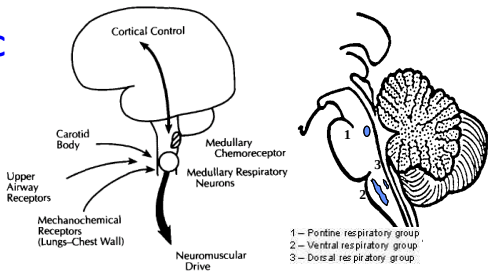
Indications de la VNI de domicile en 2014

« Hors situations d'insuffisance respiratoire aiguë »

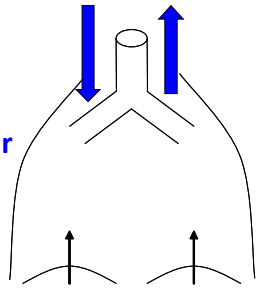
Olivier Contal, PhD
o.contal@lpge.ch
Jean Christian Borel, PhD
j.borel@agiradom.com

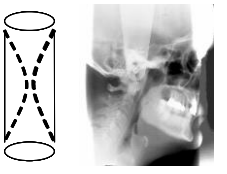
Arnaud Prigent, MD

SNC

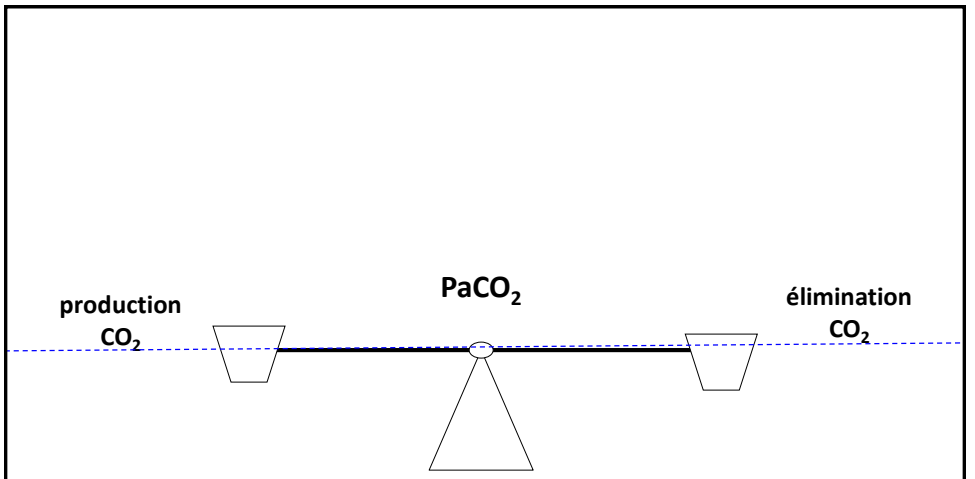


Effecteur





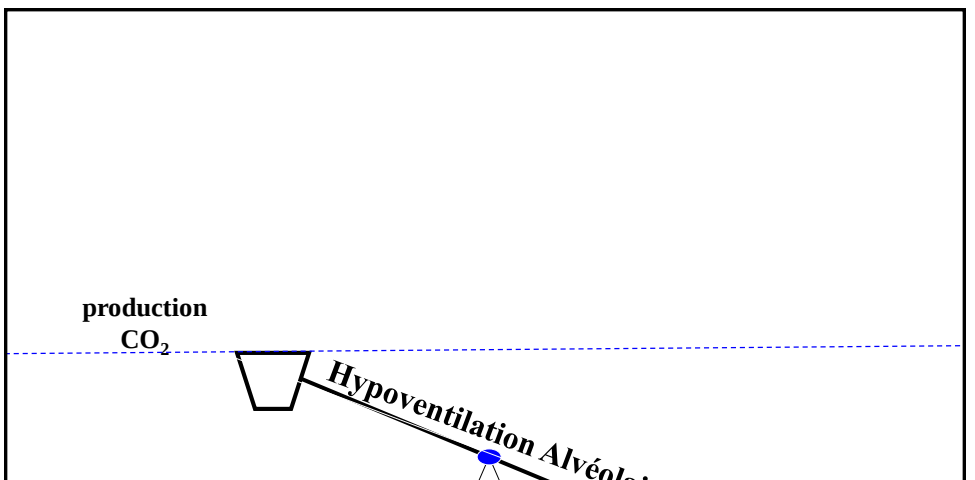
Pharynx/Larynx



4.7 kPa <normo-capnie < 6 kPa

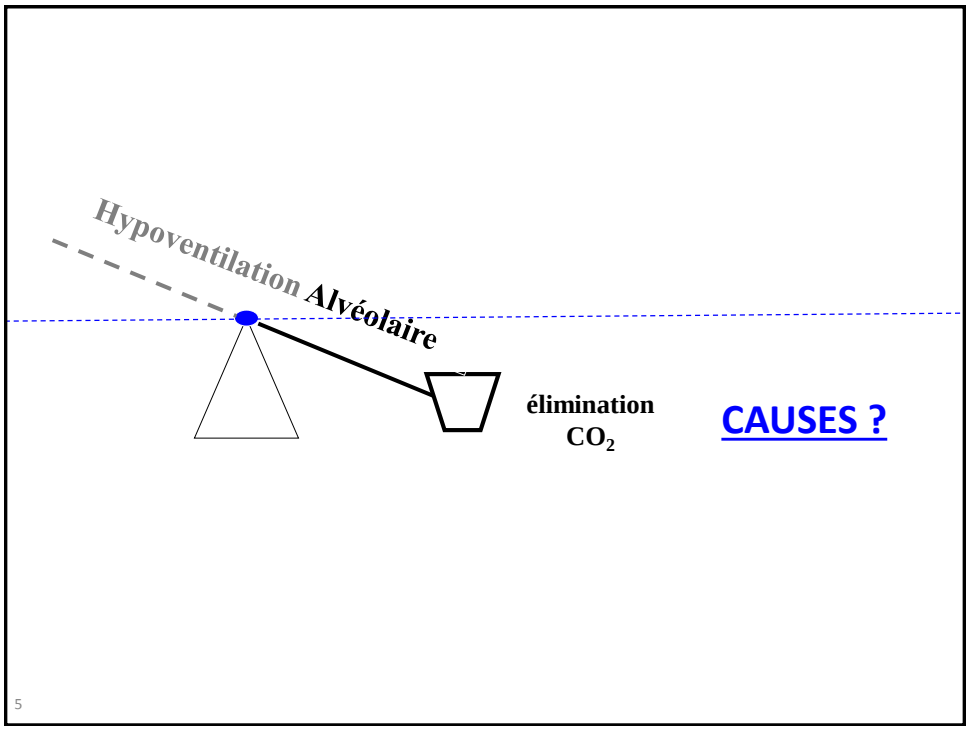
$$PaCO_2 = K (VCO_2 / V_A)$$

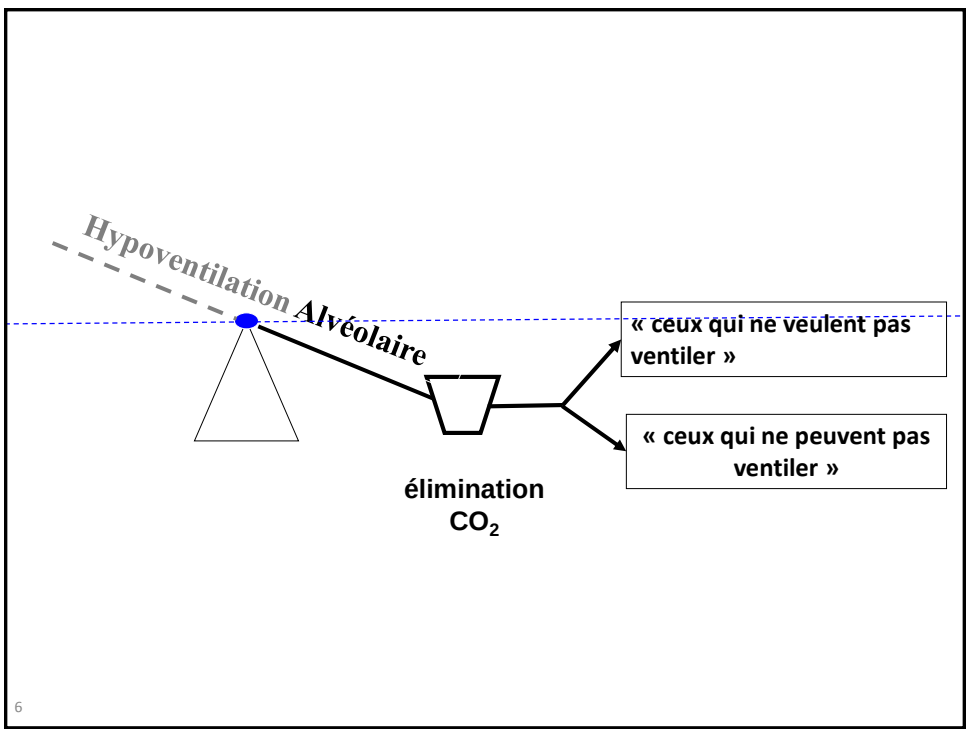
3



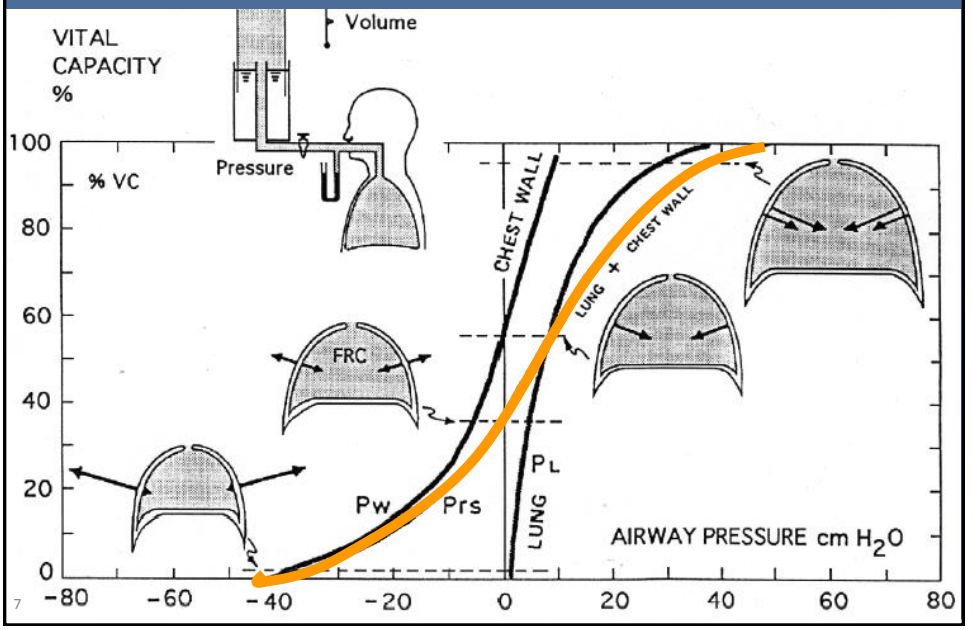
$$PaCO_2 = K (VCO_2 / V_A)$$

4


Hypoventilation Alvéolaire
élimination
CO_2
CAUSES ?
5

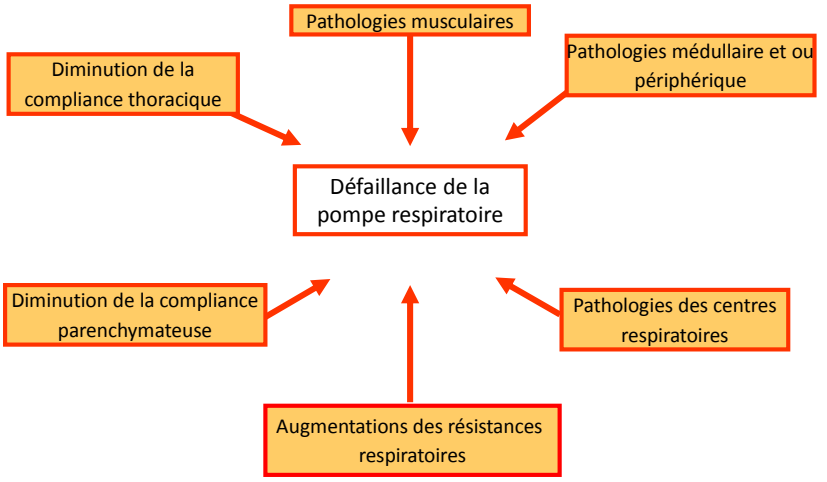

Hypoventilation Alvéolaire
« ceux qui ne veulent pas ventiler »
« ceux qui ne peuvent pas ventiler »
élimination
CO_2
6

Courbe pression volume



7

Mécanismes conduisant à une insuffisance respiratoire hypercapnique chronique



8

Pour quels patients

- « ne peuvent pas.. »
  - Pathologie neuro-musculaire (SLA- traumatismes médullaires)
  - Paralysie diaphragmatique
  - Myopathies, Myasthénie
  - Cyphoscoliose, séquelles de tuberculose…
- « ne veulent pas.. »
  - Hypoventilation alvéolaire primaire – syndrome d'Ondine
  - AVC, poliomyélite bulbaire
  - Malformation d'Arnold – Chiari
- « ne peuvent et ne veulent pas… »
  - BPCO
  - Obésité hypo-ventilation
  - ….

! Non exhaustif et il y a des overlaps…

Exemples d'indications VNI au long cours

Pathologie / Signes	Déformations thoraco-vertébrales Séquelles pleurales	NM peu ou pas évolutifs	NM évolutifs (SLA)	Obésité-hypoventilation	BPCO	Mucoviscidoses Bronchectasies
Signes cliniques + hypercapnie permanente	Oui + $PaCO_2 > 45$	Oui + $PaCO_2 > 45$	Oui + $PaCO_2 > 45$	Oui + $PaCO_2 > 45$ Avec apnées Persistance de l'hypercapnie sous PPC : VNI Sans apnées : VNI	Si traitement médical et O_2 T optimisés : rechercher un SAS Oui + $PaCO_2 > 55$ Désaturations nocturnes : 5' consécutives sous O_2 Ou instabilité exacerbations sévères répétées	Oui + $PaCO_2 > 55$ Ou instabilité exacerbations sévères répétées
Signes cliniques + hypercapnie nocturne	Oui	Oui	Oui	Non	Non	Non
Prévention de l'hypoventilation	Non	Non	Oui CV < 50 % $P_{Imax} < 60$ cmH_2O	Non	Non	Non

Hypoventilation : $PaCO_2 > 45$ et désaturations nocturnes.

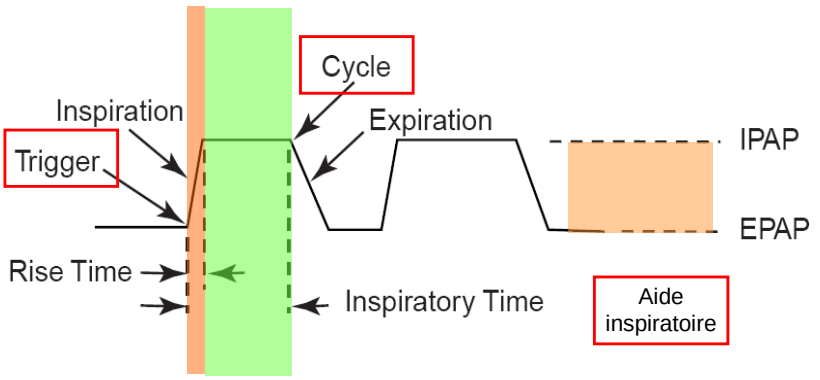
10

https://www.vitalweb.fr/EspacePro/EncycloVNI/

Ventilation synchronisée

11

Principe de la VNI



12

Courtesy JP Janssens

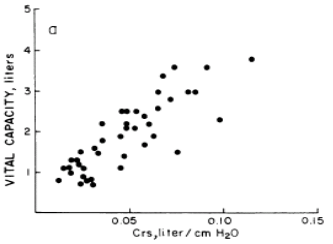
But de la VNI

- Améliorer les gaz du sang diurnes
- Améliorer la SpO_2 nocturne et corriger l'hypoventilation alvéolaire nocturne
- Améliorer les symptômes liés à l'hypercapnie et la dyspnée
- Améliorer la qualité du sommeil

13

The scoliosis of Richard III, 1452-1485 (http://www.thelancet.com/multimedia)

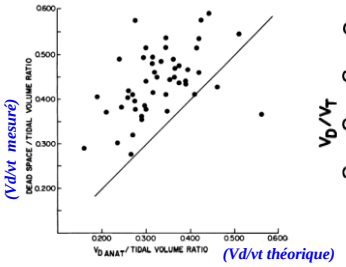
Cyphoscoliose: anomalie de la mécanique

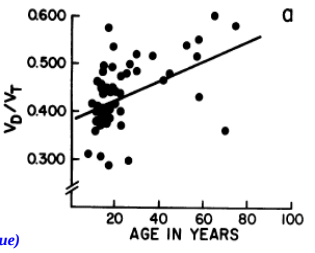


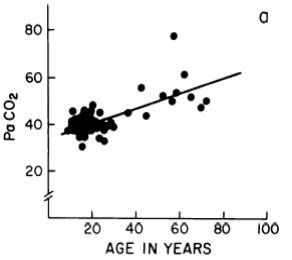
- ↘Compliance du système respiratoire
- ↘ Efficience musculaire
- ↘Croissance pulmonaire et thoracique
- ↘Diminution surface alvéolaire

ER Kafer, JCI 1975

Cyphoscoliose : anomalie de la mécanique





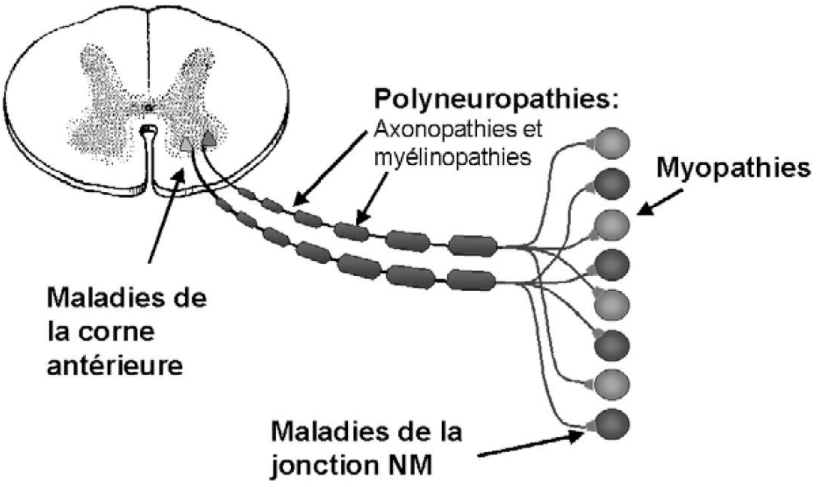


Age : facteur aggravant

↗ $PaCO_2$ 3.23 mmHg/an

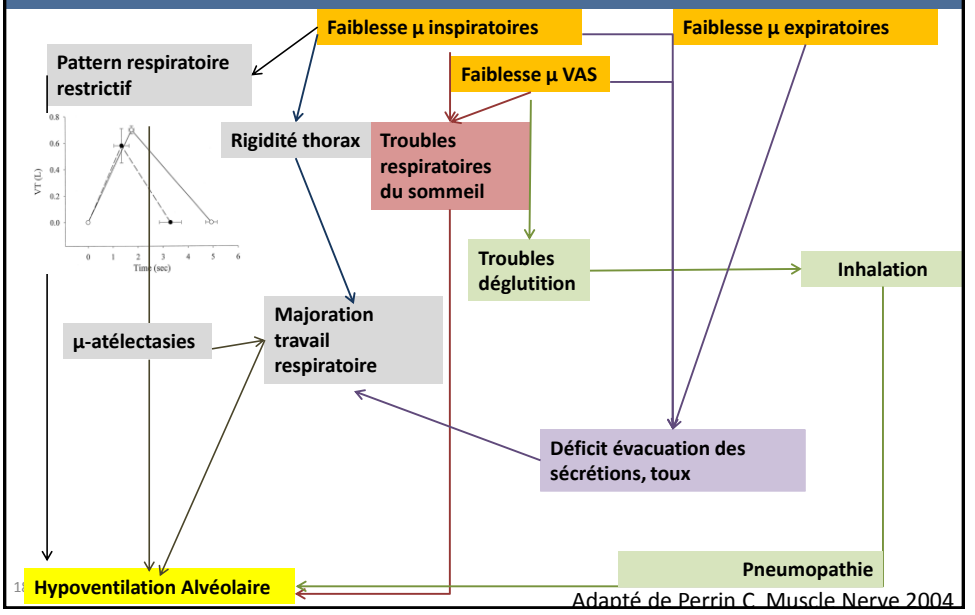
ER Kafer, JCI 1975

Maladies neuro-musculaires



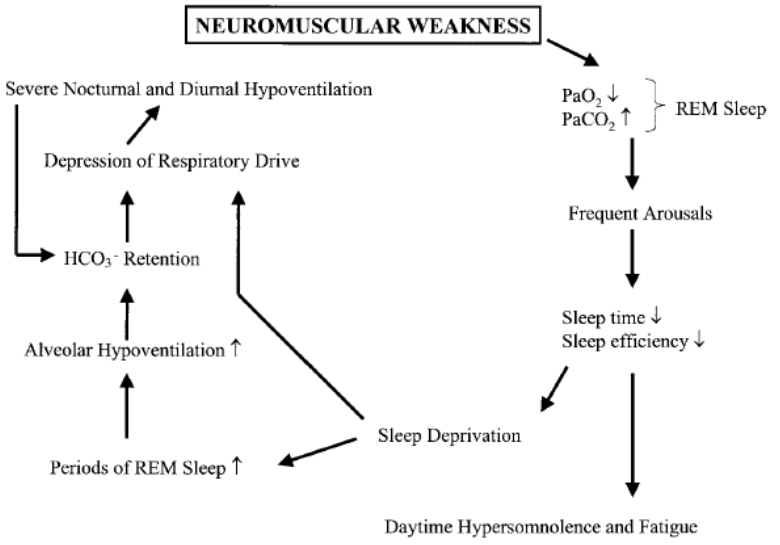
17

Maladies neuro-musculaires



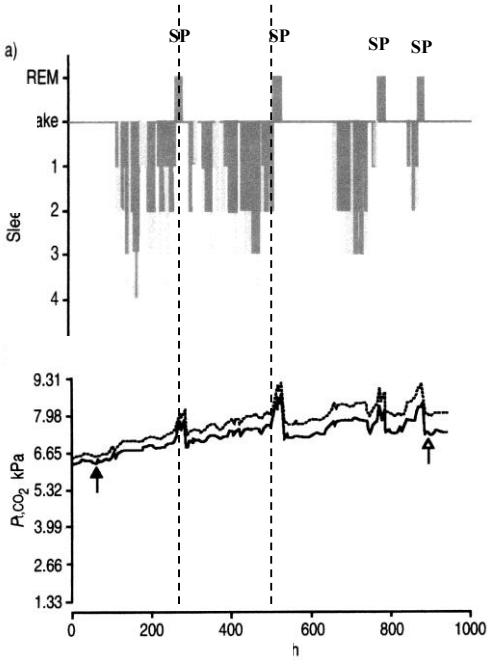
Adapté de Perrin C. Muscle Nerve 2004

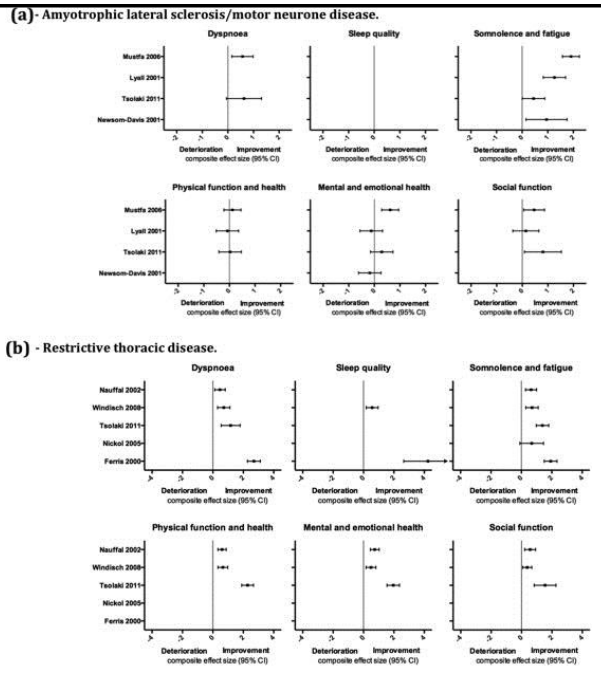
Le désordre respiratoire nocturne précède et potentiellement induit l'apparition de l'insuffisance respiratoire en situation diurne



19

Perrin C. Muscle Nerve 2004

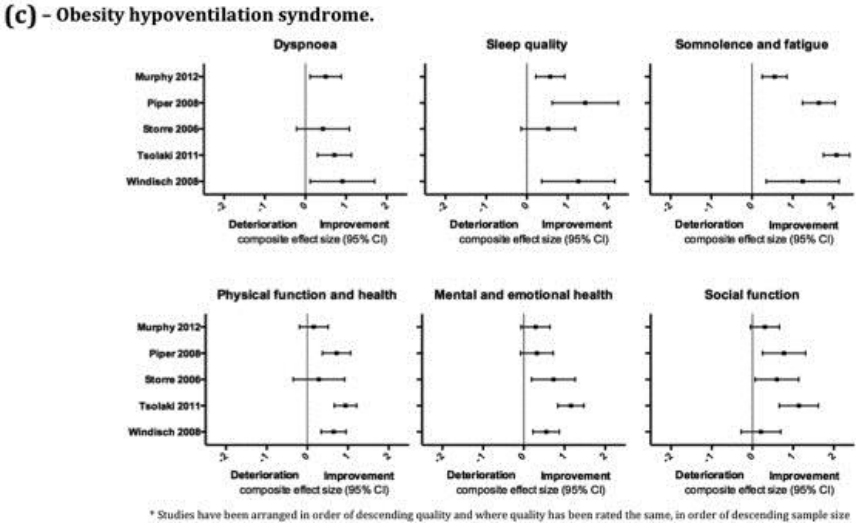




21

Hannan et al. Resp medicine 2014

22



Hannan et al. Resp medicine 2014

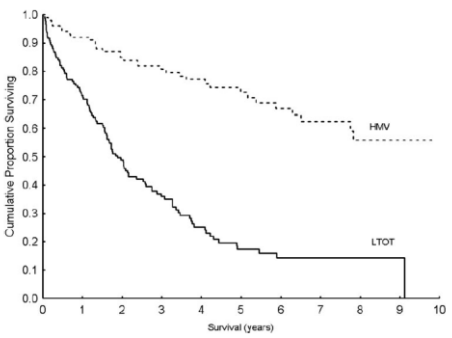
Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Total 18 = Weakest possible 6 = Strongest possible	Global rating
Bourke 2006	Moderate	Strong	Strong	Weak	Strong	Strong	9	Moderate
Mustfa 2006	Moderate	Moderate	Weak	Weak	Strong	Strong	12	Weak
Lyall 2001	Weak	Moderate	Weak	Weak	Strong	Strong	13	Weak
Newsom-Davis 2001	Weak	Moderate	Weak	Weak	Strong	Strong	13	Weak
Butz 2003	Weak	Moderate	Weak	Weak	Strong	Moderate	14	Weak
Bourke 2003	Weak	Moderate	Weak	Weak	Strong	Weak	15	Weak
Raphael 1994	Strong	Strong	Strong	Weak	Strong	Strong	8	Moderate
Ferris 2000	Weak	Moderate	Weak	Weak	Weak	Strong	15	Weak
Borel 2012	Moderate	Strong	Moderate	Moderate	Strong	Strong	9	Strong
Murphy 2012	Moderate	Moderate	Weak	Moderate	Strong	Strong	11	Moderate
Piper 2008	Moderate	Moderate	Weak	Weak	Strong	Strong	12	Weak
Storre 2006	Moderate	Moderate	Weak	Moderate	Strong	Moderate	12	Moderate
Windisch 2008	Moderate	Moderate	Weak	Weak	Strong	Moderate	13	Weak
Tsolaki 2011	Weak	Moderate	Weak	Weak	Strong	Strong	13	Weak
Nauffal 2002	Weak	Moderate	Weak	Weak	Strong	Strong	13	Weak
Domenech-Clar 2003	Weak	Moderate	Weak	Weak	Strong	Moderate	14	Weak
Nickol 2005	Weak	Moderate	Weak	Weak	Moderate	Strong	14	Weak
Guilleminault 1998	Weak	Moderate	Weak	Weak	Strong	Weak	15	Weak

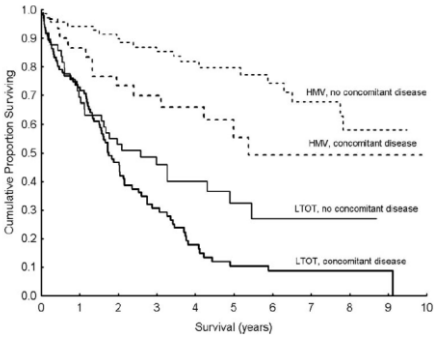
23

23

Efficacité de la VNI au long cours dans les pathologies thoraco-restricitves et les maladies neuro-musculaires.

Oxygenothérapie long terme versus VNI sans la cyphoscoliosis





25

Gustafson T, Chest 2006

Oxygenothérapie long terme versus VNI sans la cyphoscoliosis

Table 2—*Univariate Analysis of Relative Risk of Death Among Patients With Kyphoscoliosis*

Variables	HR	95% CI	p Value
Mechanical ventilation vs oxygen therapy alone	0.22	0.15–0.33	< 0.001
Age > 70 yr	3.34	2.31–4.82	< 0.001
Concomitant respiratory disease	2.43	1.72–3.44	< 0.001
Female gender	1.33	0.93–1.93	0.118
Pao_2,* mm Hg	0.97	0.96–0.99	< 0.001
$Paco_2$,* mm Hg	0.98	0.96–0.99	< 0.01

*Continuous variables.

Table 3—*Multivariate Analyses of Relative Risk of Death Among Patients With Kyphoscoliosis*

Variables	HR	95% CI	p Value
Oxygen therapy alone	1		
HMV	0.30	0.18–0.51	< 0.001
Age > 70 yr	2.63	1.74–3.98	< 0.001
Female gender	1.27	0.85–1.92	0.24
Concomitant respiratory disease	1.43	0.96–2.12	0.078
Pao_2	0.99	0.97–1.02	0.70
$Paco_2$	0.99	0.98–1.02	0.95

26

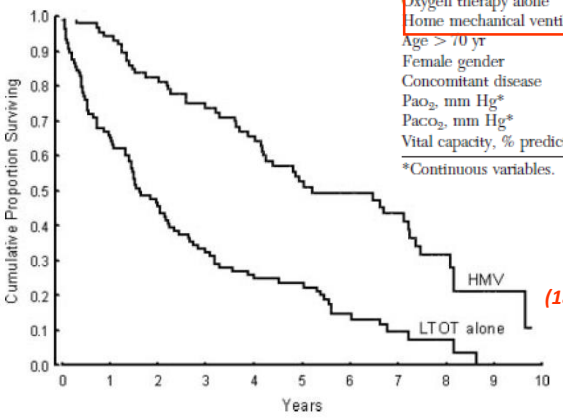
Gustafson T, Chest 2006

Oxygénothérapie long terme versus VNI dans les séquelles mutilantes de Tuberculose

Table 2—*Multivariate Analysis of Relative Risk of Death*

Variables	Hazard Ratio	95% CI	p Value
Oxygen therapy alone	1		
Home mechanical ventilation	0.35	0.17–0.70	0.0028
Age > 70 yr	2.67	1.48–4.83	0.0012
Female gender	0.76	0.50–1.16	0.20
Concomitant disease	0.85	0.45–1.61	0.62
Pao_2, mm Hg*	1.00	0.98–1.03	0.75
$Paco_2$, mm Hg*	0.98	0.95–1.01	0.19
Vital capacity, % predicted*	0.99	0.98–1.01	0.36

*Continuous variables.

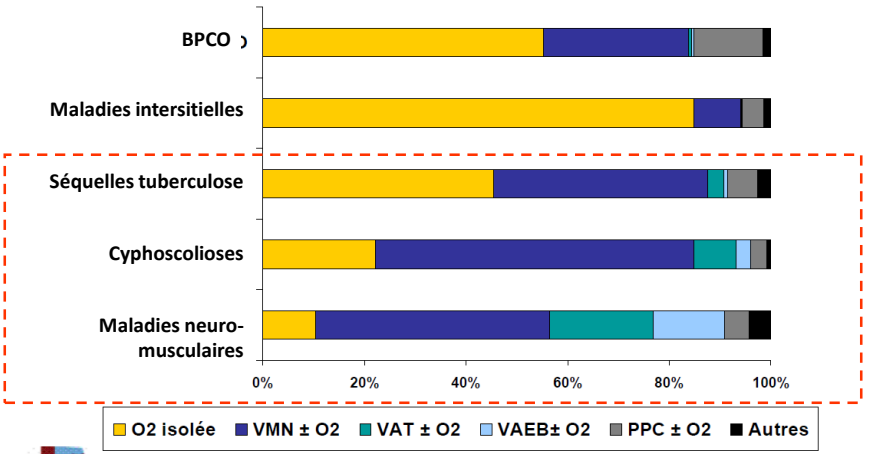


(18% concomitant O_2)

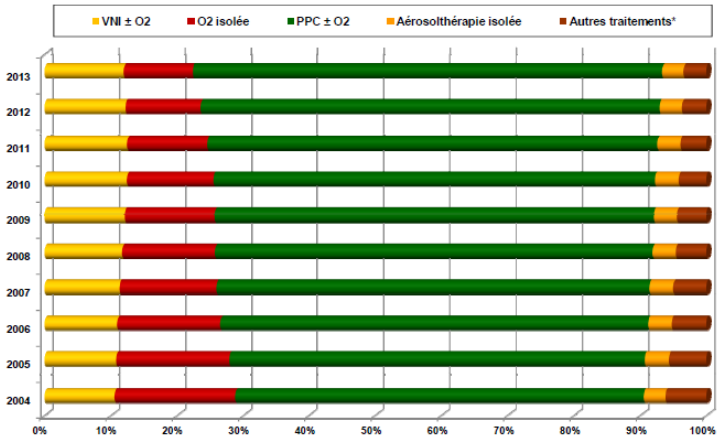
27

Jäger L, Chest 2008

Observatoire ANTADIR (2010)



Observatoire ANTADIR (2013)



* VAEB ± O2, VAT ± O2, PET, aspiration, trachéotomie

Observatoire des patients de l'ANTADIR - 2013

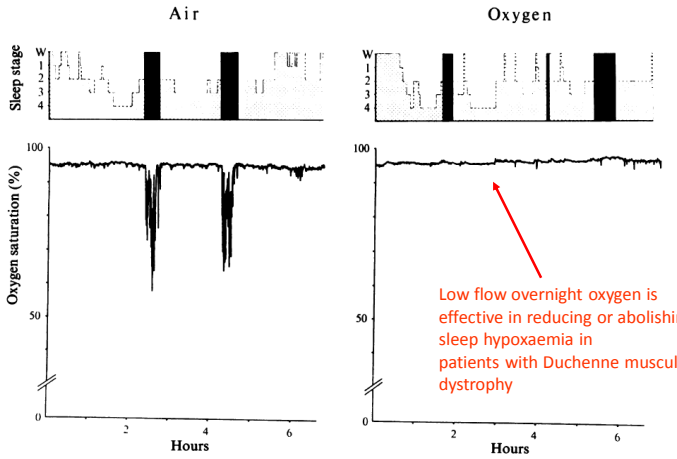
29

Oxygen treatment of sleep hypoxaemia in Duchenne muscular dystrophy

Thorax 1989;**44**:997–1001

P E M SMITH, R H T EDWARDS, P M A CALVERLEY

From the Muscle Research Centre, University Department of Medicine and Regional Thoracic Unit, Liverpool



Low flow overnight oxygen is effective in reducing or abolishing sleep hypoxaemia in patients with Duchenne muscular dystrophy

Overnight oxygen saturation with air and with oxygen in a 16 year old patient with Duchenne muscular dystrophy (vital capacity 1·0 litre, maximum static inspiratory mouth pressure −30 cm H_2O) showing repeated oxygen desaturation during REM sleep corrected by oxygen. Light shaded areas represent wakefulness (W) and stages 1–4 of non-REM sleep; REM sleep is represented by the solid bars.

30

Oxygen treatment of sleep hypoxaemia in Duchenne muscular dystrophy

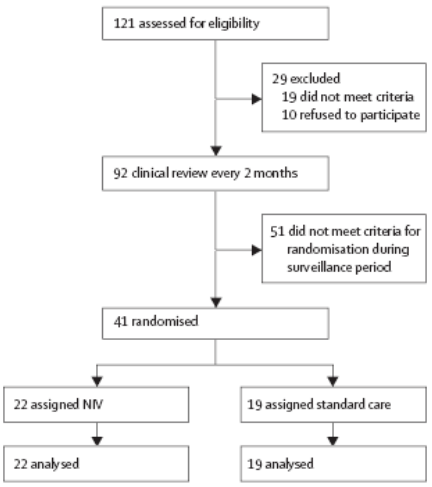
Thorax 1989;**44**:997–1001

P E M SMITH, R H T EDWARDS, P M A CALVERLEY

From the Muscle Research Centre, University Department of Medicine and Regional Thoracic Unit, Liverpool

oxygen only one subject showed any oxygen desaturation exceeding 2·5%. Oxygen desaturation was associated with periods of hypopnoea or cessation of respiratory effort. The mean duration of episodes of hypopnoea and apnoea was prolonged during oxygen breathing by 19% and the mean duration of episodes during REM sleep by 33% (the proportion of REM sleep associated with hypopnoea and apnoea increased in all subjects). Heart rate in non-REM sleep fell by 9·3%; heart rate variation in REM and non-REM sleep was unchanged. These acute studies show that oxygen reduces the sleep hypoxaemia associated with respiratory muscle weakness; whether long term treatment will be possible or desirable is not clear as oxygen potentiates the underlying ventilatory disturbance.

Sclérose latérale amyotrophique

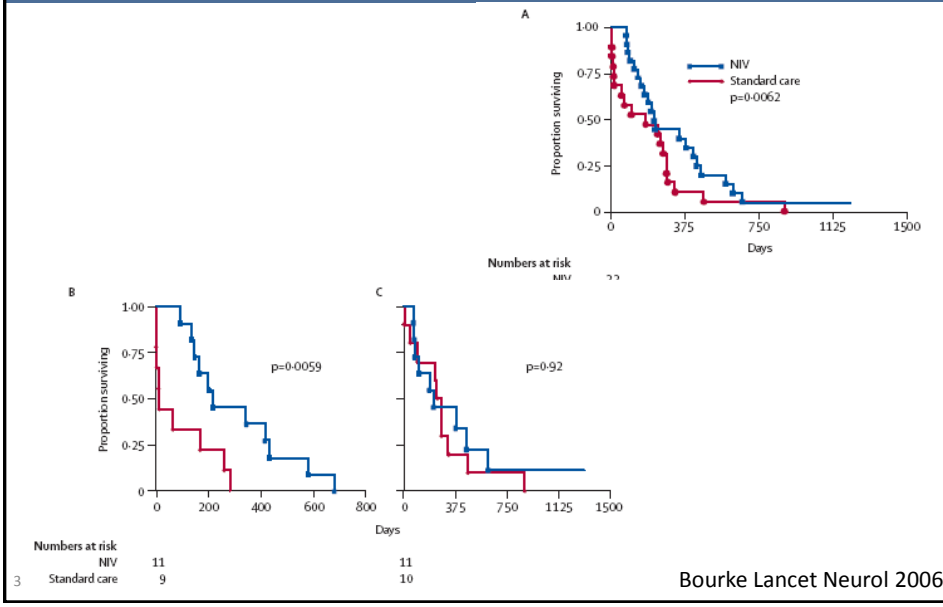


	NIV (n=22)	Standard care (n=19)
Age (years)	63·7 (10·3)	63·0 (8·1)
Sex (male)	14 (64%)	10 (53%)
Disease duration* (years)	1·9 (1·3)	2·0 (1·1)
Riluzole	19 (86%)	17 (89%)
Bulbar score	3·4 (1·7)	3·3 (1·8)
Vital capacity (% predicted)	55·6% (18·7)	48·8% (20·7)
$P_i$max (% predicted)	31·1% (11·0)	31·0% (10·6)
SNIP (% predicted)	22·6% (11·4)	24·4% (10·8)
PaO_2 (kPa)	10·0 (1·8)	10·2 (1·9)
$PaCO_2$ (mm Hg)	6·1 (1·1)	6·4 (1·2)
LEP	0·34 (0·23)	0·36 (0·31)
Body-mass index	21·6 (3·6)	21·5 (3·1)
Mean sleep SaO_2	92·7% (4·0)	91·6% (7·6)
% sleep SaO_2 <90%	27·2% (40·0)	22·9% (36·9)
Total sleep time (min)	201 (114)	273 (116)
REM sleep	5·3% (6·5)	11·9% (9·3)

32

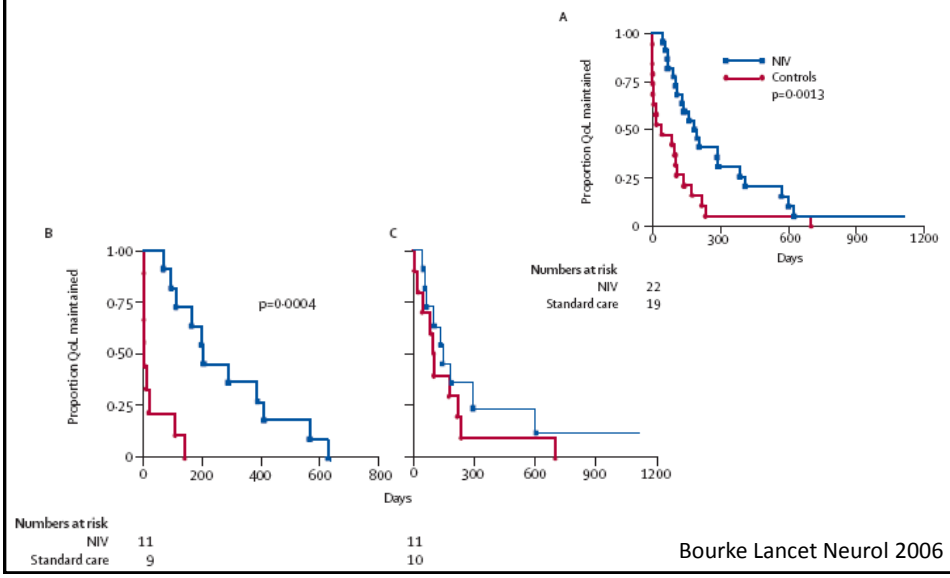
Bourke Lancet Neurol 2006

Sclérose latérale amyotrophique : Survie



Bourke Lancet Neurol 2006

Sclérose latérale amyotrophique : qualité de vie



Bourke Lancet Neurol 2006

INDICATIONS DE VNI:
Maladies Neuro-µr et Déformations Thoraco-vertébrales

1● Signes d'hypoventilation nocturne

et un critère physiologique suivant:

2● Critères physiologiques

a) PaCO2 > 45 mm Hg

b) SpO2 < 88% pdt 5 minutes consécutives (~10% de l'enregistrement)

Consensus SLA. Rev Neurol 2006; 162 : 4S320

- **Symptômes fonctionnels**
  - **. Orthopnée,**
  - **. Céphalées matinales**
  - **. Hypersomnolence diurne**
  - **. Sommeil fragmenté**
  - **. Fatigue matinale**
  - **. Nycturie**
  - **. Syndrome dépressif**

3. Dans le cas des MNM rapidement évolutives:

. CV < 50% pred.

ou

. SNIP ou PI max < 60% pred.

ou

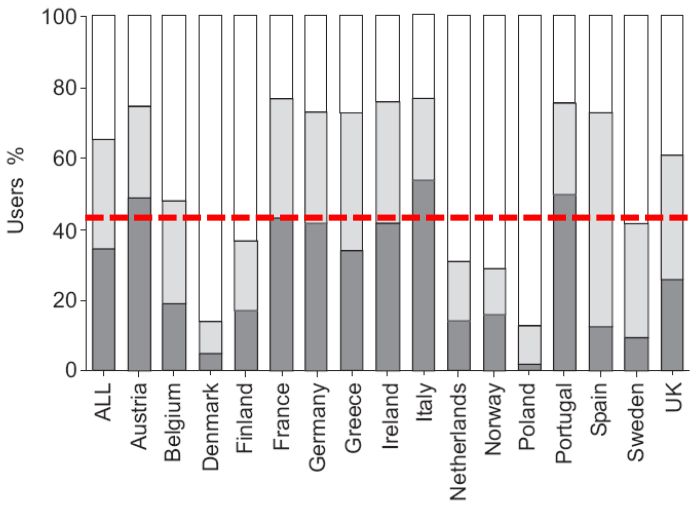
. SpO2 < 90% pdt 5% de l'enregistrement nocturne

Consensus Conference Chest 1999; 116 : 521 et Consensus SLA, Rev Neurol 2006; 162: 4S320

Ventilation non invasive au long cours

chez les BPCO….

Grande hétérogénéité utilisation en Europe Pratiquement pas utilisée aux Etats-Unis !

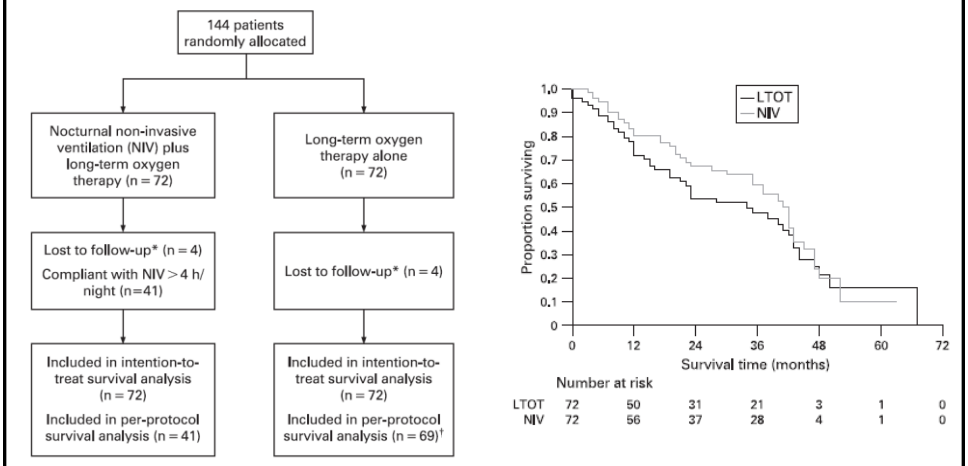


38

Lloyd-Owen et al.Eur Respir J 2005

Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial

R D McEvoy,[1] R J Pierce,[2] D Hillman,[3] A Esterman,[4] E E Ellis,[5] P G Catcheside,[1] F J O'Donoghue,[1,2] D J Barnes,[6] R R Grunstein,[6] on behalf of the Australian trial of non-invasive Ventilation in Chronic Airflow Limitation (AVCAL) Study Group

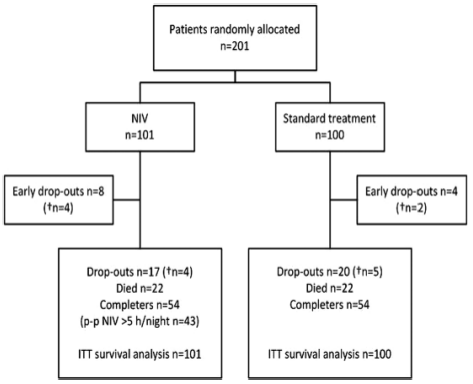


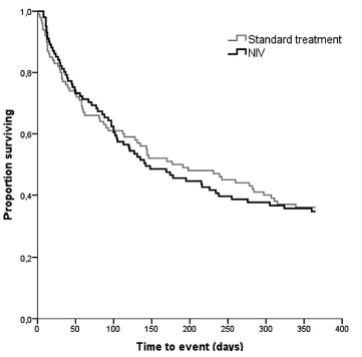
37

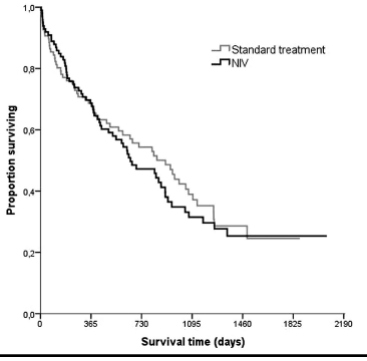
Thorax 2009

Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study

F M Struik,[1,2] R T M Sprooten,[3] H A M Kerstjens,[1,2] G Bladder,[1] M Zijnen,[4] J Asin,[5] N A M Cobben,[3] J M Vonk,[2,6] P J Wijkstra[1,2]



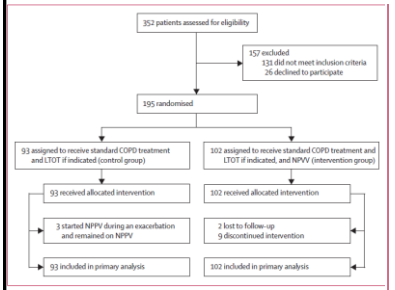


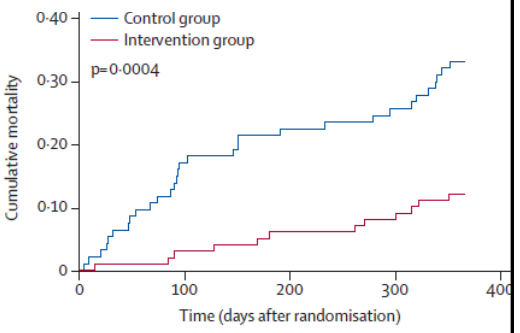


Thorax 2014

Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial

Thomas Köhnlein, Wolfram Windisch, Dieter Köhler, Anna Drabik, Jens Geiseler, Sylvia Hartl, Ortrud Karg, Gerhard Laier-Groeneveld, Stefano Nava, Bernd Schönhofer, Bernd Schucher, Karl Wegscheider, Carl P Criée, Tobias Welte





Number at risk

Control group	93	77	72	69
Intervention group	102	95	92	90

	Baseline	14 days	3 months	6 months	9 months	12 months
All patients	7·9 (0·8)	7·0 (1·1)	7·0 (1·1)	6·7 (1·0)	6·8 (0·9)	6·9 (1·1)
Control group	7·9 (0·7)	7·5 (1·1)	7·4 (0·9)	7·1 (1·0)	7·3 (0·8)	7·4 (1·2)
Non-invasive positive pressure ventilation group	8·0 (0·8)	6·6 (0·9)	6·6 (1·1)	6·4 (0·9)	6·4 (0·9)	6·5 (0·9)

Values are mean (SD).

Table 4: Arterial carbon dioxide pressure (kPa) during the 1-year study

Kohnlein, Resp Lancet 2014

Quelle conclusion

	Number of patients		Mean age (years)		FEV, litre (% predicted)		BMI (kg/m²)		$PaCO_2$ (kPa)		Settings and compliance, for NIV	Deaths (12 months)	
	NIV	Control	NIV	Control	NIV	Control	NIV	Control	NIV	Control		NIV	Control
Köhnlein et al, 2014[5]	102	93	62·2	64·4	26%	27%	24·8	24·5	7·8	7·7	I=21·6 (4·7); E= 4·8 (1·6); R=16·1 (3·6); C=5·9 (3·1)	11·8%	33%
Struik et al, 2014[6]	101	100	63·9	63·5	0·67 (26%)	0·65 (26%)	24·6	24·8	7·9	7·7	I=19·2 (3·4); E=4·8 (1·0); R=15 (3); C=6·3 (2·4)	30%	29%
McEvoy et al, 2009[4]	72	72	68·8	67·2	0·55 (23%)	0·63 (25%)	25·4	25·5	7·25	7·0	I=12·9 (10·9–14·3); E=5·1 (4·8–5·3); R= nil; C=4·5 (3·2)	17%*	22%*
Windisch et al, 2005[7]	34	..	63·4	..	1·03	..	28·3	..	7·1	..	I=27·7 (5·9); E=0; R=20·8 (2·5); C=not stated	14%† 3%‡	..
Clini et al, 2002[2]	43	47	64	66	27%	31%	26	25	6·7	6·6	I=14 (3); E=2 (1); R=8; C=9 (2)§	18%	17%

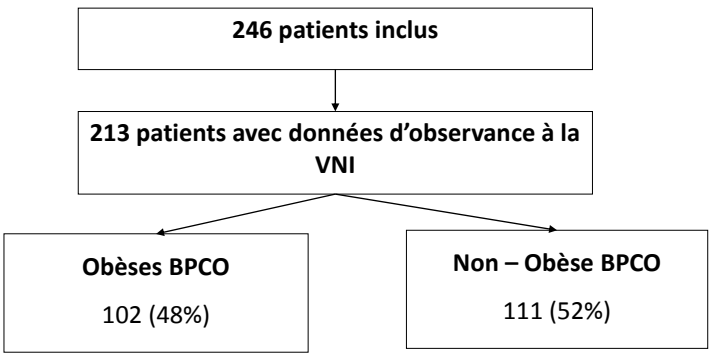
Data are mean (SD or range), unless otherwise indicated. NIV=non-invasive ventilation. FEV_1=forced expiratory volume in 1 s. BMI=body-mass index. I=inspiratory positive airway pressure cm H_2O. E=expiratory positive airway pressure cm H_2O. R=back up rate breaths per minute. C=compliance in h. *personal communication from D McEvoy. †2-year mortality as published. ‡1-year mortality (personal communication from W Windisch). §Mean daily use in compliant patients.

Table: **Summary of key data from long-term studies of domiciliary NIV in COPD**

42

Elliot, Resp Lancet 2014

BPCO et BPCO



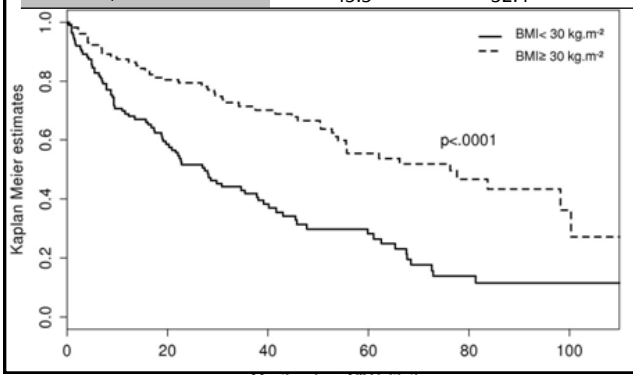
Médiane de suivi = 48 [28 ; 73] months

46 % de décès à la date de censure

Borel, respiology 2014

Suivi, observance et mortalité

	Ensemble des patients n=213	BPCO Obèse n=102	BPCO non Obèse n=111	p-value
Observance moyenne quotidienne VNI, *h/jour*	5.9 [3.9 ; 8.3]	6.9 [4.1 ; 8.6]	5.3 [3.2 ; 7.9]	0.007
Suivi médian, mois	47.7 [27.8 ; 73]	55.9 [33.1 ; 77.7]	38.5 [22.6 ; 69.7]	0.002
Mortalité, *%*	45.5	32.4	57.7	0.0002



Borel, respiology 2014

INDICATIONS DE VNI: BPCO

Echec de l ’Oxygénothérapie Longue Durée

ET

Signes cliniques d ’hypoventilation alvéolaire nocturne

ET

PaCO2 > 55 mmHg

OU

Echec de l ’Oxygénothérapie Longue Durée

ET

PaCO2 > 55 mmHg et instabilité traduite par une fréquence élevée des hospitalisations pour décompensation

Recommandations SPLF. Rev Mal Respir 2003

Mucoviscidose et VNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung function - chest physiotherapy including directed cough	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 FEV_1	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.41, 0.31]
1.2 FVC	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.35, 0.38]
1.3 FEF_{25-75}	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.39, 0.33]
2 Lung function - chest physiotherapy including PEP	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 FEV_1	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.43, 0.30]
2.2 FVC	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.37, 0.35]
2.3 FEF_{25-75}	3	118	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.36, 0.36]
3 Respiratory muscle strength (cmH_20)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 PImax	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 PEmax	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Airway resistance % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Oxygen saturation during airway clearance (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Oxygen saturation during airway clearance (change in SpO_2 % during treatment)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Oxygen saturation after airway clearance (SpO_2) - chest physiotherapy including directed cough	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Oxygen saturation after airway clearance (SpO_2) - chest physiotherapy including PEP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9 Sputum wet weight (g) - chest physiotherapy including directed cough	3	118	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-3.06, 1.67]
10 Sputum wet weight (g)- chest physiotherapy including PEP	3	118	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-3.96, 0.89]

46

Ventilation non invasive au long cours

Syndrome Obésité Hypoventilation…

Syndrome Obésité hypoventilation (SOH):

Faut-il faire évoluer la définition?

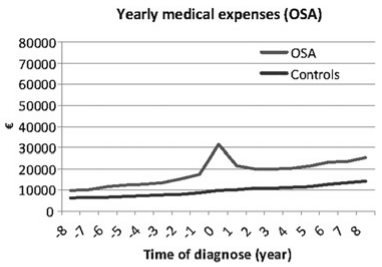
Hart N, Mandal S, Manuel A, Mokhlesi B, Pépin JL, Piper A, Stradling J. Thorax 2013/08/28.

- **IMC ≥ 30 kg/m²**
- **$PaCO_2$ diurne > 45mmHg**
- **sans autre cause d'hypoventilation**
- **80 à 90% SAOS**

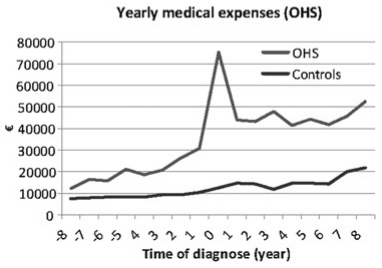
- **ou [$HCO3^-$] > 27 mmol/L ou excès de base + 3 mmol/L**

« [$HCO3^-$], peut-être vu comme l'HbA1c du CO_2, en l'absence d'autre facteurs confondants sur l'équilibre acido-basique (alcalose métabolique) »

SOH est associé à une morbi-mortalité importante et des coûts de santé élevés



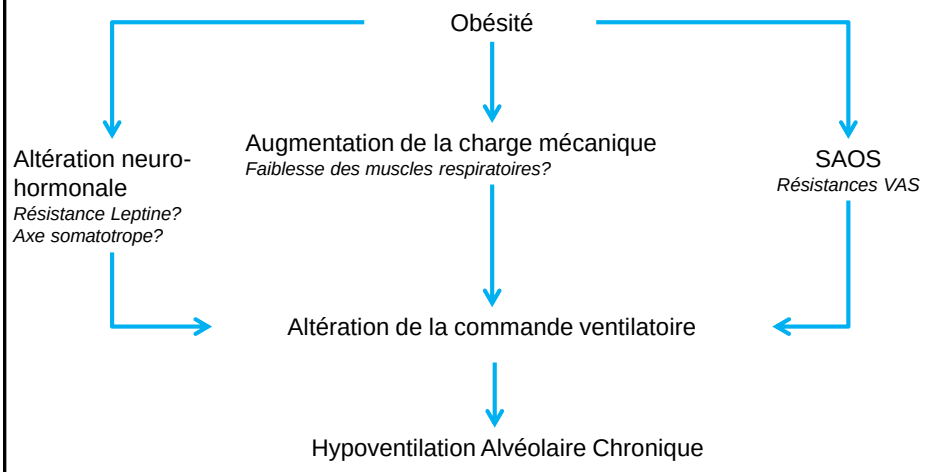
- **Mortalité à 2 ans SAS vs contrôles 6.1% vs 4.4%, p<0.0001**



- **Mortalité à 2 ans OHS vs contrôles: 25.4% vs 6.8%, p<0.001**

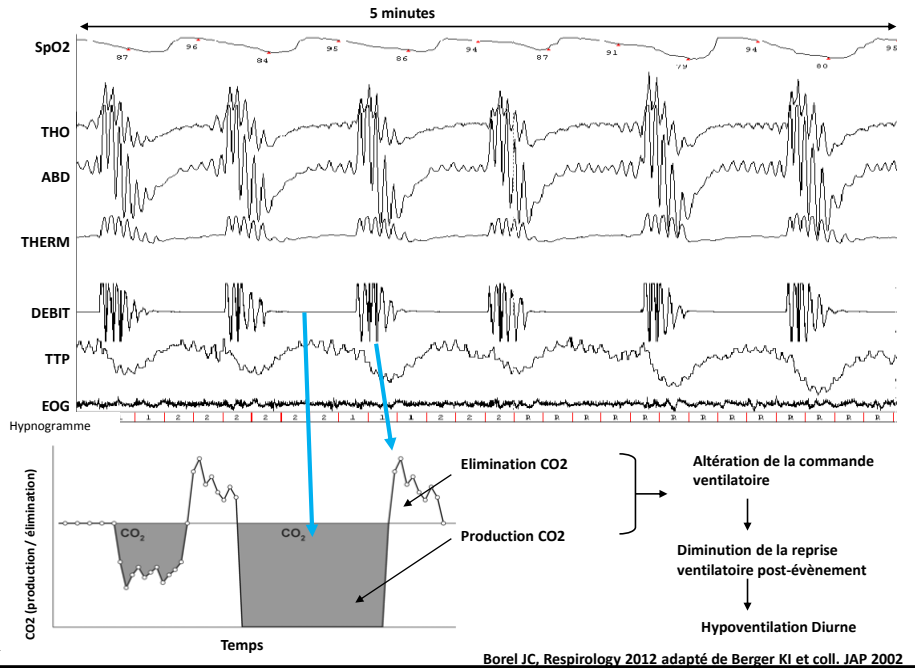
Jennum P et al. Thorax 2011

Mécanismes de l'hypercapnie diurne dans le SOH (état stable)



Adaptée de Mokhlesi B Respiratory Care 2010; 55: 1347-62

Syndrome d'apnées obstructives du sommeil

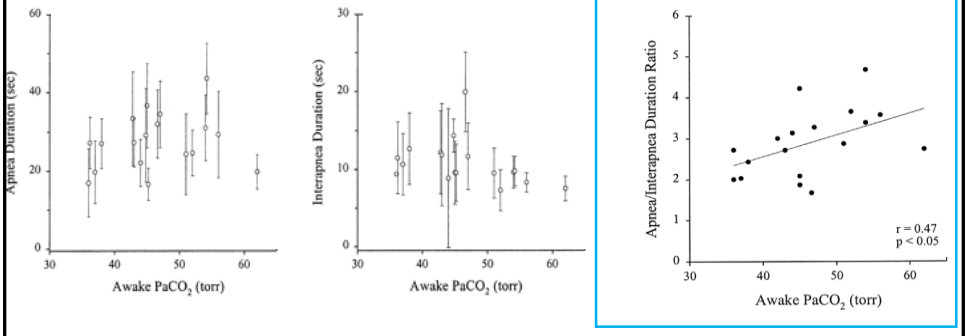


51

Borel JC, Respirology 2012 adapté de Berger KI et coll. JAP 2002

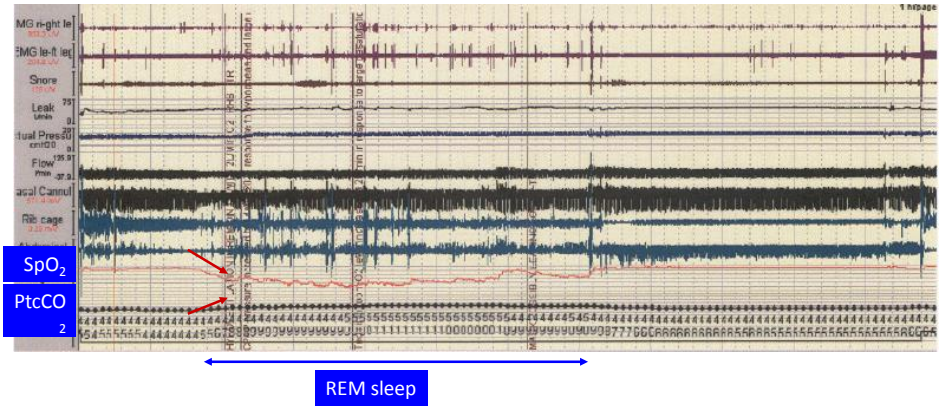
Hypercapnie diurne associé au SAOS

Rapport (Durée de l'apnée / Durée reprise ventilatoire)



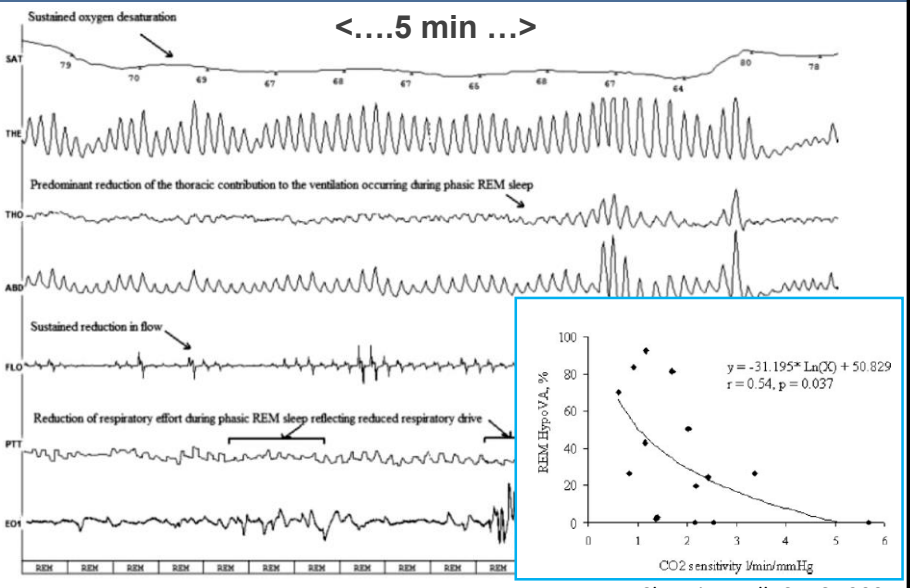
Ayappa I et Coll. AJRCCM 2002

Réponse incomplète à la PPC au cours du sommeil paradoxal



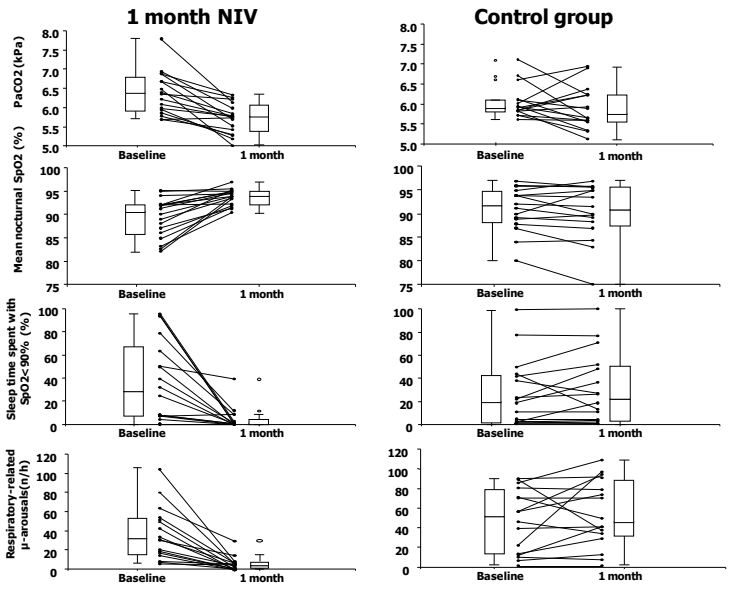
Crummy, Thorax 2008

Hypoventilation au cours du sommeil paradoxal



Chouri et coll, CHEST 2007

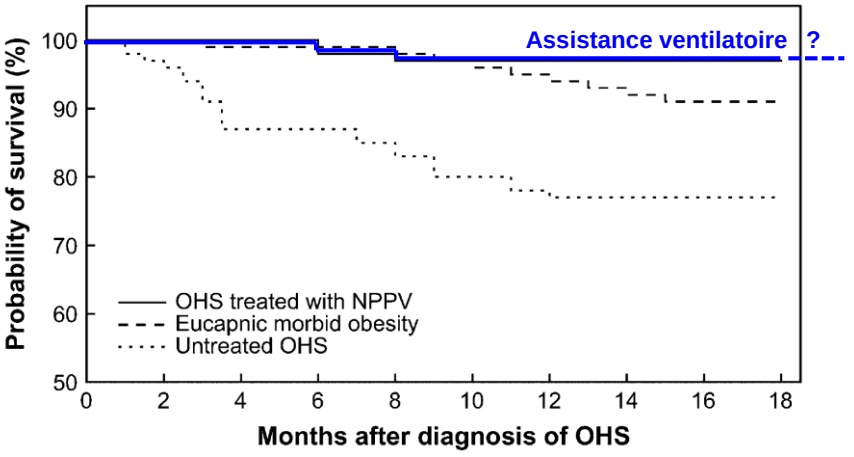
54



Borel JC et al. Chest 2012

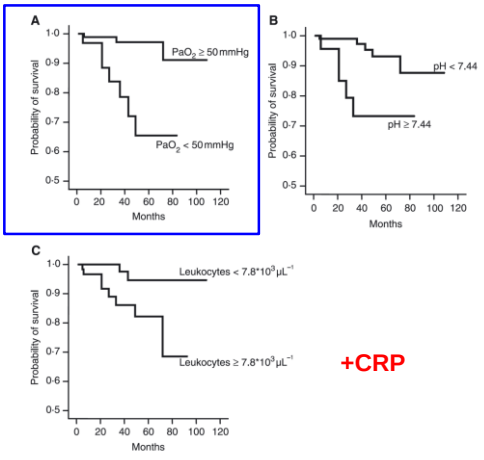
55

Assistance ventilatoire non-invasive, traitement de première ligne

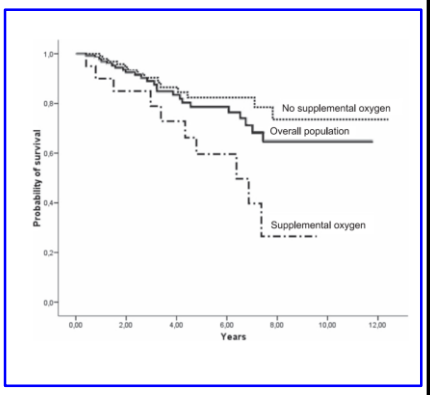


Adapté par B Mokhlesi Respir Care 2010 (Nowbar 2004 et Budweiser 2007)

Impact de la sévérité de l'atteinte respiratoire sur le pronostic

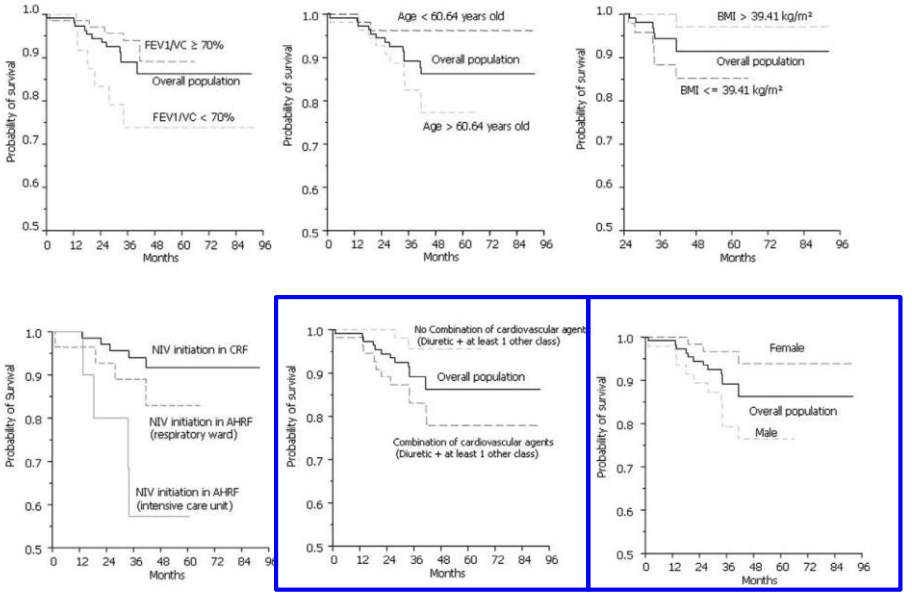


Budweiser S et al. J Int Med 2007



Priou P et al. CHEST 2010

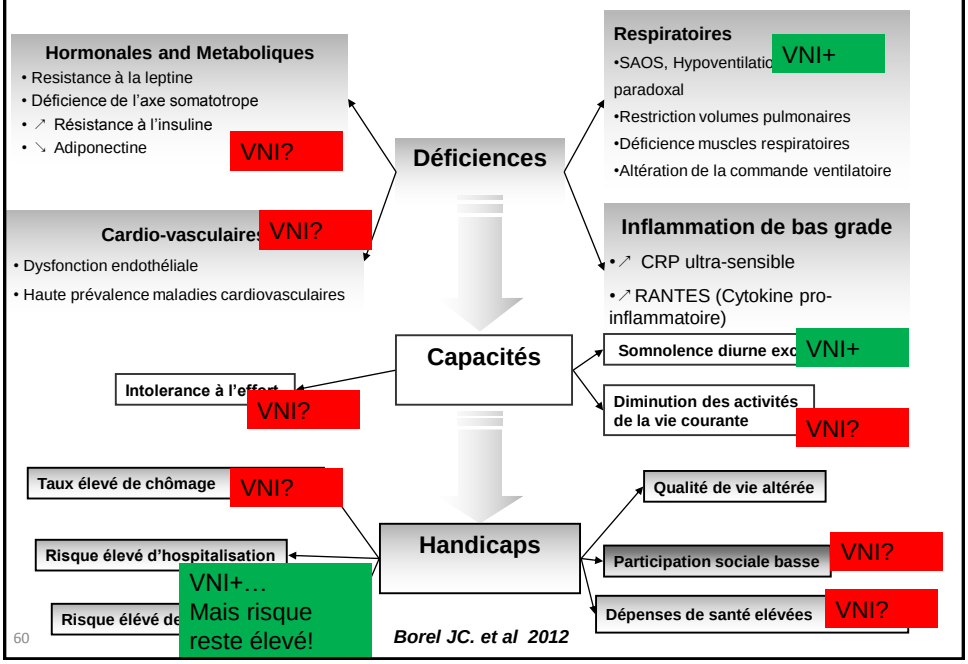
Impact du mode de présentation clinique (aigu versus chronique) et des comorbidités



59

Borel JC et al. Plos One 2013

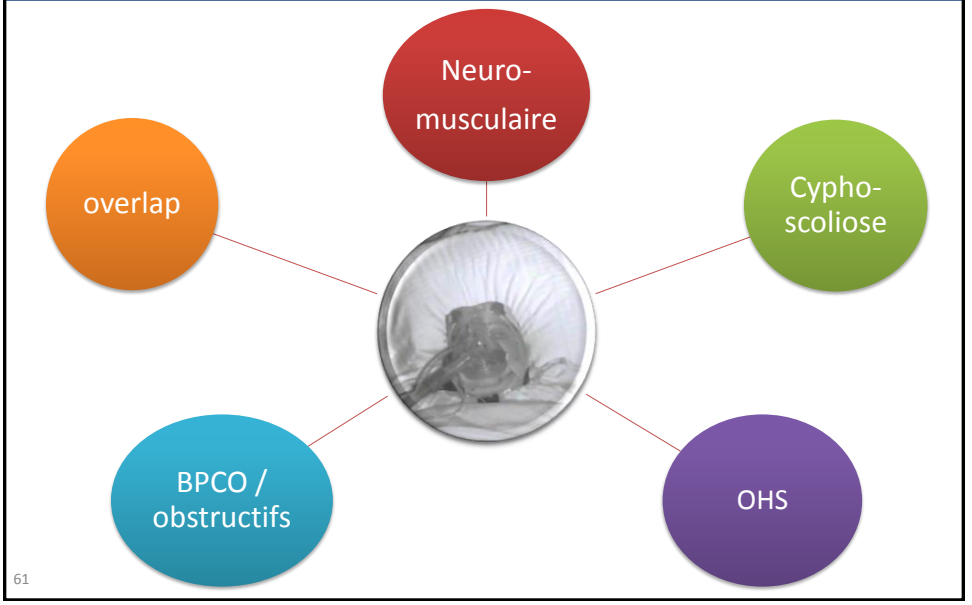
SYNDROME OBÉSITÉ-HYPOVENTILATION



60

Borel JC. et al 2012

Conclusion



61

62