II° CONGRESSO
INTERREGIONALE SIMEU ABRUZZO MOLISE
"ITINERARI IN EMERGENZA URGENZA"

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Gestione della dispnea nell'insufficienza respiratoria end-stage

Salvatore M. Maggiore, MD, PhD

salvatore.maggiore@unich.it

Ud'A
Università degli Studi "G. d'Annunzio"

Anesthesia and Intensive Care
"SS. Annunziata" Hospital
"Gabriele d'Annunzio" University of Chieti-Pescara

Definition of dyspnea

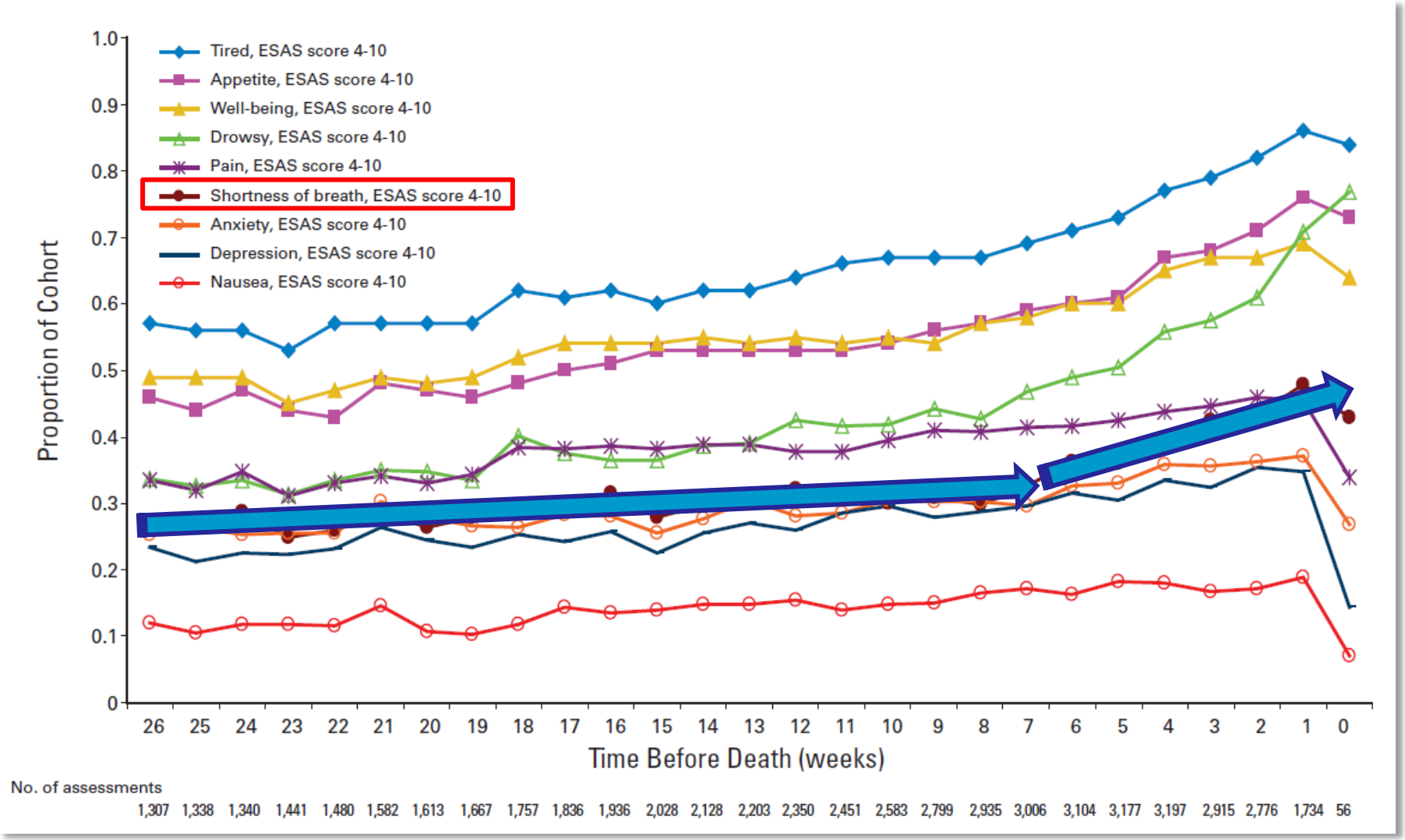
Dyspnea is a term used to characterize a ***subjective experience of breathing discomfort*** *that consists of qualitatively distinct sensations that vary in intensity. The experience derives from* ***interactions among multiple physiological, psychological, social, and environmental factors****, and may induce secondary physiological and behavioral responses.*

American Thoracic Society Consensus Statement. Am J Respir Crit Care Med 1999;159:321-340

Prevalence of dyspnea

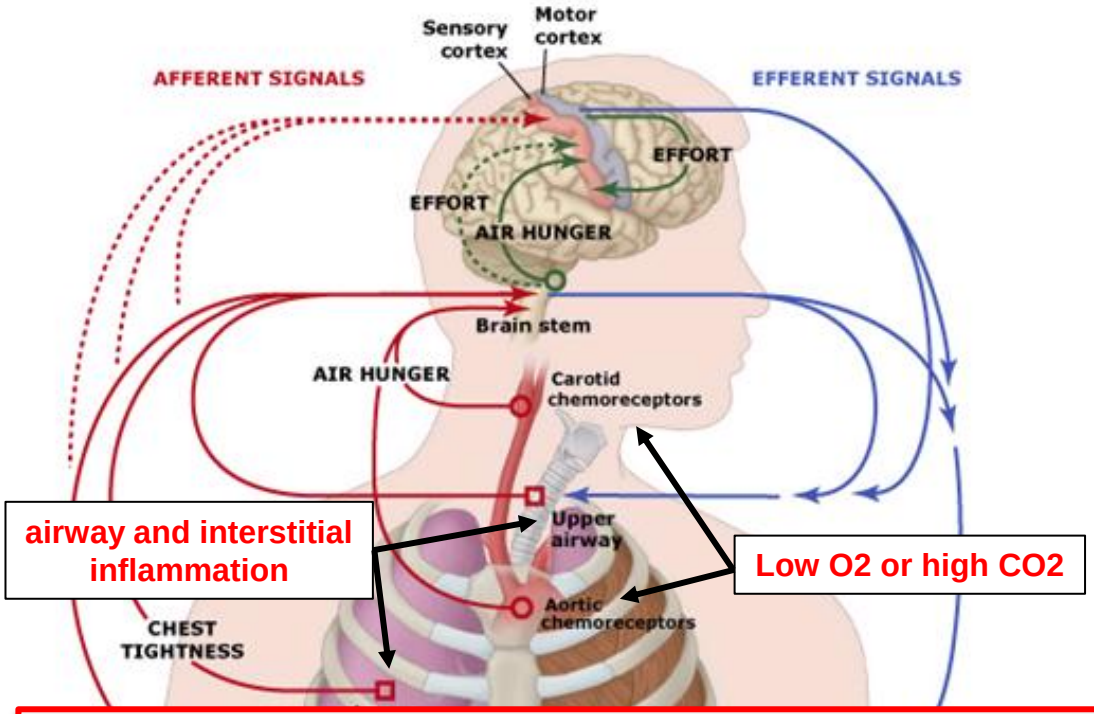
POPULATION	PREVALENCE OF DYSPNEA (%)	REFERENCES
Cancer (mixed)	**10-70**	Solano 2006
AIDS	**10-62**	Solano 2006
Lung cancer (primary or metastatic)	**62-95**	Currow 2010
Heart disease	**60-88**	Solano 2006
COPD	**90-95**	Solano 2006
Renal disease	**11-62**	Solano 2006
Stroke	**37**	Addington-Hall 1995
ALS	**47-50**	O'Brien 1992 , Hicks 1993
Dementia	**70**	Lloyd-Williams 1996
No cardiorespiratory disease (ie, no primary or secondary lung malignancy, cardiac failure, or respiratory disease)	**45-81**	Currow 2010

Prevalence & severity increase in the last 6 months



Seow H et al. J Clin Oncol 2011;29:1151-1158

Efferent & afferent signals contributing to dyspnea



Intensity of dyspnea increases when there is a perceived mismatch between the outgoing efferent messages to the ventilatory muscles and incoming afferent signals from the lungs and chest wall

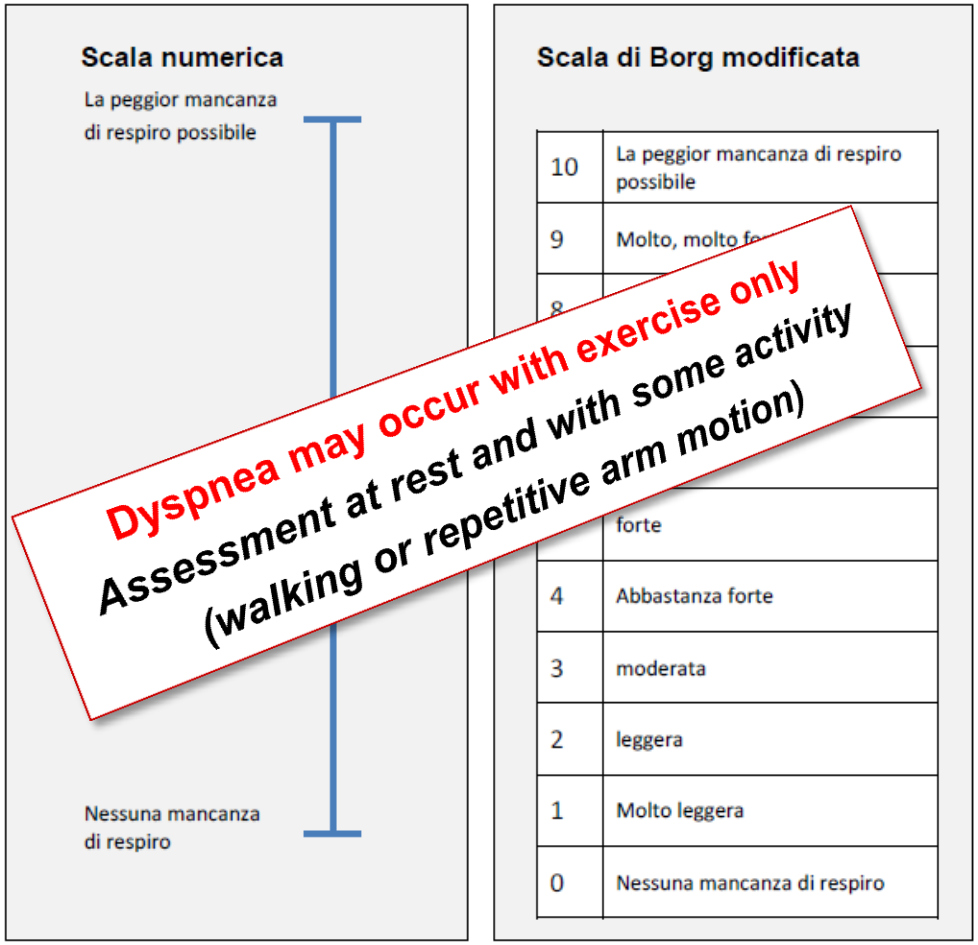
A variety of emotional changes (anxiety, anger, and depression) can intensify dyspnea. The quality and intensity of dyspnea are also thought to be shaped by patient experience, expectation, behavioral style, and emotional state

Assessment of dyspnea

- **Discrepancy** between severity of disease and intensity of dyspnea is frequent.
- **Subjective** symptom: best assessment based on patient report (problematic in unconscious patients).
- **Qualitative differences** in reporting dyspnea by patients may be related to differences in the underlying cause (asthmatics: "*chest tightness*"; COPD: "*inability to get a deep breath*").

Assessment of dyspnea

- **Visual analogue scales** are widely used.
- Few scales have been validated across different patient groups and diagnoses (most in COPD or asthma).
- **Functional scales** that describe the occurrence of dyspnea based on activity are useful:
  - Level 1, no dyspnea
  - Level 2, dyspnea on vigorous exertion (e.g., climbing stairs)
  - Level 3, dyspnea with routine ambulation



- Assess the role of **cultural and psychological factors** (fear and anxiety of choking, of dying alone by suffocation, or of abandonment, etc.)
- Assess **anxiety of family** (can contribute to the patient's dyspnea)

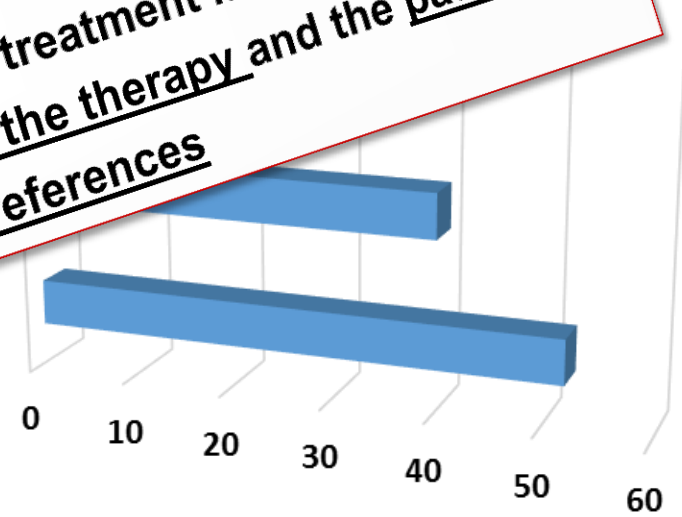
Treatable causes of dyspnea

Search for a treatable underlying cause, even if the patient is terminally ill

- chest X-ray
- CT

Causes of dyspnea are often untreatable but…

if a treatable cause is found, specific treatment may be appropriate depending on the invasiveness of the therapy and the patient's values and preferences



Dudgeon DJ et al. J Pain Symptom Manage 1998;16:212

Treatment of dyspnea

Ultimate goal: to reduce the distress the symptom causes

- **Non-pharmacologic management**
  - General measures
  - Oxygen
  - NIV
- **Pharmacologic management**
  - Opioids, benzodiazepines, etc.

General measures for the management of dyspnea

Minimize production of symptom

- Exercise training (lower- or upper-limb endurance training, neuroelectrical muscle stimulation)
- Breathing techniques (pursed-lips breathing, diaphragmatic breathing)
- Maximize nutrition
- **Supplemental oxygen**
- **Noninvasive ventilation**

Diminish perception of symptom

- Fan blowing cool air on face
- Distraction strategies (relaxati… …erapy, acupuncture, music)
- Stimulation of respi…

Reduce the in…

- E… …ttention to posture and ergonomics)
- … …ving arrangement, altered activities, frequent rests)

Mod… …mptom

- Ac… …bations
- Addi… …ent's interpretation of symptom meaning
- If present, treat associated mood/anxiety disorder

Multidisciplinary approach

ICU and PC physicians, nurses, physioterapists, respiratory therapists, dieticians, psychologists, and chaplains

Oxygen for the management of dyspnea

Mechanisms by which O2 may reduce dyspnea
• Reversal of hypoxemia
• Reduced serum lactic acid
• Reduced pulmonary artery pressure
• Reduced dynamic hyperinflation
• Reduced ventilatory muscle and diaphragm fatigue
• Relief of bronchoconstriction
• Stimulation of facial, nasal or pharyngeal receptors
• Increased capacity for exercise training
• Placebo effect

Oxygen for the management of dyspnea

Hypoxemic vs. non-hypoxemic

Study	Design	Patients	Intervention	Measurement	Results
Hypoxemic					
Bruera 1992[1]	RDB, crossover	n = 1, six trials of O_2 versus air	5 L/min O_2 versus 5 L/min air for five mins	- VAS	- Significant improvement in VAS of O_2 over air. Both patient and investigator chose O_2 over air in five of six cases.
Bruera 1993[2]		n = 14, inpatients	100 percent O_2 versus air at 5 L/min by nasal prongs at rest till SaO_2 stable for five min	- VAS - Degree of benefit (Likert scale) - Patient preference	- Significant improvement from baseline in VAS dyspnea scores with O_2, but not with air - 12 of 14 patients prefer O_2; 12 of 14 patients rate degree of benefit with O_2 as moderate or greater

Effective

Oxygen for the management of dyspnea

Hypoxemic vs. non-hypoxemic

Study	Design	Patients	Intervention	Measurement	Results
Combined hypoxemic and non-hypoxemic					
Booth 1996[3]	Randomized, single-blind, crossover	n = 45, inpatients, baseline SaO_2 range 80 to 9[illegible] percent	100 percent O_2 versus air at 4 L/min by nasal prongs for 15 min at rest	- VAS	- Both O_2 and air resulted in significant improvement from baseline, no statistical difference in magnitude of improvement between groups - Neither baseline oxygen saturation (SpO_2), lung disease nor cardiac status predicted greater improvement with O_2
Philip [illegible]	RDB, crossover	n = 51, inpatients and outpatients, baseline SaO_2 range 70 to 98 percent	100 percent O_2 versus air at 4 L/min for 15 min, then crossover to alternative	- Patient preference - VAS	- No patient preference for oxygen - No difference in change in dyspnea VAS - No correlation between O_2 saturation and VAS score

Not effective

Oxygen for the management of dyspnea

Hypoxemic vs. non-hypoxemic

Study	Design	Patients			Results
Non-hypoxemic					
Abernethy 2010[5]	RDB				o difference in athlessness at any lar proportions in rms achieved ≥1 eduction on NRS
					28 >28 percent or distance >air for Borg nd of six inute walk - Borg scale for 28 percent O_2 was better than non-enriched air, but did not achieve statistical significance
Bruera 20			100 percent O_2 versus air at 5 L/min by nasal prongs for six minute walk test	- Dyspnea NRS - Fatigue NRS - Distance walked	- No difference in dyspnea, fatigue or distance walked

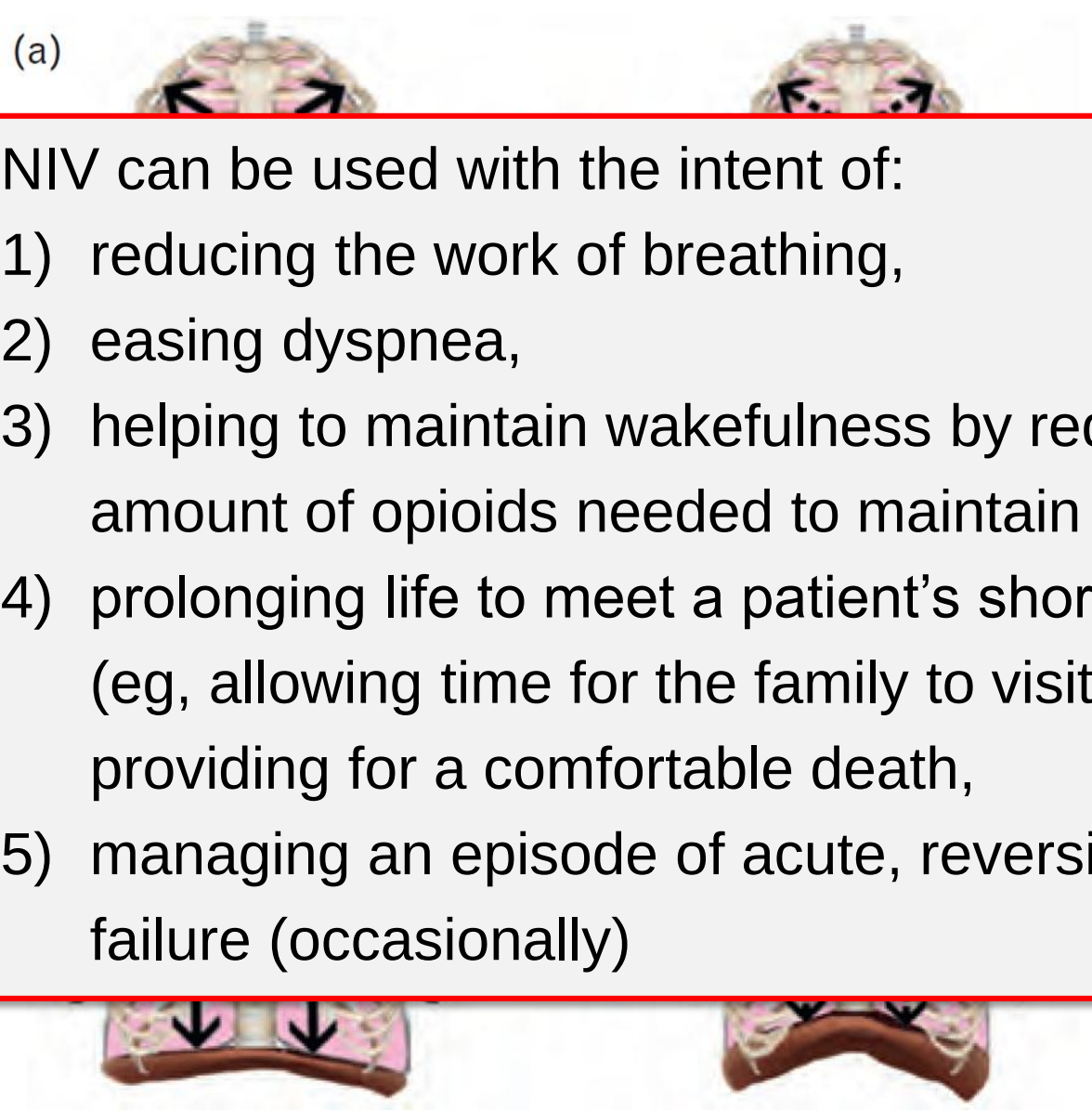
Evidence-Based Interventions to Improve Palliative Care at the End of Life

clinicians should use therapies of proven effectiveness to manage dyspnea, which include … oxygen for short-term relief of hypoxemia.

(Grade: strong recommendation, moderate quality of evidence)

Qaseem A et al. Ann Intern Med. 2008;148:141-146

NIV for the management of dyspnea



NIV can be used with the intent of:

1) reducing the work of breathing,
2) easing dyspnea,
3) helping to maintain wakefulness by reducing the amount of opioids needed to maintain comfort,
4) prolonging life to meet a patient's short-term goals (eg, allowing time for the family to visit) while providing for a comfortable death,
5) managing an episode of acute, reversible respiratory failure (occasionally)

Gifford AH et al. Curr Opin Support Palliat Care 2014; 8:218-224

NIV for the management of dyspnea

Dyspnea related to a reversible factor

(e.g., pulmonary edema, infection, or drug overdose)

- NIV evaluated in association with interventions that target the cause

(e.g., diuretics, antibiotics, antidotes, or physical therapy)

Terminal dyspnea

(carcinomatous lymphangitis, nerve compression, amyotrophic lateral sclerosis, or other advanced degenerative neuromuscular diseases)

- NIV controversial

(futile care or a tool for improving patient comfort?)

Studies on palliative NIV

10 studies, 458 patients with decisions to forego ETI

Authors	Year of publication	*N* patients	Type of patients	Hospital mortality	
Benhamou et al. [42]	1992	30			
				ND	ical service
	2006	458	Unselected	About 50%	ity was 84.3%. 10% survived years or more. Survival was highest in the COPD patients 1-year survival was 43.5% Worst outcomes in cancer patients All patients improved their respiratory distress. In one, NIV was stopped because of discomfort and deterioration of consciousness Overall, palliative NIV is feasible, successful in 50 to 70% of patients, and usually well tolerated

1) NIV is often offered to patients receiving palliative care;
2) among patients given palliative NIV for ARF related to reversible events, nearly half survive and can return home;
3) survival varies with the underlying condition (being higher in patients with COPD or acute pulmonary edema than in patients with cancer) and with the cause of ARF;
4) survival is lower in patients with a coma at NIV initiation or with an ineffective cough;
5) patient comfort and family satisfaction, although not specifically measured, are not described as poor.

Azoulay E et al. Intensive Care Med 2011; 37:1250–1257

Palliative NIV for management of dyspnea at the End-of-Life

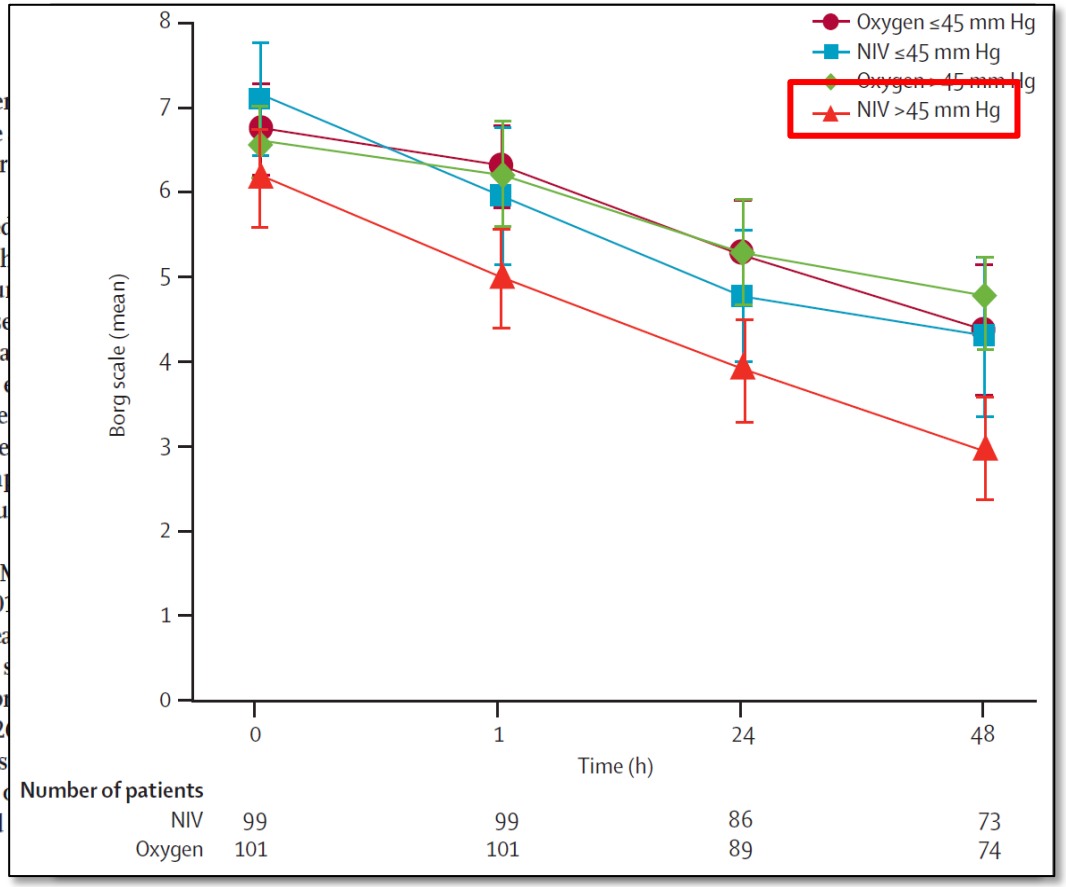
Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial

Stefano Nava, Miguel Ferrer, Antonio Esquinas, Raffaele Scala, Paolo Groff, Roberto Cosentini, Davide Guido, Ching-Hsiung Lin, Anna Maria Cuomo, Mario Grassi

200 patients (7 centres) with solid tumours and ARF and a life expectancy < 6 months: 99 NIV vs. 101 oxygen

and assigned treatment allocation using opaque, sealed
subcutaneous morphine to reduce their dyspnoea score
endpoints were to assess the acceptability of NIV used sole
reducing dyspnoea and the amount of opiates needed com
to treat. This study is registered with ClinicalTrials.gov, nu

Findings We recruited patients between Jan 15, 2008, and
randomly allocated 200 (85%) to treatment: 99 to NIV and 10
treatment; no patients in the oxygen group discontinued trea
compared with the oxygen group (average change in Borg
benefit seen after the first hour of treatment and in hypercapn
was lower in the NIV group than it was in the oxygen group (2
difference –32·4 mg, 95% CI –47·5 to –17·4). Adverse events
intolerance and anxiety. Morphine was suspended because
sudden respiratory arrest (one patient in the NIV group), and



Nava S et al. Lancet Oncol 2013; 14: 219–27

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Interpretation Our findings suggest that NIV is more effective compared with oxygen in reducing dyspnoea and decreasing the doses of morphine needed in patients with end-stage cancer. Further studies are needed to confirm our findings and to assess the effectiveness of NIV on other outcomes such as survival. The use of NIV is, however, restricted to centres with NIV equipment, our findings are not generalisable to all cancer or palliative care units.

	Overall (NIV vs oxygen)			$PaCO_2 \leq 45$ mm Hg			$PaCO_2 > 45$ mm Hg			Interaction (interaction hazard ratio)
	NIV	Oxygen	Hazard ratio	NIV	Oxygen	Hazard ratio	NIV	Oxygen	Hazard ratio	
Morphine (mg)										
In-h										
3 m										
6 m										
Data										

11 (11%) patients in the NIV group discontinued treatment, mainly because of mask intolerance and anxiety

Table 5: Survival over time

Nava S et al. Lancet Oncol 2013; 14: 219–27

Goals of palliative NIV at the End-of-Life

Noninvasive positive pressure ventilation in critical and palliative care settings: Understanding the goals of therapy*

J. Randall Curtis, MD, MPH; Deborah J. Cook, MD; Tasnim Sinuff, MD, PhD; Douglas B. White, MD; Nicholas Hill, MD; Sean P. Keenan, MD, MSc(Epid); Joshua O. Benditt, MD; Robert Kacmarek, PhD, RRT; Karin T. Kirchhoff, RN, PhD, FAAN; Mitchell M. Levy, MD; the Society of Critical Care Medicine Palliative Noninvasive Positive Pressure Ventilation Task Force

Primary goals of care	Determination of success	Response to failure	What is said to the family
Category 1: life support without preset limits			
Assist ventilation and/or oxygenation Alleviate dyspnea Achieve comfort Reduce risk of intubation Reduce risk of mortality Avoidance of intubation	Improved oxygenation and/or ventilation Tolerance of NPPV or minor discomfort that is outweighed by potential benefit	Intubation and mechanical ventilation	Goals are to restore health and use intubation if necessary and indicated
Category 2: life support with preset limit (do not intubate)			
Includes same as category 1 except intubation declined Also could include briefly prolonging life for a specific purpose (e.g., arrival of family member)	Improved oxygenation and/or ventilation Tolerance of NPPV or minor discomfort that is outweighed by potential benefit	Change to comfort measures only and palliate symptoms without NPPV	Goal is to restore health without using endotracheal intubation and without causing unacceptable discomfort
Category 3: comfort measures only			
Palliation of symptoms (relief of dyspnea)	Improved symptoms Tolerance of NPPV	Palliate symptoms without NPPV	Goal is to maximize comfort while minimizing adverse effects of opiates

Randall Curtis J et al. Crit Care Med 2007; 35:932–939

Nasal High-Flow Oxygen Therapy

Matching pt's inspiratory flow (stable FiO2)

CPAP effect (lung recruitment)

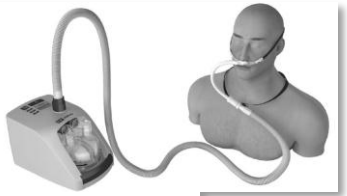
Washout of nasopharyngeal deadspace

Better humidification & comfort

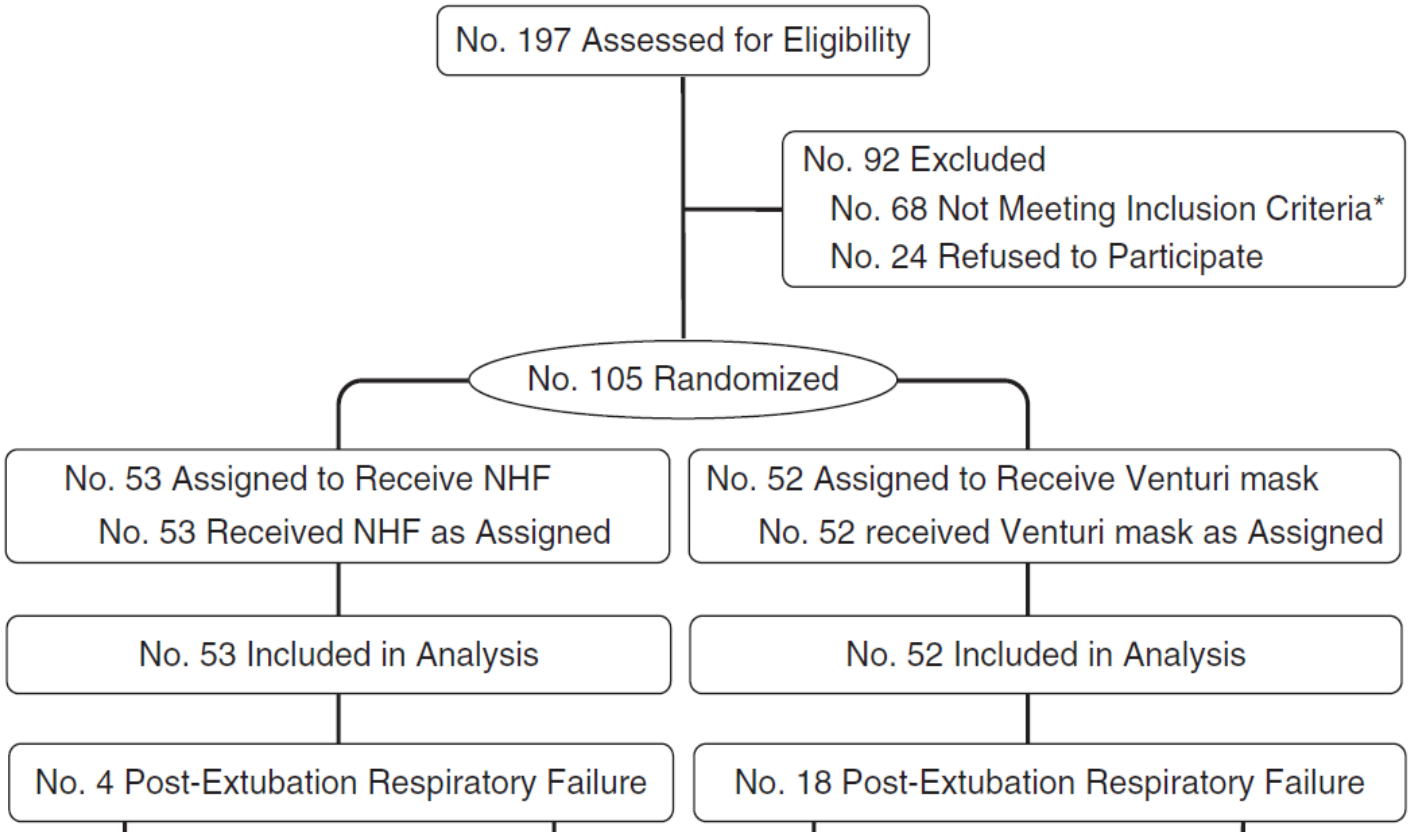
Efficacy of NHF in hypoxemic patients

Nasal High-Flow versus Venturi Mask Oxygen Therapy after Extubation

Effects on Oxygenation, Comfort, and Clinical Outcome

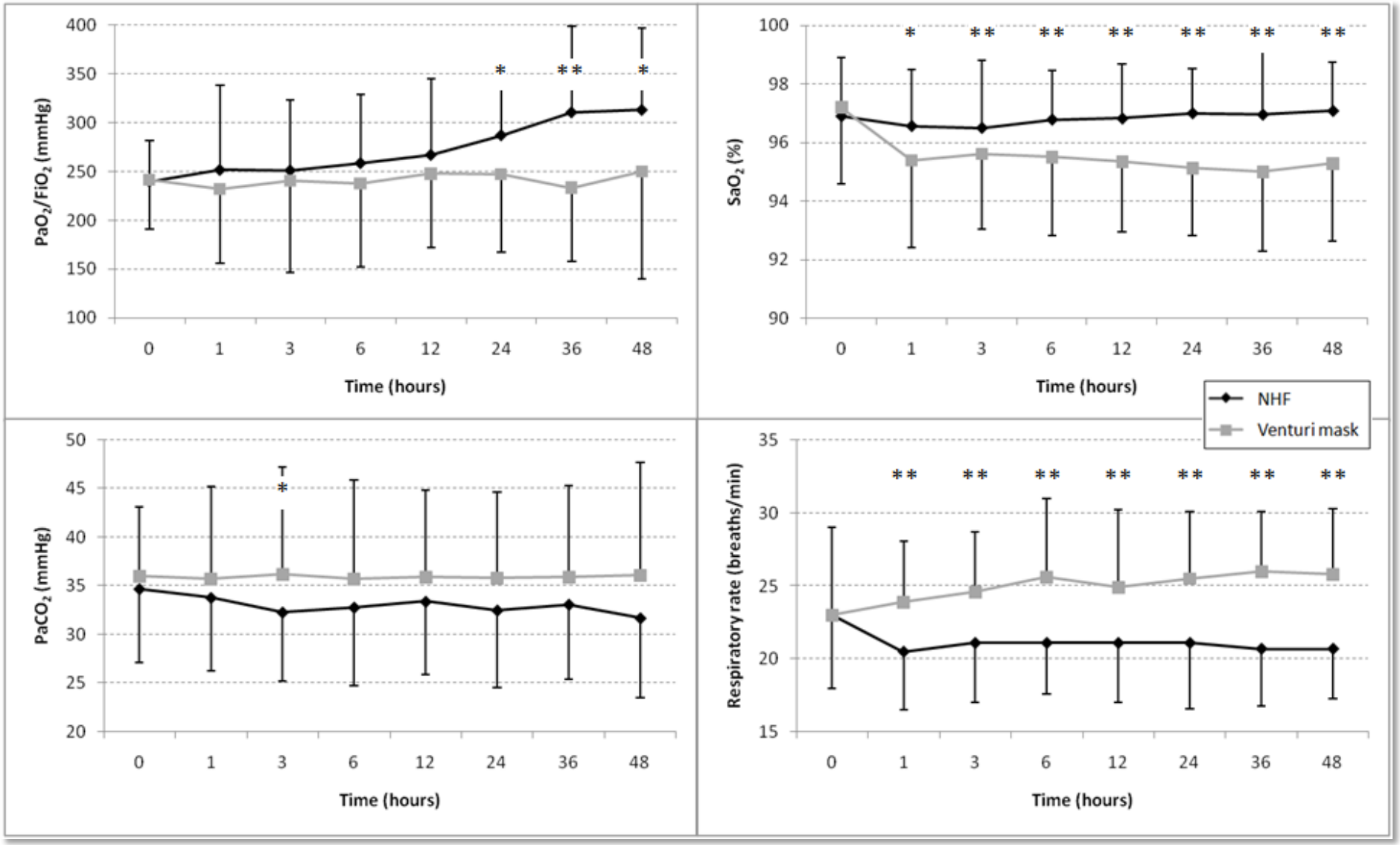


Salvatore Maurizio Maggiore[1], Francesco Antonio Idone[1], Rosanna Vaschetto[2], Rossano Festa[1], Andrea Cataldo[1], Federica Antonicelli[1], Luca Montini[1], Andrea De Gaetano[3], Paolo Navalesi[4,5,6], and Massimo Antonelli[1]



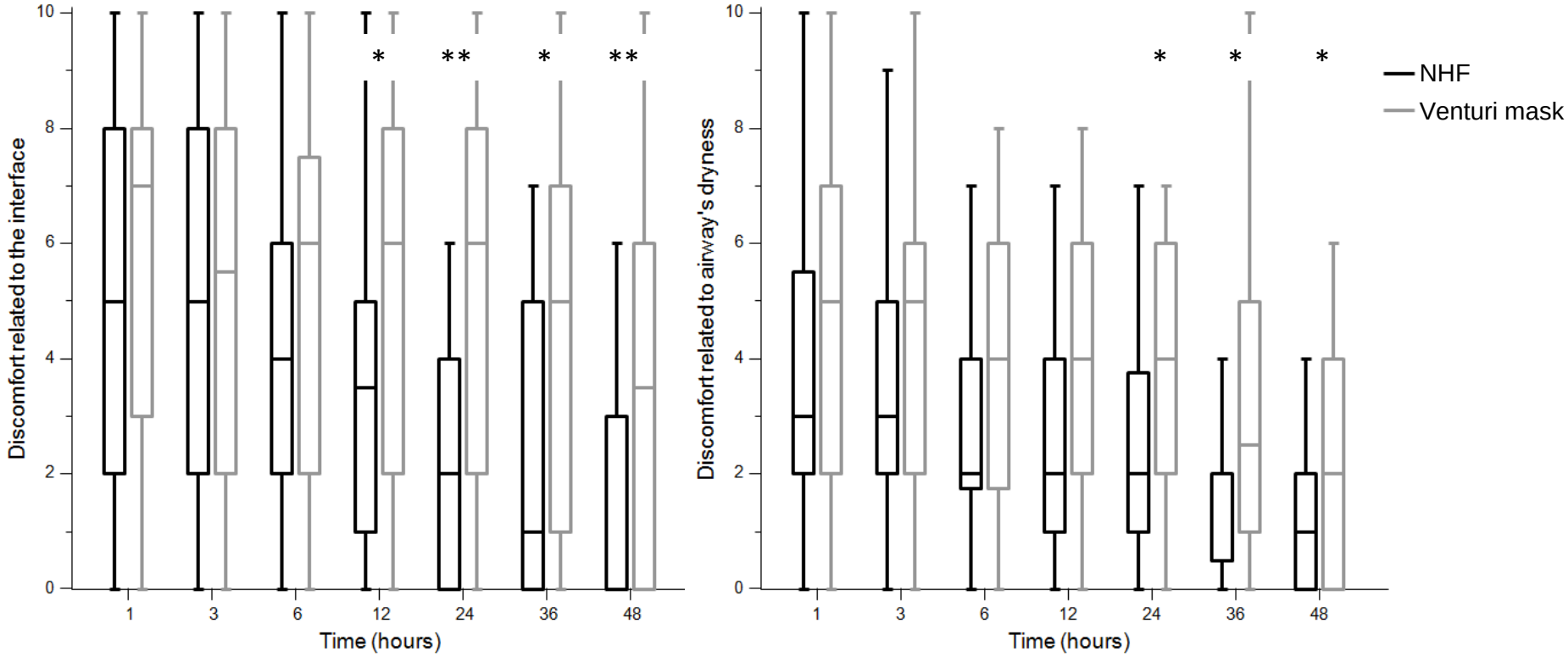
Maggiore SM et al. AJRCCM 2014;190:282-288

NHF improves gas exchange and respiratory rate



Maggiore SM et al. AJRCCM 2014;190:282-288

NHF improves patient's comfort



N intervention	48	49	49	48	47	40	37
N control	45	42	40	34	33	26	23

N intervention	48	49	49	48	47	40	37
N control	45	42	40	34	33	26	23

Maggiore SM et al. AJRCCM 2014;190:282-288

Palliative NHF for management of hypoxemic patient

High-Flow Nasal Cannula Therapy in Do-Not-Intubate Patients With Hypoxemic Respiratory Distress

Steve G Peters MD, Steven R Holets RRT, and Peter C Gay MD

	Pre-HFNC	Post-HFNC	*P*
Breathing frequency, breaths/min	30.6	24.7	< .001
O_2 saturation	89.1	94.7	< .001

NHF can provide adequate oxygenation for many patients with hypoxemic ARF and may be an alternative to NIV for DNI pts

Peters SG et al. Respir Care 2013;58:597–600

Pharmacologic management of dyspnea: Opioids

American Thoracic Society Documents

An Official American Thoracic Society Clinical Policy Statement: Palliative Care for Patients with Respiratory Diseases and Critical Illnesses

The physiologic component of dyspnea may be relieved by supplemental oxygen, noninvasive positive-pressure ventilation for hypercapnic adult patients, or blowing cool air on the face using a fan (90–92). Opioids and anxiolytics are the primary pharmacologic treatments of dyspnea for adults and chil
(Table 4). Opioids can be given orally, subcutaneo
venously (Table 4) (84, 93–96). Although

ACP Clinical Practice
American College of Physicians
GUIDELINES

CLINICAL GUIDELINES

Evidence-Based Interventions to Improve the Palliative Care of Pain, Dyspnea, and Depression at the End of
A Clinical Practice Guideline from the American
icians

Recomm
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Opioids are the primary pharmacologic therapy for dyspnea

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12. Oral and/or parenteral opioids can provide relief of dyspnea.
13. Opioids should be dosed and titrated for the individual patient with consideration of multiple factors (eg, renal, hepatic, pulmonary function, and current and past opioid use) for relief of dyspnea.
14. Respiratory depression is a widely held concern with the use of opioids for the relief of dyspnea.

Pharmacologic management of dyspnea: Opioids

Decreased metabolic rate and ventilatory requirements
Reduced medullary sensitivity to hypercarbia or hypoxia
Blunted medullary response to hypercarbia or hypoxia
Alteration of neurotransmission within medullary respiratory centre
Cortical sedation (suppression of respiratory awareness)
Analgesia - reduction of pain-induced respiratory drive
Anxiolytic effects
Blunted afferent transmission from pulmonary mechanoreceptor to the CNS
Vasodilation (improved cardiac function)

Pharmacologic management of dyspnea: Opioids

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An Official American Thoracic Society Clinical Policy Statement: Palliative Care for Patients with Respiratory Diseases and Critical Illnesses

Paul N. Lanken, Peter B. Terry, Horace M. DeLisser, Bonnie F. Fahy, John Hansen-Flaschen, John E. Heffner, Mitchell Levy, Richard A. Mularski, Molly L. Osborne, Thomas J. Prendergast, Graeme Rocker, William J. Sibbald†, Benjamin Wilfond, and James R. Yankaskas, on behalf of the ATS End-of-Life Care Task Force

TABLE 4. STARTING DOSAGES OF OPIOIDS AND THEIR DURATION OF EFFECT IN OPIOID-NAIVE PATIENTS WITH MODERATE TO SEVERE PAIN OR DYSPNEA*

	Adult Duration	Adult	Pediatric	Pediatric	
Agent	IV	Oral	IV	Oral	Oral
Oxycodone	N/A	5–10 mg	N/A	0.05–0.15 mg/kg†	4–6 h
Methadone	2.5–10 mg	5–10 mg	0.1 mg/kg†	0.1 mg/kg†	4–12 h
Morphine	2–10 mg	5–10 mg	0.1–0.2 mg/kg†	0.2–0.5 mg/kg†	3–4 h
Hydromorphone	0.3–1.5 mg	2–4 mg	0.015–0.03 mg/kg†	0.03–0.08 mg/kg†	3–4 h
Fentanyl	50–100 μg	N/A	1–2 μg/kg†	N/A	0.5–1 h

Lanken PN et al. Am J Respir Crit Care Med 2008; 177: 912–927

Pharmacologic management of dyspnea: Opioids

Opioids prescription for symptoms relief and the impact on respiratory function: updated evidence

José Mario López-Saca and Carlos Centeno

Purpose of review

Opioids are used for treating dyspnea and other symptoms in oncological and nononcol
The relief of respiratory fatigue and anxiety that these opioids offer is well kno
frequent, but very much feared side-effects is respiratory depression. Th
determine whether or not the
opioids are risk factors for re

Recent findings

Studies conducted on respir
no recent review th

Sum

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high CO_2 levels in blood (P=
respiratory function; they are

Keywords

dyspnea, morphine, palliative care, respiratory function, respiratory insufficiency

Opioids are safe and effective

8 studie
ange in oxygenation

- No change in CO2 levels
- No impact on respiratory function

Lopez-Saca J et al. Curr Opin Support Palliat Care 2014; 8:383–390

Pharmacologic management of dyspnea: Benzodiazepines

Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)

Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C

There is **no evidence for a bene**

for the relief of bre

and CO

odiazepines as

individual therapeutic

pharmacological measures have failed

ssness.

However, they are important adjunct to therapy when anxiety is significant

Simon ST et al. Cochrane Database Syst Rev 2010; CD007354

Conclusions

- Dyspnea is very frequent during end-stage respiratory failure
- Its assessment is important for delivering optimal palliative care
- Whenever possible (treatable cause), specific treatment should be offered
- Main therapy is pharmacologic (opioids, benzodiazepines), supplemented by other non-pharmacologic maneuvers
- Oxygen should be given in hypoxemic patients. NIV may be useful, particularly in hypercapnic patients.
- New devices for oxygen therapy may prove useful