Test for overall effect z=-5.13 p<0.00001
## Results

### Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>NPPV n/N</th>
<th>UMC n/N</th>
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<td>Brochard 1995</td>
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<td>12 / 42</td>
<td></td>
<td>21.1</td>
<td>0.33[0.11,0.93]</td>
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<td>1 / 15</td>
<td></td>
<td>2.6</td>
<td>0.33[0.01,7.58]</td>
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<td></td>
<td>3.5</td>
<td>0.50[0.05,5.01]</td>
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<tr>
<td>Plant 2000</td>
<td>12 / 118</td>
<td>24 / 118</td>
<td></td>
<td>41.6</td>
<td>0.50[0.26,0.95]</td>
</tr>
<tr>
<td><strong>Total (95%CI)</strong></td>
<td><strong>23 / 262</strong></td>
<td><strong>57 / 261</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.41[0.26,0.64]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.82 df=5 p=0.98
Test for overall effect z=-3.96 p=0.00008
## Results: Summary of Primary Outcome Measures

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Relative risk</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx Failure</td>
<td>0.51 (0.38 – 0.67)</td>
<td>5 (4 – 7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.41 (0.26 – 0.64)</td>
<td>8 (6 – 13)</td>
</tr>
<tr>
<td>Intubation</td>
<td>0.42 (0.31 – 0.59)</td>
<td>5 (4 – 7)</td>
</tr>
<tr>
<td>Complications</td>
<td>0.32 (0.48 – 0.56)</td>
<td>3 (2 – 4)</td>
</tr>
</tbody>
</table>

BMJ 2003;326:185-187
Results: Secondary Outcome Measures

NPPV group:
• ↓ length of hospital stay by 3 days
• Improvements in Respiratory rate at one hour
  pH
  PaCO$_2$
In AE COPD NIV is *better* than intubation

Compared to invasive ventilation

- Same short term outcome, but fewer readmissions & lower LTOT requirements.
  

- Lower mortality rates (decreased incidence of pneumonia)
  
A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease

A. P. S. Cheung, V. L. Chan, J. T. Liong, J. Y. M. Lam, W-S. Leung, A. Lin, C-M. Chu

Division of Respiratory Medicine, Department of Medicine, United Christian Hospital, Hong Kong Special Administrative Region, China

INT J TUBERC LUNG DIS 14(5):642–649

CPAP
5cmH₂O
Use 7-9hrs/night
Time to first readmission 56 days

NIV
14.8+5cmH₂O
Use 7-9hrs/night
Time to first readmission 71 days
UK multicentre RCT HOT – HMV COPD Trial

Global Medical Excellence Cluster, NIHR Portfolio (UKCRN)

Patrick Murphy & Nicholas Hart – St Thomas’

Enrolment

PaCO\textsubscript{2} still >7 kPa 2 wks post acute hypercapnic COPD exacerbation

Randomisation to HOT or HOT + HMV with titrated IPAP

Assessments

Primary Outcome
Admission free survival

Secondary Outcome
Compliance with NIV
HRQL
PaCO\textsubscript{2}, PaO\textsubscript{2}, pH, HCO\textsubscript{3}^-Lung function
BMI
FFMI
6-MWT
HCVR
COPD-related admissions
Compliance with LTOT
Withdrawal of LTOT
Courses of antibiotics
Courses of steroids

Follow up at 6 wks, then 3, 6 & 12 mnths
NIV use in acute cardiogenic pulmonary oedema
Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Alasdair Gray, M.D., Steve Goodacre, Ph.D., David E. Newby, M.D., Moyra Masson, M.Sc., Fiona Sampson, M.Sc., and Jon Nicholl, M.Sc., for the 3CPO Trialists*

Multicentre (26), open RCT
Standard oxygen therapy, CPAP or NIV
Primary end points: O2 alone vs resp support: death within 7 days
CPAP vs NIV: death or intubation within 7 days
N @ 1,000
pH < 7.35: actually mean = 7.22
<table>
<thead>
<tr>
<th></th>
<th>Oxygen Support</th>
<th>OR; 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ Dyspnoea at 1 hr*</td>
<td>3.9</td>
<td>4.6</td>
<td>0.7; 0.2-1.3</td>
</tr>
<tr>
<td>∆ HR at 1 hr*</td>
<td>13</td>
<td>16</td>
<td>4; 1 – 6</td>
</tr>
<tr>
<td>∆ pH at 1 hr*</td>
<td>0.08</td>
<td>0.11</td>
<td>0.03; 0.02 – 0.04</td>
</tr>
<tr>
<td>Mortality at 7 days</td>
<td>9.8%</td>
<td>9.5%</td>
<td>0.97; 0.63 – 1.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CPAP</th>
<th>NIV</th>
<th>Stats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality or intubation at 7 days</td>
<td>11.7%</td>
<td>11.1%</td>
<td>0.59 – 1.51</td>
</tr>
</tbody>
</table>
30 day mortality difference NS
16.4% vs 15.2%; CI 0.64 – 1.31 (pp = 0.64)
30 day mortality difference NS
15.4% vs 15.1%; (p = 0.92)

No. at Risk
CPAP  325  298  288  285  282  277  275
NIPPV 342  311  303  298  295  293  292
Conclusion:

• Consider CPAP/ NIV in acute pulmonary oedema with severe respiratory distress as an adjunct to therapy, or for patients whose condition does not improve with pharmacologic therapy

• Results supported by Cochrane Collaboration database (2013)
Where are we now: current BTS guidelines
Indications for NIV

\[ \text{PaCO}_2 > 6 \text{kPa and pH} < 7.35 \]

... Despite maximal medical therapy for 1 hr+

\[ \text{pH} < 7.26 \text{ should be managed on the HDU/ ICU} \]
NIV advantages

Morbidity of intubation avoided
Avoids sedation
Applied intermittently
Allows patient to eat, drink and mobilise
Able to talk
Upper airway defence mechanisms preserved
- decreased risk of VAP
NIV disadvantages

No airway control
Airway suctioning/ lavage difficult
Leak compromises efficiency of ventilation
Mask claustrophobia
Facial skin necrosis (2 – 18%)
Gastric distension (2%)
Not always successful: failure rates 9 – 50%
May delay intubation
Workload of staff increased
Not universally tolerated by patients
Relative contraindications to NIV

GCS<13
Inability to protect airway
Recent upper airway surgery
Copious secretions
Weak cough
Vomiting
Life-threatening hypoxaemia
Haemodynamic instability
Bowel obstruction and patient choice (assuming capacity)
Levels at which NIV may be used

- As a holding measure to assist ventilation at an earlier stage than NIV would be considered
- As a therapeutic trial with a view to intubation if NIV fails
- As a ceiling of treatment
  - Decide prior to starting NIV
  - Document discussions with family
How do we do in the UK in the ‘real life’ situation?

Data compiled by Michael Davies,
Consultant Chest Physician, Papworth
NHS Atlas of Variation

Proportion of patients admitted with COPD receiving NIV

Death rate at 30 days post admission in COPD

- Substantial comorbidities
- Performance status limited in 36%; v limited 43%
- CXR consolidation in 40%
- Indication for NIV
  - COPD 61%
  - Pulmonary oedema 8%
  - Obesity 8%
  - Chest wall/ neuromuscular weakness 4%

- Oxygen toxicity contributed to respiratory failure in 17%

- Progressive reduction in pre-NIV pH values 7.30 to 7.24 in successive years
  Prior to NIV 47% COPD pt had pH < 7.26

- 91% had ward-based treatment despite low pH
  Recommendation is for these patients to receive care in an HDU/ ICU setting
Safe oxygen use

Beware excessive oxygen for the patient who is *not* working hard (unless planning to intubate)

Titrate to $\text{SaO}_2$ – usually 85 – 92%
CO₂ sensitivity is blunted in ventilatory failure
Pre-NIV

Post-NIV

$V$ (l/min)

PetCO$_2$ (kPa)
Increased ventilatory drive post-NIV mirrors that post altitude exposure

Adapted from Kellog (1963)
Oxygen dissociation curve

$\text{SaO}_2$ vs. $\text{PaO}_2 \text{kPa}$
Tenzing and Hillary Get Ready to Launch the Expedition's Second Assault

While Evans and Bourdillon rested a day for their attempt on the summit, the second team started moving into position in case the first attack should fail short. Tenzing's oxygen set, working fine here at Camp IV, later choked up with ice. Flares are wrapped hopefully around his ice ax for display at the top (page 58).

- $\text{PaCO}_2$ 10.2 kPa
  - fell by 1.3 kPa at 1 hr
  - 1.9 kPa at 4-6hrs

- Acidosis resolved in 45% cases

- 66% achieved ‘success’ (pH > 7.3 and reduced $\text{PaCO}_2$ by 0.5kPa)

- 30% failed to achieve benefit
- 3% went on to intubation
- Failure was due to general deterioration, intolerance or agitation
- Ceiling of therapy in 67%
High hospital mortality
Outcome worse in patients with consolidation on CXR (also with patients with the lowest pH values)
What are the barriers to excellent outcomes?

- Doctor and nurse training: rolling programme essential
- Patient selection: morbidities and pH outside trial criteria
- Limited HDU and ICU resource
- Nihilistic attitudes
- Patients often have NIV as ceiling of care

What next?

- NCEPOD study focusing upon delivery an acute NIV service in 2016