COVID-19

HYPOXEMIA

KEY CLINICAL POINTS

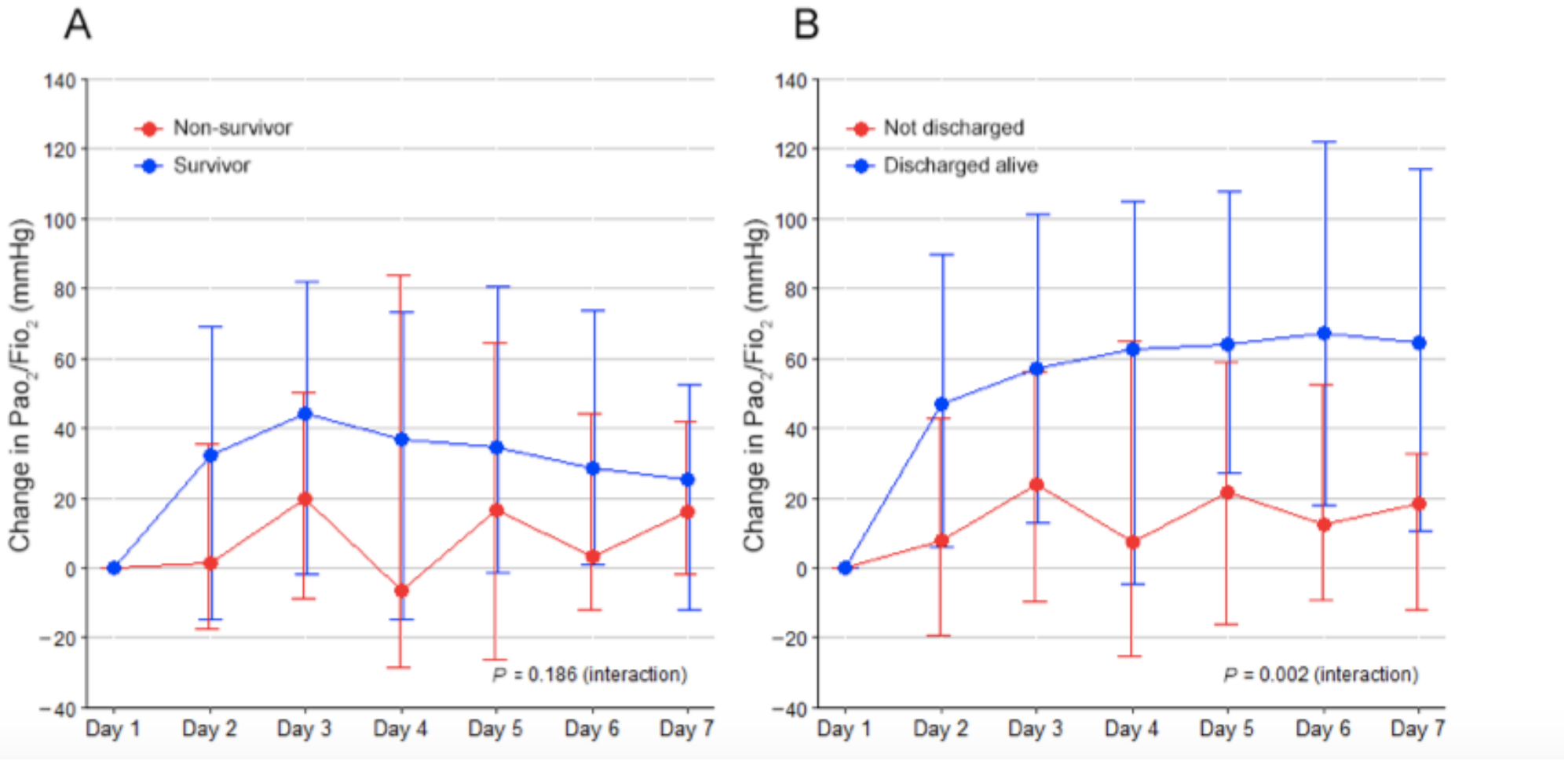
MILD OR MODERATE COVID-19

- Covid-19 (the illness caused by SARS-CoV-2) has a range of clinical manifestations, including cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia.
- Diagnosis of Covid-19 is usually based on detection of SARS-CoV-2 by PCR testing of a nasopharyngeal swab or other specimen.
- Evaluation and management of Covid-19 depends on the severity of the disease; patients with mild disease typically recover at home.
- Patients with moderate or severe Covid-19 are usually hospitalized for observation and supportive care.
- There are no proven therapies for Covid-19; thus, referral of patients to clinical trials is critical.
- Infection control and prevention efforts center on personal protective equipment for health care workers, social distancing, and testing.

Characteristics	Day 1	Day 2	Day 3
Total number of patients	73	73	73
Laboratory tests, median (IQR)			
Pao_2/Fio_2 (mmHg)	110.0 (80.0–158.5)	141.6 (104.7–177.2)	156.8 (113.3–193.8)
Pao_2 (mmHg)	76.0 (62.7–89.4)	78.5 (67.1–89.7)	74.5 (66.2–85.6)
$Paco_2$ (mmHg)	46.4 (40.0–51.3)	48.5 (43.3–53.0)	47.8 (43.3–52.7)
Arterial pH	7.38 (7.31–7.444)	7.41 (7.35–7.46)	7.43 (7.36–7.48)
Vital signs, median (IQR)			
Mean arterial pressure	79 (66–93)	82 (71–94)	88 (75–97)
Urine output (24 h)	2180 (1300–3150)	3535 (2402–4687)	3467 (2336–4695)
Ventilatory support			
Previous use of non-invasive ventilation	20/70 (28.6%)	na	na
Mode of ventilation			
Controlled	64/70 (91.4%)	54/70 (77.1%)	51/67 (76.1%)
Assisted	6/70 (8.6%)	16/70 (22.9%)	16/67 (23.9%)
Tidal volume (mL/kg PBW), median (IQR)	6.7 (6.0–7.5)	6.7 (6.0–7.5)	6.7 (6.1–7.4)
PEEP (cmH_2O), median (IQR)	12 (10–14)	12 (10–14)	12 (10–14)
Fio_2 (mmHg), median (IQR)	0.70 (0.52–0.80)	0.60 (0.50–0.70)	0.50 (0.40–0.65)
Peak airway pressure (cmH_2O), median (IQR)	28.5 (25.2–30.0)	26.0 (20.5–29.5)	26.0 (23.8–30.0)
Driving pressure (cmH_2O),† median (IQR)	12.0 (7.0–16.5)	10.0 (6.0–15.0)	11.0 (9.0–11.0)
Dynamic compliance (mL/cmH_2O),‡ median (IQR)	28.6 (21.8–34.0)	31.7 (25.4–39.6)	30.0 (25.7–34.6)

Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy
Alberto Zangrillo, Luigi Beretta, Anna Mara Scandroglio, Giacomo Monti, Evgeny Fominskiy, Sergio Colombo, Federica Morselli, Alessandro Belletti, Paolo Silvani, Martina Crivellari, Fabrizio Monaco, Maria Luisa Azzolini, Raffaella Reineke, Pasquale Nardelli, Marianna Sartorelli, Carmine D Votta, Annalisa Ruggeri, Fabio Ciceri, Francesco De Cobelli, More- no Tresoldi, Lorenzo Dagna, Patrizia Rovere-Querini, Ary Serpa Neto, Rinaldo Bellomo and Giovanni Landoni; for the

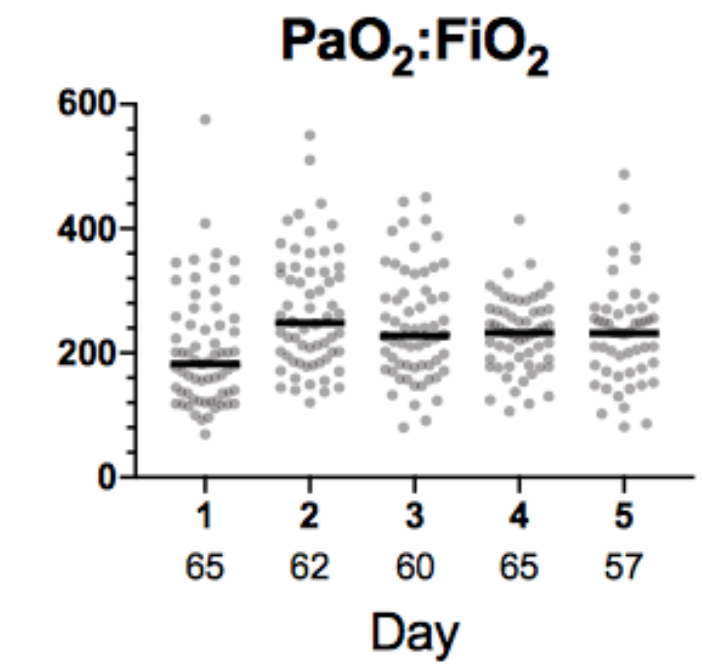
Figure 2. Effect of changes in Pao_2/Fio_2 ratio in the first 7 days on mortality and on the chance of being discharged alive from the intensive care unit (ICU) at the latest follow-up

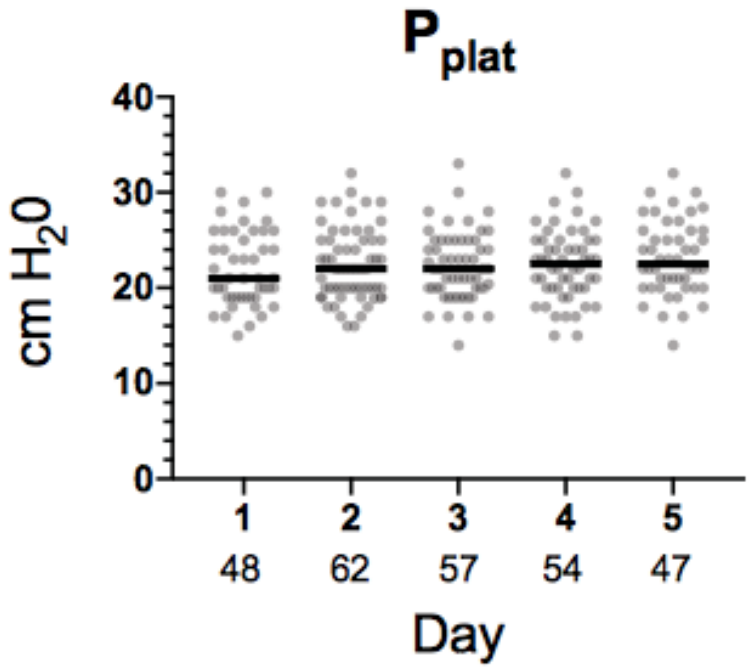


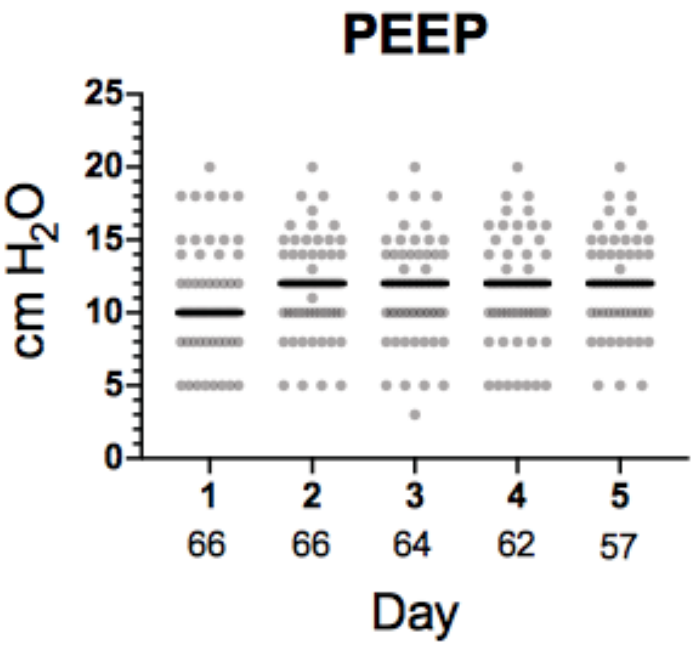
Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy
Alberto Zangrillo, Luigi Beretta, Anna Mara Scandroglio, Giacomo Monti, Evgeny Fominskiy, Sergio Colombo, Federica Morselli, Alessandro Belletti, Paolo Silvani, Martina Crivellari, Fabrizio Monaco, Maria Luisa Azzolini, Raffaella Reineke, Pasquale Nardelli, Marianna Sartorelli, Carmine D Votta, Annalisa Ruggeri, Fabio Ciceri, Francesco De Cobelli, More- no Tresoldi, Lorenzo Dagna, Patrizia Rovere-Querini, Ary Serpa Neto, Rinaldo Bellomo and Giovanni Landoni; for the

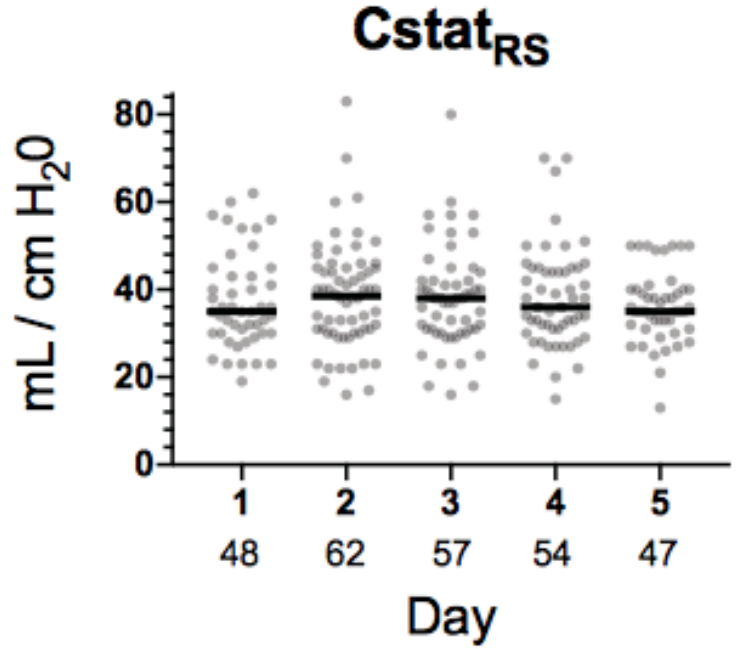
	All patients	
Characteristics	% patients (n = 66)	# patients
Site		
Massachusetts General Hospital	73%	(48/66)
Beth Israel Deaconess Medical Center	27%	(18/66)
Demographics		
Age, year, median (range)	58 (23-87)	(66/66)
Gender, n (%)		
Male	65%	(43/66)
Body mass index, median (IQR)	30 (27-35)	(66/66)
Co-morbidities		
Pulmonary disease	12%	(8/66)
Current smoker or former smoker	34%	(22/64)
Hypertension	44%	(29/66)
Diabetes mellitus	26%	17/66)
Chronic kidney disease	6%	(4/66)
Immunocompromise	9%	(6/66)
Malignancy	8%	(5/66)
Median symptom onset to intubation (days, IQR)	8 (6-10)	(66/66)
Presenting symptoms		
Fever	86%	(57/66)
Cough	88%	(58/66)
Dyspnea	91%	(60/66)
Congestion	15%	(10/65)
Nausea/vomiting	22%	(14/65)
Diarrhea	28%	(18/65)
Myalgias	55%	(36/66)
Fatigue	67%	(44/66)

Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study
David R. Ziehr*, MD1,2, Jehan Alladina*, MD1, Camille R. Petri, MD1,2, Jason H. Maley, MD1,2, Ari Moskowitz, MD2, Benjamin D. Medoff, MD1, Kathryn A. Hibbert, MD1, B. Taylor Thompson, MD1, C. Corey Hardin, MD, PhD1
1Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA
2Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA









Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study

David R. Ziehr*, MD1,2, Jehan Alladina*, MD1, Camille R. Petri, MD1,2, Jason H. Maley, MD1,2, Ari Moskowitz, MD2, Benjamin D. Medoff, MD1, Kathryn A. Hibbert, MD1, B. Taylor Thompson, MD1, C. Corey Hardin, MD, PhD1

1Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA

2Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Our experience

Characteristics		Floor	ICU/IMC
		80	45
Age (median)		51	62
Gender (%M)		60	52
BMI (median)		33	32
Presenting Symptoms (%)			
fever		92	90
Cough		73	82
Dyspnea		60	82
Myalgia		70	66
Fatigue		80	71
GI		25	13
Sinus		30	28
PaO2 (mmhg) (median)		75	62
PaO2/FIO2 (mmhg) (median)		357	124
PaCO2 (mmhg) (median)		41	46
Ph		7.41	7.37

Table 1. Demography and pulmonary function characteristics of discharged patients with COVID-19

	Total (n=110)	Mild illness (n=24)	Pneumonia (n=67)	Severe Pneumonia (n=19)	*p* value
Age, years	49.1 ± 14.0	46.8 ± 15.6	47.9 ± 13.7	56.5 ± 11.0[a,b]	0.04
Female	55 (50.0%)	13 (54.2%)	36 (53.7%)	6 (31.6%)	0.21
Smoker	13 (11.8%)	4 (16.7%)	7 (10.4%)	2 (10.5%)	0.707
BMI	23.5 ± 3.0	23.1 ± 2.8	23.6 ± 3.2	23.5 ± 2.7	0.794
Duration (onset to discharge)	27±9	20±6	29±8 [a']	34±7 [a',b]	<0.001
Diffusion capacity					
DLCO%pred	78.18 ± 14.29	84.70 ± 13.88	79.76 ± 11.99	64.79 ± 14.35[a',b']	<0.001
<80%pred, No.(%)	51 (47.22)	7 (30.43)	28 (42.42)	16(84.21)[a',b']	0.001
DLCO/VA%pred	92.09 ± 16.68	99.35 ± 18.25	92.30 ± 15.70	82.58 ± 13.91[a',b]	0.004
<80%pred, No.(%)	29 (26.85)	3 (13.04)	18 (27.27)	8 (42.11)	0.09
Lung volume					
TLC%pred	86.32 ± 11.32	87.13 ± 10.43	88.11 ± 10.72	79.16 ± 12.13[a,b']	0.008
<80%pred, No.(%)	27 (25.00)	4 (17.39)	14 (21.21)	9 (47.37)[a,b]	0.049
RV%pred	86.83 ± 19.37	87.17 ± 16.88	89.79 ± 19.21	76.16 ± 19.96[b']	0.024
<65%pred, No.(%)	10 (9.26)	2 (8.70)	3 (4.55)	5 (26.32)[b]	0.021
RV/TLC%pred	96.99 ± 16.72	98.00 ± 14.93	98.53 ± 17.55	90.42 ± 14.86	0.168

Abnormal pulmonary function in COVID-19 patients at time of hospital discharge
Xiaoneng Mo, Wenhua Jian, Zhuquan Su, Mu Chen, Hui Peng, Ping Peng, Chunliang Lei, Shiyue Li, Ruchong Chen, Nanshan Zhong
Please cite this article as: Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID- 19 patients at time of hospital discharge. Eur Respir J 2020

COVID-19 patients with respiratory failure: what can we learn from aviation medicine? W. Ottestad and S. Søvik. Br J Anaesth. [Epub ahead of print] Apr 18, 2020. pii: S0007-0912(20)30226-9. doi: 10.1016/j.bja.2020.04.012.

Patients with coronavirus disease 2019 (COVID-19) may present to hospitals and emergency medical services with an atypical form of acute respiratory distress syndrome. Although anecdotal, a common clinical pattern has emerged, with a remarkable discrepancy between relatively well preserved lung compliance and a severely compromised pulmonary gas exchange, leading to grave hypoxaemia yet without proportional signs of respiratory distress.

Experiments in hypobaric chambers have revealed that hypocapnic hypoxia is not usually accompanied by air hunger; instead, a paradoxical feeling of calm and well-being may result. This phenomenon has been coined ‘silent hypoxia’.

End-tidal CO2 values in the 1.4e2.0 kPa range [~5.5kPA is normal] have been reported in COVID-19 patients, but apart from a rapid respiratory rate the clinical presentation in these patients can be misleading. We have observed patients with extreme hypoxaemia showing little distress; rather they tend to be impassive, cooperative, and haemodynamically stable.

In a simulated high-altitude parachute jump from 30,000 ft, nine volunteers from the Norwegian Special Operations Command underwent repeated blood gas testing while breathing air at different ambient pressures. Despite PaO2 values of 3.3 (2.9e3.7) kPa [25 mmHg], eight out of nine participants showed no signs of respiratory distress and were cooperative and alert with stable haemodynamics.

Extreme hypocapnic hypoxia in patients with respiratory failure has previously been relatively unusual; therefore, this [COVID-19] presentation challenges our intuitive thinking and clinical pattern recognition. The physiology of hypocapnic hypoxia has implications for how we interpret physiological parameters.

In COVID-19 patients, a low end-tidal CO2 should alert the physician that respiratory failure is evolving and that decompensation might be imminent.

Dyspnea is a common problem affecting up to half of patients admitted to acute, tertiary care hospitals and one quarter of ambulatory patients.

In the United States, “shortness of breath” and “labored or difficult breathing (dyspnea)” account for 3 to 4 million emergency department visits annually.

The presence of dyspnea is a potent predictor of mortality, often surpassing common physiological measurements in predicting the clinical course of a patient. Respiratory discomfort may arise from a wide range of clinical conditions, but also may be a manifestation of poor cardiovascular fitness in our increasingly sedentary population. Diagnosis and treatment of the underlying cause of dyspnea is the preferred and most direct approach to ameliorating this symptom, but there are many patients for whom the cause is unclear or for whom dyspnea persists despite optimal treatment.

A wide range of information arising from numerous sensory afferent sources contributes to multiple sensations of dyspnea. Specific physiological processes may be linked to corresponding sensory descriptors, the best characterized of which are sensations of work or effort, tightness, and air hunger/unsatisfied inspiration.

An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. M.B. Parshall, R.M. Schwartzstein, L. Adams, R.B. Banzett, H.L. Manning, J. Bourbeau, P.M. Calverley, A.G. Gift, A. Harver, S.C. Lareau, D.A. Mahler, P.M. Meek and D.E. O’Donnell; on behalf of the ATS Committee on Dyspnea THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, October, 2011. Am J Respir Crit Care Med Vol 185, Iss. 4, pp 435–452, Feb 15, 2012

TABLE 3

CLUSTERS AND DESCRIPTORS FROM k-MEANS ANALYSIS

Cluster	Descriptors
Work/effort	My breathing requires effort I feel out of breath My breathing requires work I can not get enough air in
Suffocating	I feel that I am smothering I feel that I am suffocating
Exhalation	My breath does not go out all the way
Tight	My chest feels tight My chest is constricted
Inhalation	My breath does not go in all the way
Shallow	My breathing is shallow
Rapid	My breathing is rapid
Breathing more	I feel that I am breathing more
Heavy	My breathing is heavy
Air hunger	I feel a hunger for air

TABLE 5

RELATIONSHIPS AMONG CLUSTERS BASED ON DESCRIPTORS OF BREATHLESSNESS AND DISEASE CONDITIONS*

Cluster	COPD ($n = 85$)	Asthma ($n = 56$)	ILD ($n = 37$)	CHF ($n = 17$)	CF ($n = 9$)	DECOND ($n = 8$)	NM ($n = 6$)
Work/effort	x	x	x	x	x	x	x
Suffocating							
Exhalation				x			
Tight		x			x		
Inhalation				x			x
Shallow							
Rapid			x			x	x
Breathing more						x	
Heavy					x	x	
Air hunger							

For definition of abbreviations, *see* Table 2.

* Selection of a cluster was considered to characterize a particular diagnosis when the ratio (number of times the descriptors within the cluster were chosen as the "best three" to describe a condition divided by the product of the number of descriptors within that cluster and the number of patients with that particular condition) was greater than 0.25.

Descriptors of Breathlessness in Cardiorespiratory Disease. D.A. Mahler, A. Harver, T. Lentine, J.A. Scott, K. Beck and R.M. Schwartzstein. Am J Respir Crit Care Med. 154: 1357-1363, 1996.

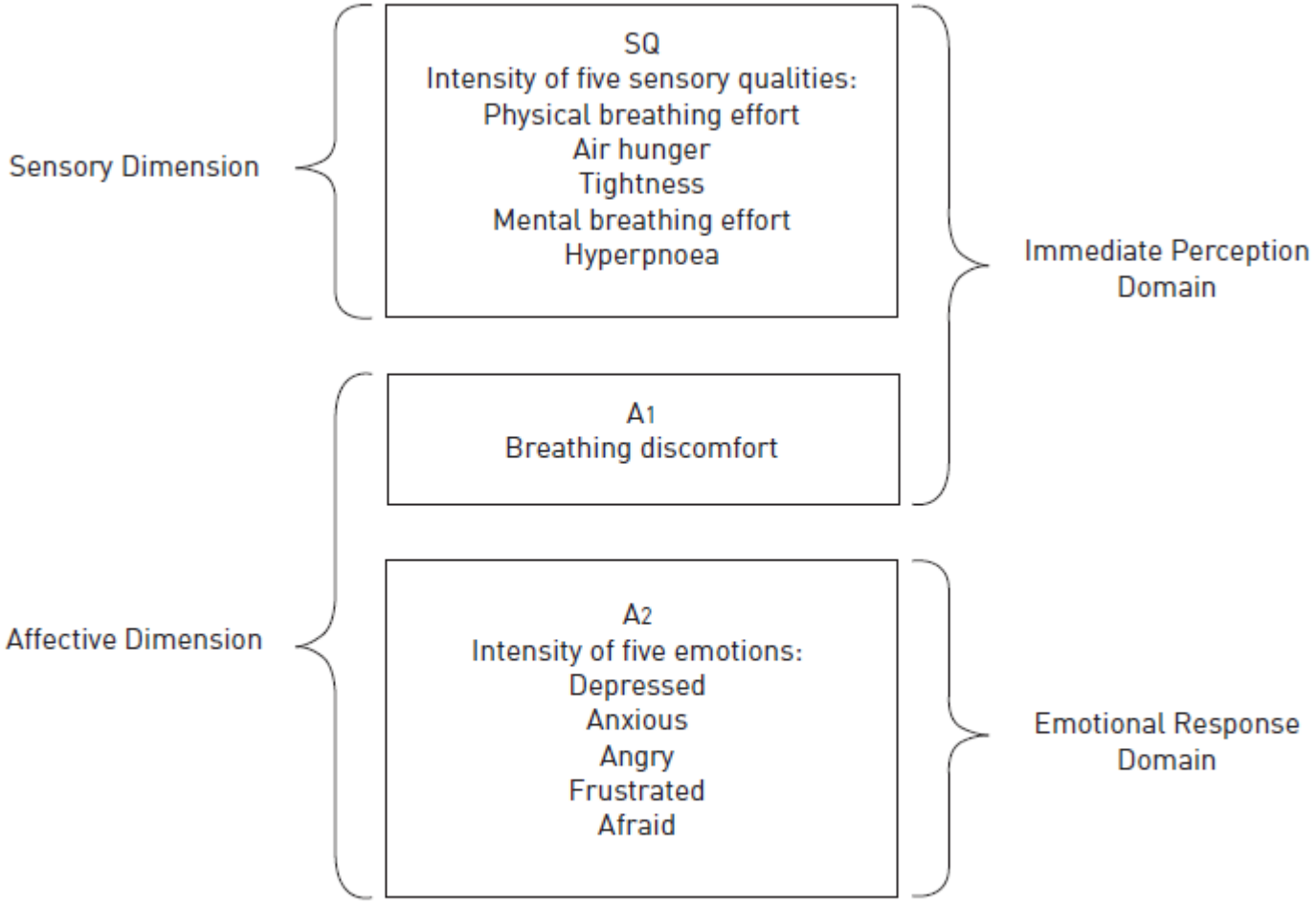


FIGURE 1 Model of the components of dyspnoea underlying the Multidimensional Dyspnea Profile. The division into sensory (SQ) and affective dimensions unpleasantness (A_1) and emotional response (A_2) (shown on the left) is based on a well-developed conceptual model of pain perception [26]. The division into Immediate and Emotional Response Domains (shown on the right) is based on empirical evidence from emergency department patients [36].

Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. R.B. Banzett, C.R. O'Donnell, T.E. Guilfoyle, M.B. Parshall, R.M. Schwartzstein, P.M. Meek, R.H. Gracely and R.W. Lansing. Eur Respir J; 45: 1681–1691, 2015

It is well established that Dyspnea/Breathlessness/Short of Breath is a multidimensional cognitive awareness of difficulty to breathe.

The fundamental question is how this perception is multidimensional yet specific.

The cognitive awareness of breathing is a neural process, hence elements of the nervous system must be mediating dyspnea providing the awareness and specificity.

Many diagrams and models have been used to illustrate what is known and what is predicted for dyspnea neural mechanisms.

All models have 3 critical features:
1. peripheral afferent transduction of respiratory interoceptive conditions;
2. central neural sensory processing;
3. efferent motor response.

Central Hypothesis:

Respiratory sensations are
a gated component of the brain
Urge-to-Breathe
Motivation System

Fundamental properties of respiratory interoceptive processing

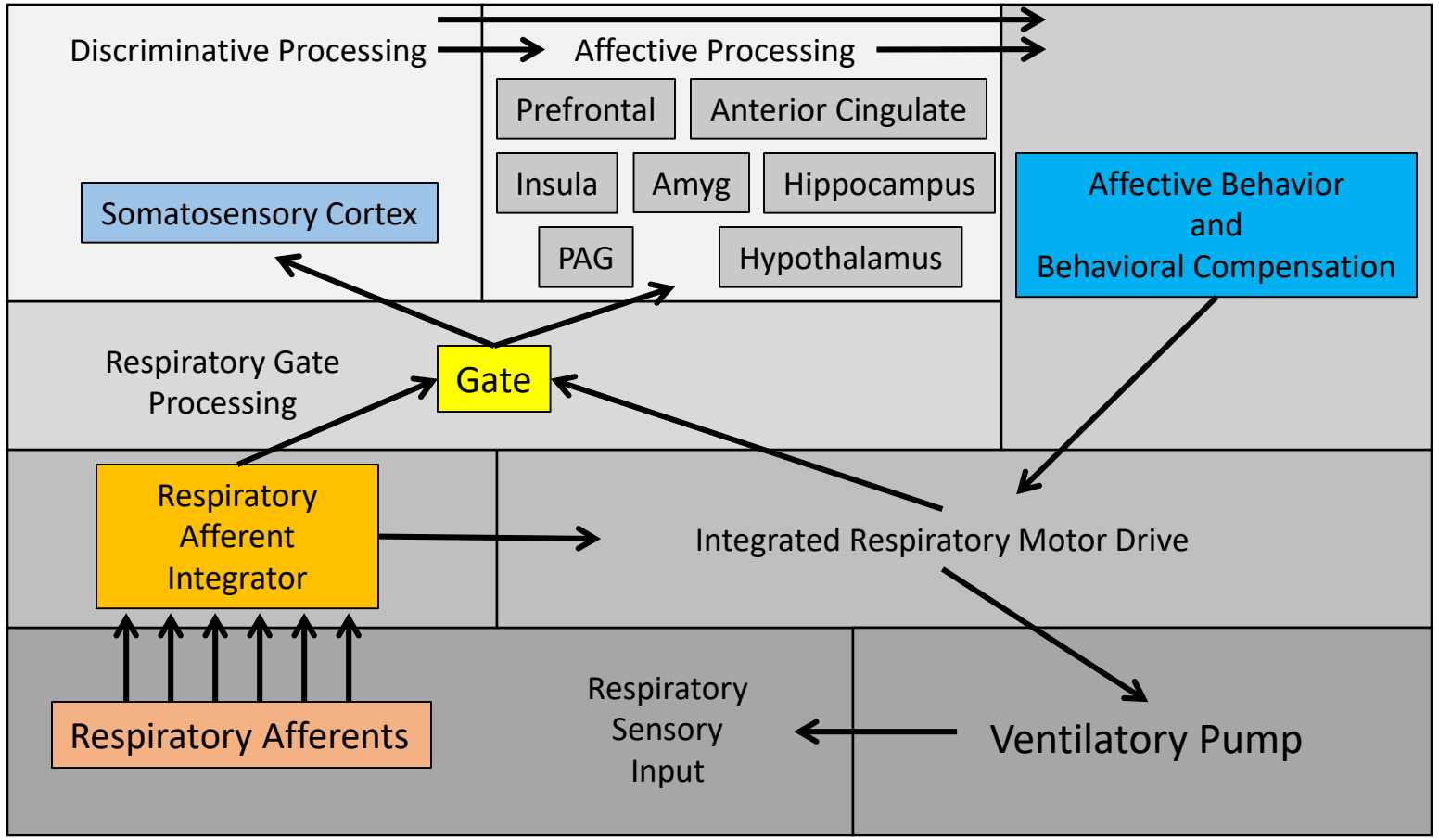
- Cognitive sensory events reflect neural processes
- Sensory afferent transduction of respiratory related parameters
- Threshold for cognitive awareness
- Perceptual quantification of magnitude
- Modality specific
- Modulated by initial conditions
- Multimodal respiratory afferent activation
- Activation of affective mechanisms
- Elicits compensatory responses

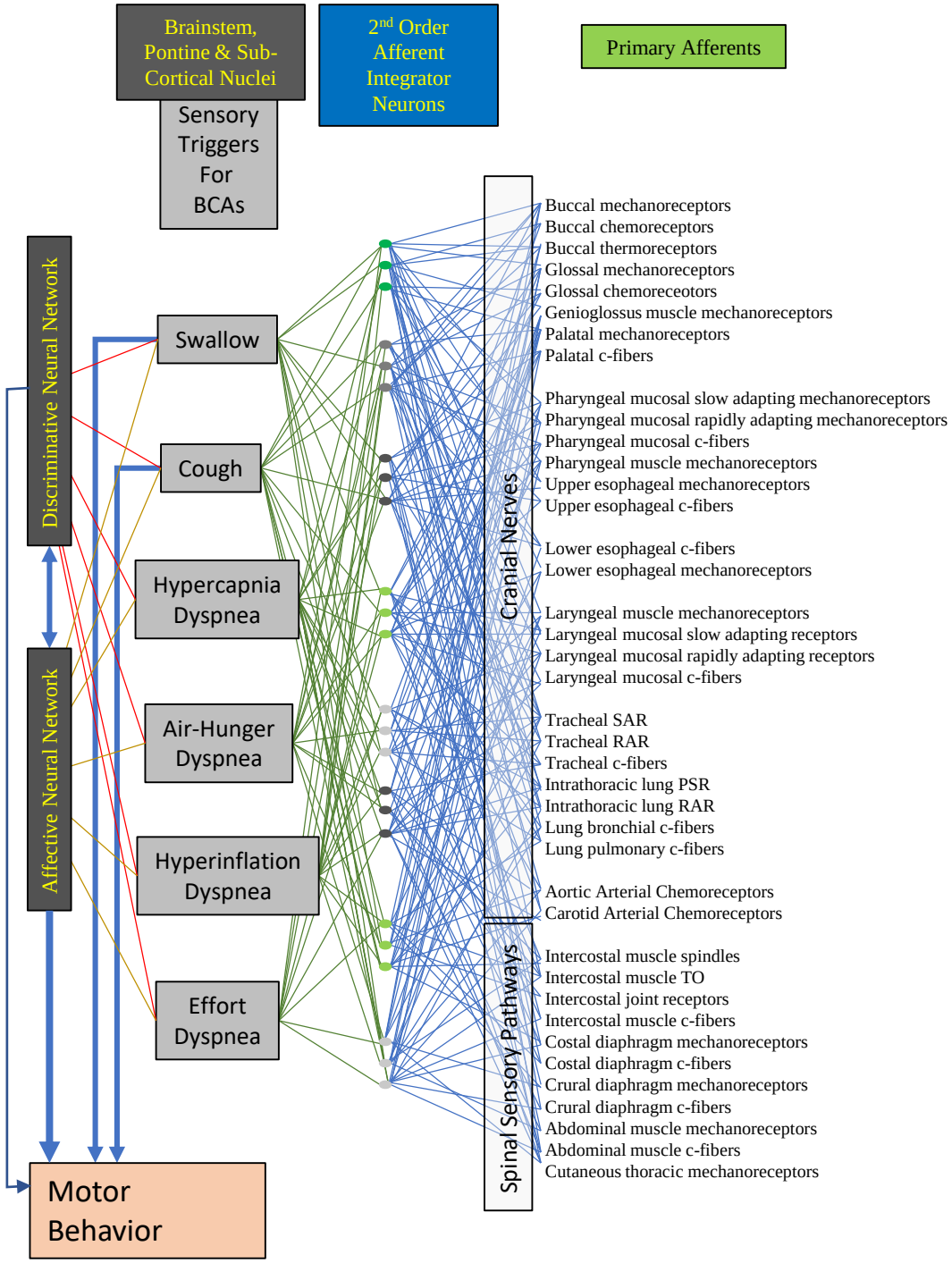
TABLE 2. POSSIBLE AFFERENT SOURCES FOR RESPIRATORY SENSATION*

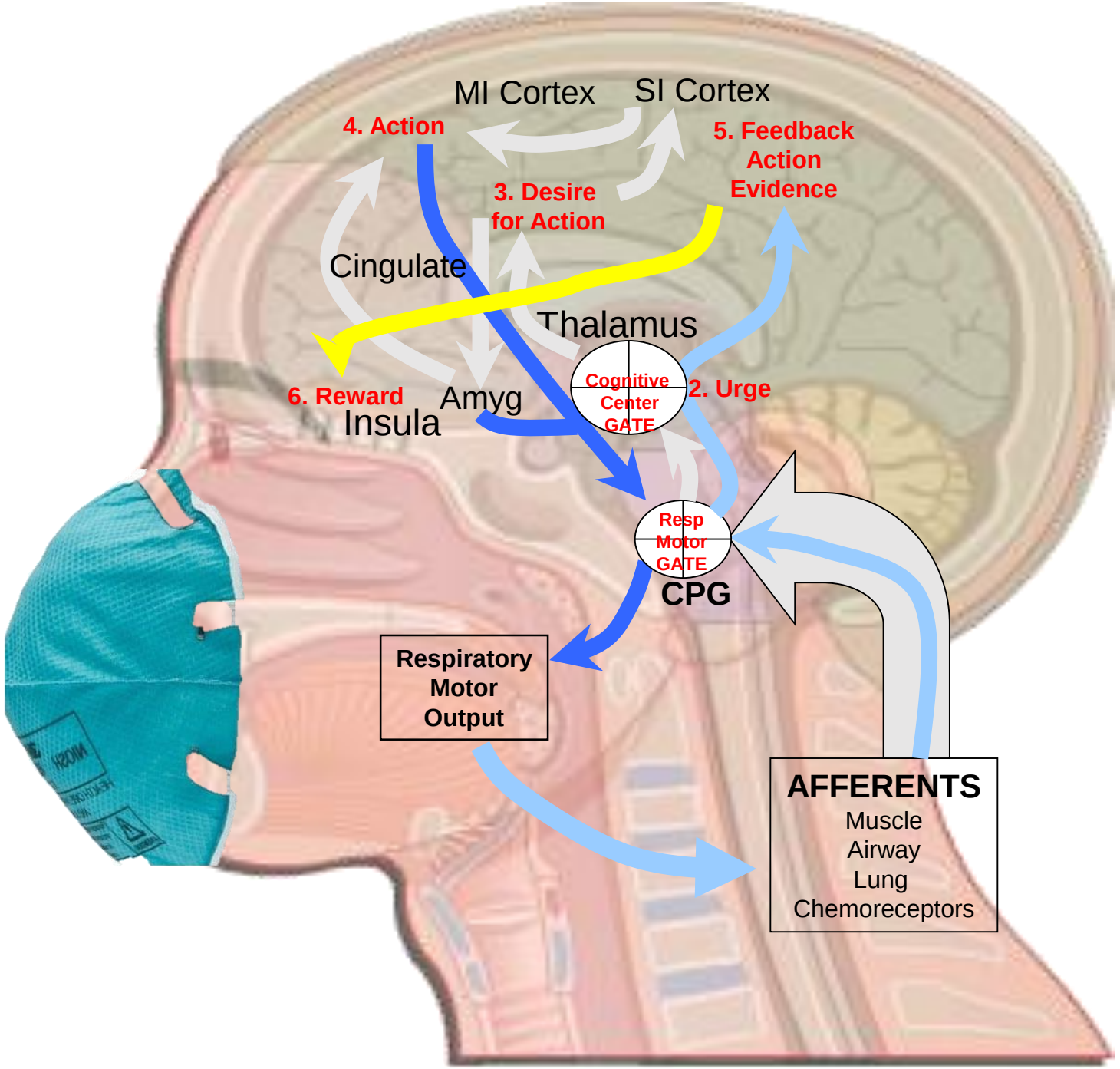
Source of Sensation	Adequate Stimulus
Medullary respiratory corollary discharge	Drives to automatic breathing (hypercapnia, hypoxia, exercise)
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Carotid and aortic bodies	Hypercapnia, hypoxemia, acidosis
Medullary chemoreceptors	Hypercapnia
Slowly adapting pulmonary stretch receptors	Lung inflation
Rapidly adapting pulmonary stretch receptors	Airway collapse, irritant substances, large fast (sudden) lung inflations/deflations
Pulmonary C-fibers (J-receptors)	Pulmonary vascular congestion
Airway C-fibers	Irritant substances
Upper airway "flow" receptors	Cooling of airway mucosa
Muscle spindles in respiratory pump muscles	Muscle length change with breathing motion
Tendon organs in respiratory pump muscles	Muscle active force with breathing motion
Metaboreceptors in respiratory pump muscles	Metabolic activity of respiratory pump
Vascular receptors (heart and lung)	Distention of vascular structures
Trigeminal skin receptors	Facial skin cooling
Chest wall joint and skin receptors	Tidal breathing motion

*Reviewed, for example, in References 24–26 and 39–41.

An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. M.B. Parshall, R.M. Schwartzstein, L. Adams, R.B. Banzett, H.L. Manning, J. Bourbeau, P.M. Calverley, A.G. Gift, A. Harver, S.C. Lareau, D.A. Mahler, P.M. Meek and D.E. O'Donnell; on behalf of the ATS Committee on Dyspnea THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, October, 2011. Am J Respir Crit Care Med Vol 185, Iss. 4, pp


Discriminative Processing
Affective Processing
Prefrontal
Anterior Cingulate
Insula
Amyg
Hippocampus
PAG
Hypothalamus
Somatosensory Cortex
Affective Behavior
and
Behavioral Compensation
Respiratory Gate
Processing
Gate
Respiratory
Afferent
Integrator
Integrated Respiratory Motor Drive
Respiratory Afferents
Respiratory
Sensory
Input
Ventilatory Pump


Brainstem, Pontine & Sub-Cortical Nuclei
2nd Order Afferent Integrator Neurons
Primary Afferents
Sensory Triggers For BCAs
Discriminative Neural Network
Affective Neural Network
Swallow
Cough
Hypercapnia Dyspnea
Air-Hunger Dyspnea
Hyperinflation Dyspnea
Effort Dyspnea
Motor Behavior
Cranial Nerves
Spinal Sensory Pathways
Buccal mechanoreceptors
Buccal chemoreceptors
Buccal thermoreceptors
Glossal mechanoreceptors
Glossal chemoreceotors
Genioglossus muscle mechanoreceptors
Palatal mechanoreceptors
Palatal c-fibers
Pharyngeal mucosal slow adapting mechanoreceptors
Pharyngeal mucosal rapidly adapting mechanoreceptors
Pharyngeal mucosal c-fibers
Pharyngeal muscle mechanoreceptors
Upper esophageal mechanoreceptors
Upper esophageal c-fibers
Lower esophageal c-fibers
Lower esophageal mechanoreceptors
Laryngeal muscle mechanoreceptors
Laryngeal mucosal slow adapting receptors
Laryngeal mucosal rapidly adapting receptors
Laryngeal mucosal c-fibers
Tracheal SAR
Tracheal RAR
Tracheal c-fibers
Intrathoracic lung PSR
Intrathoracic lung RAR
Lung bronchial c-fibers
Lung pulmonary c-fibers
Aortic Arterial Chemoreceptors
Carotid Arterial Chemoreceptors
Intercostal muscle spindles
Intercostal muscle TO
Intercostal joint receptors
Intercostal muscle c-fibers
Costal diaphragm mechanoreceptors
Costal diaphragm c-fibers
Crural diaphragm mechanoreceptors
Crural diaphragm c-fibers
Abdominal muscle mechanoreceptors
Abdominal muscle c-fibers
Cutaneous thoracic mechanoreceptors



Central Neural Processing of the Urge-to-Breathe