Peripheral mechanisms of dyspnoea

Miriam Johnson 2012

A complex interaction

- respiratory motor areas of the brain receive information and "commands" required ventilation
- ascending copy of descending motor activity sent to perceptual areas (corollary discharge)
- if ventilatory demand exceeds the capacity → imbalance between the motor drive to breathe, as sensed via corollary discharge, and afferent feedback from mechanoreceptors of the respiratory system.

Mismatch

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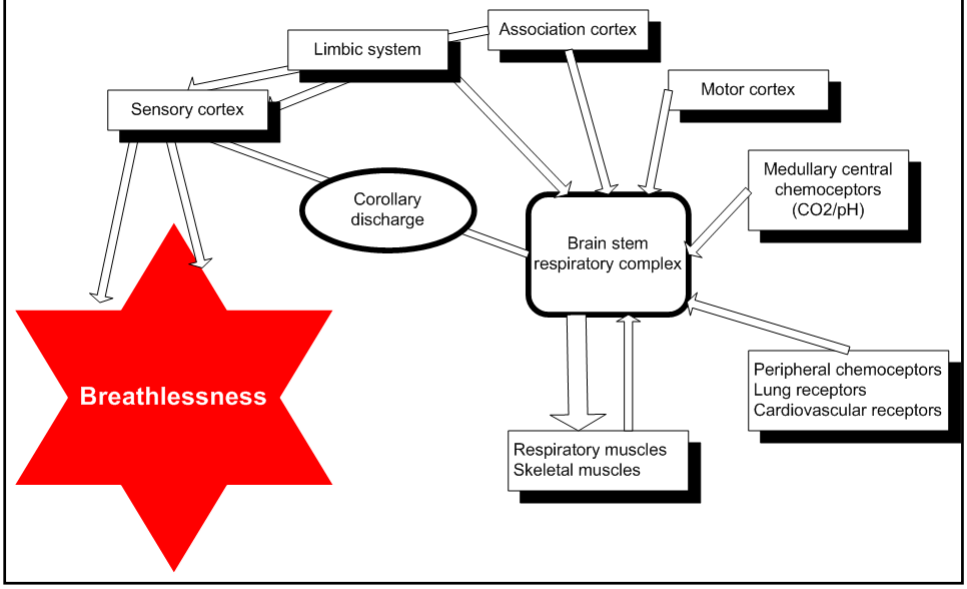
- Variously referred to as
  - length–tension inappropriateness ,
  - efferent–reafferent dissociation
  - neuroventilatory dissociation
  - afferent mismatch
  - neuromechanical uncoupling
  - neuromuscular dissociation

none fully captures the interplay among neurophysiological mechanisms

A proposed model for the genesis of breathlessness and its relationship to respiratory control

From: Dyspnoea by Adams + Stulbarg in
"Manifestations of Respiratory Disease" Murray & Nadel 1991



Sensory afferent sources: adapted; ATS statement 2012

Source of sensation	Adequate stimulus
Carotid and aortic bodies	Hypercapnia, hypoxaemia, acidosis
Slowly adapting pulmonary stretch receptors	Lung inflation
Rapidly adapting pulmonary stretch receptors	Airway collapse, irritants, sudden inflation/deflations
Pulmonary C- fibres (J – receptors)	Pulmonary vasculature congestion
Airway C - fibres	irritants
Upper airway “flow” receptors	Cooling upper airway mucosa
Trigeminal skin receptors	Cooling facial skin
Muscle spindles in respiratory pump muscle	Muscle length change with breathing motion
Tendon organs in respiratory pump muscle	Muscle active force with breathing motion
Metaboreceptors in respiratory pump muscle	Metabolic activity of muscle pump
Chest wall and skin receptors	Tidal breathing motion
Vascular receptors (heart and lung)	Distension of vascular structures

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airflow

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- Healthy volunteers; facial airflow reduces sensation of breathlessness Schwartzstein 1987
- COPD, treadmill + fan to face; reduced exercise induced breathlessness Baltzan 2000
- COPD, leg ergometry + fan to face: increased exercise tolerance vs fan to leg (breathlessness intensity no difference Marchetti 2004
- COPD, exercise in cool air cf room air: increased exercise performance and reduced end exercise breathlessness intensity Spence 1993

Airflow or nasal mucosae stimulation

Liss and Grant 1988

- 8 people with COPD
- Zero, 2L/min; 4L/min flow of O2 or air via nasal cannulae
- Repeated after topical lidocaine to nasal mucosae
- Arterial O2, VAS breathlessness intensity
- Pre lidocaine; no difference in O2 or VAS
- Post lidocaine; no difference in O2 or VAS
- Pre lidocaine VAS compared with post lidocaine VAS:
  - 44mm vs 52 mm (p= 0.005)

Authors' conclusions:

- Nasal mucosae stimulation by nasal cannulae
- Discounted airflow (no difference between flow rates)

Hand held battery operated fan

Completed

- crossover RCT of breathless patients; fan to face, fan to leg – benefit Galbraith et al JPSM 2010
- fan to face or seaband RCT – no benefit More ambulatory patients Bausewein et al BMC Palliat Care 2010

imminent

- RCT: fan^{h}; fan^{l};no fan. Endpoints activity, intensity, self-efficacy
- Feasibility of MEG scanning as a tool to investigate airflow across the face

"placebo" arm of oxygen studies

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Systematic reviews

- Cranston et al Cochrane Database Syst Rev 2008 (cancer, CHF, kyphoscoliosis)
- Uronis HE et al Br J Cancer 2008 (cancer)
- Uronis HE et al Cochrane Database of Systematic Reviews 2011 (COPD)
- Ben-Aharon et al J Clin Oncol 2008 (cancer)
- Booth S et al Respir Med 2004 (cancer, COPD, HF)

Powered parallel RCT

- Abernethy et al Lancet 2010 (COPD, cancer, CVD)

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Airflow is as good – therefore, benefit due to airflow?

Inflammation/cachexia

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- Systemic inflammation: cancer, heart failure, lung disease
- Cachexia syndrome – disproportionate muscle wasting , poorly responsive to nutritional supplementation
- Complex interaction
  - inflammatory mediators,
  - oxidative stress
  - growth factors
- Imbalance between protein synthesis and breakdown
- Imbalance in processes governing:
  - maintenance of skeletal muscle mass
  - muscle plasticity; skeletal muscle fibre degeneration, apoptosis and regeneration

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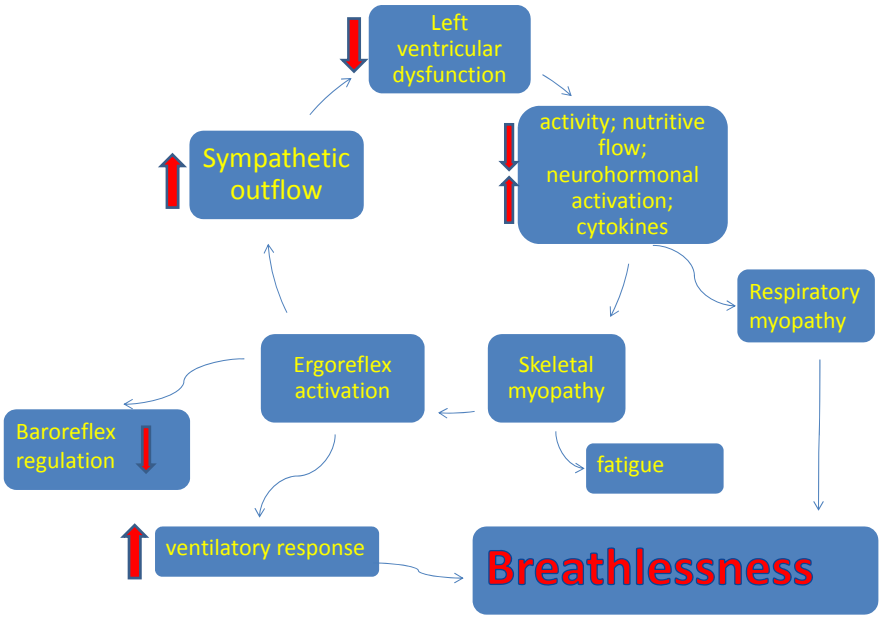
Skeletal muscle and dyspnoea

- Muscle abnormalities in COPD and HF
  - Decreased mechanical efficiency
  - Oxidative type I shift to glycolytic type II fibres
- Lead to
  - Enhanced lactic acid production during exercise
  - Rapid decline and impaired recovery of phospho-creatine stores
- Oxidative capacity partly reversible in COPD with pulmonary rehab
- Some evidence to suggest need nutritional approach as well as exercise– eg Poly unsat fatty acids (PUFA)/creatine

Skeletal muscle

- Directly related to exercise tolerance, fatigue and breathlessness
- Muscle bulk is important
- Unifying picture to explain the origin of the link between muscles, increased sympathetic drive, breathlessness and inflammation has been put forward in HF
- Intervention to preserve muscle function or even reverse myopathy may be helpful
- A reason why people with HF may be breathlessness without pulmonary congestion



opioids

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- Action at central and peripheral sites
- In HF,
  - opioid receptor activation inhibits sympathetic drive by reducing intracellular cAMP (Wong and Shan 2001)
  - increases exercise tolerance (Chua et al JACC1997, Williams et al. Heart, 2003)
- therefore, immediate central effects may enable longer term benefits through peripheral mechanisms
- implications for study endpoints

Central and peripheral mechanisms – important therapeutic targets