Walter J. O’Donohue, Jr., MD was a charter member of NAMDRC. Prior to his death in July 2002, Dr. O’Donohue served on NAMDRC’s Board of Directors, and was President from 1995-97. Throughout his career in pulmonary medicine, Dr. O’Donohue worked tirelessly to remove the bureaucratic obstacles that impeded quality patient care. His efforts shaped the goals and mission of NAMDRC, and his many contributions epitomized the professionalism, leadership, and ethics to which everyone in pulmonary medicine should aspire.

The O’Donohue Lecture is dedicated to Walter’s leadership in communicating the importance of participation in public policy debate.

O’Donohue Lecturers include:
- Atul Grover, MD 2004
- The Honorable Duncan Hunter (R-CA) 2005
- Dennis Doherty, MD, FCCP 2006
- The Honorable Norman Y Mineta 2007
- Neil R MacIntyre, MD, FCCP 2008
- Dennis Doherty, MD, FCCP & Kent Christopher, MD 2009
- Richard Casaburi, PhD, MD 2010
- Christine Garvey, FNP, MSN, MPA, FAACVPR 2012
- Frank L. Powell, PhD 2013
Dr. Powell has received research support from NIH/NHLBI 2R01HL081823-05A1 - Neural Plasticity during Acclimatization to Hypoxia, PI = F Powell (07/14/2011 - 06/30/2015); NIH/NHLB 1P01HL098053-01-A1 - Molecular mechanisms of hypoxia tolerance and susceptibility, PI = G. Haddad (07/01/10 - 6/30/15), but these do not create a conflict related to his presentation.
Hypoxia in Lung Disease and at High Altitude: How is it different?

Frank L. Powell, Ph.D.

U.C. San Diego, Dept. of Medicine
Create Portfolios – Customized Lists of Measures

- Easily **track of measures** you use or are interested in
- **Receive an email update** when any measure in your portfolio changes
- **Share your portfolios** with others, privately or publicly
Create Portfolios – Customized Lists of Measures

- Easily track of measures you use or are interested in
- Receive an email update when any measure in your portfolio changes
- Share your portfolios with others, privately or publicly
Air is too thin for mortals on Mt. Olympus (2919 m) Aristotle, 350 BC
Barometric Pressure and the weight of the atmosphere

Torricelli’s mercury barometer (1644)

\[ P_{O_2} = P_{BAROMETRIC} \times F_{O_2} \]
\[ = 180 \times 0.21 \]
\[ = 38 \text{ mmHg} \]
Barometric Pressure and the weight of the atmosphere

Torricelli’s mercury barometer (1644)

\[ P_{O_2} = P_{BAROMETRIC} \times F_{O_2} \]
\[ = 180 \times 0.21 \]
\[ = 38 \text{ mmHg} \]

Inspired \( P_{O_2} \) (\( P_{IO_2} \))

\[ P_{IO_2} = (P_{BAROMETRIC} - P_{H_2O}) \times F_{O_2} \]
\[ = (180 - 47) \times 0.21 \]
\[ = 28 \text{ mmHg} !!! \]

Glaisher at 11,278 m (1868)
Low $O_2$ Partial Pressure is the main physiological effect of altitude

- sea level: $21\% \times 760$
  \[ P_{O_2} = 160 \text{ mm Hg} \]
- sea level: $10.5\% \times 760$
  \[ P_{O_2} = 80 \text{ mm Hg} \]
- 5,500m: $21\% \times 380$
  \[ P_{O_2} = 80 \text{ mm Hg} \]
- 5,500m: $42\% \times 380$
  \[ P_{O_2} = 160 \text{ mm Hg} \]

La Pression Barometrique
(Bert, 1878)
Hypoxemia at high altitude

Graph showing saturation (%) against oxygen partial pressure (kPa) for sea level and 3,800m. The graph includes lines for other mammals, Vicuña, and Llama.
Hypoxemia at high altitude and with lung disease

Arterial $O_2$ in healthy people at 12,500’ (3,800m) meets insurance requirements for supplemental $O_2$. 
## People at High Altitude

<table>
<thead>
<tr>
<th>Group</th>
<th>Number at risk per year</th>
<th>Sleeping altitude</th>
<th>AMS incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western USA hikers/skiers</td>
<td>40 million</td>
<td>2400-2800 m</td>
<td>15% (6 million)</td>
</tr>
<tr>
<td>Mt. Ranier climbers</td>
<td>9,000</td>
<td>3000 m</td>
<td>67% (6000)</td>
</tr>
<tr>
<td>Mt. Everest trekkers</td>
<td>6,000</td>
<td>3000 – 5200 m</td>
<td>35% (2100)</td>
</tr>
<tr>
<td>Mt. McKinley climbers</td>
<td>1,000</td>
<td>3000 – 5300 m</td>
<td>30% (300)</td>
</tr>
</tbody>
</table>

1500-3500 m \( \text{SaO}_2 \geq 90\% \)

AMS, sleep disturbance

3500-5500 m \( \text{SaO}_2 < 80\% \)

HAPE, HACE, cognition
Alveolar and arterial blood gases on Mt. Everest in ambient air

<table>
<thead>
<tr>
<th>BAROMETRIC PRESSURE</th>
<th>INSPIRED $\text{P}_2$</th>
<th>ALVEOLAR $\text{P}_2$</th>
<th>ARTERIAL $\text{P}_2$</th>
<th>$\text{Pc}_2$</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>253</td>
<td>43</td>
<td>35</td>
<td>28</td>
<td>7.5</td>
<td>&gt;7.7</td>
</tr>
</tbody>
</table>

"Death Zone" > 6100m or 20,000ft

Hillary and Tenzing, May 1953

Habeler and Messner, May 1978
Carotid bodies explain essentially all of Hypoxic Ventilatory Response (HVR)

Carotid body resection

HVR

Carotid body activity

Pao₂ = 93 mmHg

Carotid body stimulus is P\(_{O_2}\), *not* O\(_2\) Saturation or Concentration
1. \(\text{CO}_2\) effects on the HVR at high altitude versus lung disease

- Increased by hypercapnia in lung disease
- Decreased by hypocapnia at high altitude

[Graph showing pulmonary ventilation (L/min) vs. \(P_AO_2\) (mm Hg) with points indicating changes at hypercapnic and normocapnic conditions.]
Alveolar $\text{PO}_2$ and $\text{PCO}_2$ at High Altitude

Ventilatory acclimatization to hypoxia decreases $\text{Paco}_2$ and increases $\text{Pao}_2$.

(Rahn & Otis 1949)
Hypoxia Inducible Factor-1α (HIF-1α) – “master switch” for O₂-sensitive genes

- *not* necessary for acute HVR;
- necessary in CNS respiratory centers for ventilatory acclimatization.
2. Does chronic hypoxia increase HIF-1α and the HVR in patients with lung disease like it does in healthy subjects at high altitude???
2a. What is role of genetics in physiological response to chronic hypoxia?

**SHERPA**
- Normal ventilation
- Normal hematocrit

**ANDEAN**
- Blunted ventilation
- Increased hematocrit
- Chronic Mountain Sickness (CMS)
Physiological “Time Domains” of the HVR

**INTERMITTENT HYPOXIA**

- Increase in ventilatory drive
- 5 min

**SUSTAINED HYPOXIA**

- Long Term Facilitation
- Ventilatory Acclimatization to Hypoxia
- HVD
- VAH
- HD
- 15 min
- hrs - days
- months - years

Both intermittent and sustained hypoxia increase ventilatory drive
LTF could stabilize upper airways during sleep.

Increased upper airway drive balances increased drive to the diaphragm and reduces obstructive sleep apnea.
Evolutionary basis for differential sensitivity of respiratory muscles to hypoxia

Intermittent hypoxia

Intermittent hypoxia + spinal antioxidant

sham

Intermittent hypoxia +/− spinal antioxidant

sham

(MacFarlane et al., 2009)
3. How do increases in ventilatory drive with sustained and intermittent hypoxia interact?

- Periodic breathing increases during sleep at high altitude (central apnea, Cheyne-Stokes).
- Increased ventilatory drive (loop gain) increases obstructive and central apnea (Wellman et al., *J. Appl. Physiol.* 1110:1627-1637, 2011.)
4. What are effects of inflammation on breathing with intermittent versus sustained hypoxia?

• Responses to hypoxia and inflammation are evolutionarily ancient and use common mechanisms (Rius J, et al., *Nature* 453:807-811, 2008)

• Inflammatory signals are increased in patients with obstructive sleep apnea and sustained hypoxia.

• Intermittent hypoxia causes hypertension but sustained hypoxia at altitude does not. (Why not??)
Is inflammation involved in ventilatory acclimatization to hypoxia?

- (Left) Ibuprofen has no effect on HVR in normoxic rats.
- (Right) Ibuprofen blocks increase in HVR in chronically hypoxic rats.

(Popa et al., 2012)
Effects of intermittent hypoxia and age on cognitive function

“Mental Grunt”

Judged by the ordinary standards of efficiency in laboratory work, we were in an obviously lower category at Cerro [de Pasco, 4,330m] than at the sea-level. By a curious paradox this was most apparent when it was being least tested...

When we knew we were undergoing a test, our concentration could by an effort be maintained over the length of time taken for the test...

(Barcroft et al., 1923).

(Ayalon et al., AJRCCM 182: 413-419, 2010)
No effect of sustained hypoxia (3,800m) on cognition in students

but “perceived effort” (mental grunt) increases

5. Does hypoxia block mental grunt?
“Compensatory Recruitment” after sleep deprivation correlates with cognitive performance

HYPOTHESIS: Mental Grunt = Compensatory Recruitment
(Need to compare fMRI BOLD images at different $O_2$ levels)

(Drummond et al. Psyc Res 140: 211-23, 2005)
Great things are done when Men & Mountains meet...
This is not Done by jostling in the Street“
(William Blake)
What are the potential clinical applications of a drug that increases (or decreases) ventilatory drive or the ventilatory response to hypoxia?