Advances in non invasive ventilation

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Overview

- *Introduction*
- *Ventilators and interfaces in NIV*
- *Modes in NIV*
- *CPAP and its modifications*
- *AutoPAP*
- *BPAP*
- *PAV*
- *VT PSV and AVAPS*
- *ASV*
- *Summary of NIV treatment of central sleep apnea and its rationale*

Basic differences

- **Mechanical ventilation**
- Sedated patient with a reduced level of consciousness
- No problem with interface
- More risk of infection

- **NIV**
- Conscious patient – more sensitive
- Careful selection of ventilator-patient interface needed
- Risk of infection is less

Ventilators used in NIV

- *Typical ICU ventilators* – monitoring possible, two separate circuits
- *Portable home ventilators*
- *Hybrid ventilators* – can be used in intubated and non intubated patients

Interfaces in NIV

- Nasal – nasal mask, plugs, pillows
- Oral – mouthpiece
- Facial – oronasal mask, full face mask, mask with helmet

Modes used in NIV

- Continuous positive airway pressure (CPAP)
- Proportional assist ventilation (PAV)
- Bi-level positive airway pressure (BPAP)
- Volume targeted pressure support ventilation (VT PSV)

  includes Average volume assured pressure support

  ventilation(AVAPS^{TM}), intelligent volume assured PS(iVAPS^{TM})
- Adaptive servo (support) ventilation (ASV)

Modes used in NIV (modifications)

- Auto-titrating positive airway pressure (APAP)
- Pressure relief systems in CPAP (EPR™, C flex) in APAP (A flex™) BPAP (Bi flex™)

NIV jargon

- VPAP ™ series – BPAP series from ResMed
- VPAP-ST A – iVAPS (intelligent volume assured pressure support)
- Malibu – auto adjusting bilevel device in the VPAP series

NIV in acute cardiogenic pulmonary edema

- Evidence from 34 studies
- CPAP and NIPPV better than standard therapy
- However no significant difference between NIPPV vs. CPAP
- Primary outcome – in hospital mortality
- Secondary- need for intubation and MV, MI, ICU and hospital stay
- Tertiary outcome – PaO_2, $PaCO_2$, HR, BP

NIV in chronic setting

Sleep-related disordered breathing

Central sleep apnea syndromes *Normal nocturnal CO_2*	Sleep related hypoventilation disorders *Increased nocturnal CO_2*
• Primary central sleep apnea • CSA due to Cheyne stokes breathing • CSA due to high altitude periodic breathing • CSA due to opioids, drugs	• Ventilatory control abnormalities • Chest wall disorders • Neuromuscular disorders • Lung diseases

Complex sleep apnoeas

- Central sleep apnoeas which arise during, persist or has been present before
- Transiently it may arise when CPAP is instituted for OSA
- Persist from before CPAP institution

Summary of PAP devices

Positive Pressure Modality	General Features
Continuous positive airway pressure (CPAP)	• The clinician may prescribe the CPAP level. • Positive pressure delivered during inspiration equals that delivered during expiration.
"Pressure-relief" CPAP	• The clinician may prescribe the CPAP level. • Positive pressure delivered during expiration decreases in proportion to the increasing expiratory airflow early in expiration and increases back to the prescribed CPAP level as the patient's expiratory airflow decreases with the approaching end of exhalation. • The clinician can set the degree of pressure relief.
Bilevel positive pressure	• The clinician may prescribe the level of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). • EPAP may be set independent of IPAP, but EPAP may not be higher than IPAP. • Some models permit prescribing a timed backup rate.
Pressure-relief bilevel positive pressure	• Same as for bilevel positive pressure except the clinician may also prescribe inspiratory and expiratory pressure relief.
Autotitrating CPAP	• CPAP level fluctuates over the period of use according to a manufacturer-designed algorithm. • The clinician may prescribe the minimum-maximum range within which the pressure may fluctuate.
Autotitrating bilevel positive pressure	• IPAP and EPAP levels fluctuate over the period of use according to a manufacturer-designed algorithm. • The clinician may prescribe the minimum EPAP and maximum IPAP within which the pressure may fluctuate. • The clinician may prescribe the maximum IPAP-EPAP gradient ("pressure support") up to a manufacturer-designed limit.
Adaptive servo-ventilation	• The clinician prescribes an EPAP level. • Different brands have different algorithms for establishing the minimum and maximum IPAP level and minimum level of pressure support. • In general, the pressure support varies to maintain a target ventilation or a target airflow; there is a default timed backup rate.

Sanders MH. Strollo PJ et al. Chapter 25**. Sleep Disorders Medicine**

Summary of PAP devices

- CPAP: positive pressure in inspiration equals expiration
- “pressure relief” CPAP : positive

CPAP

- Pneumatic splinting
- Widening of larger airway due to lung inflation (increase in lung volume) by positive airway pressure and pull down (similar to a “tracheal tug”)
- First introduced in 1981
- Established as a standard care for OSA

Why not CPAP?

- Poor compliance to CPAP is the major problem. Hence investigators have tried to come up with devices which have better acceptability from patients
- Adherence to CPAP varies from 40 to 70% despite proven efficacy

Variations of CPAP modalities

- Pressure ramping
- Pressure relief CPAP (C flex, C flex+), BPAP (Bi flex). Auto-PAP(A flex)
- Empirical CPAP therapy!

Pressure relief

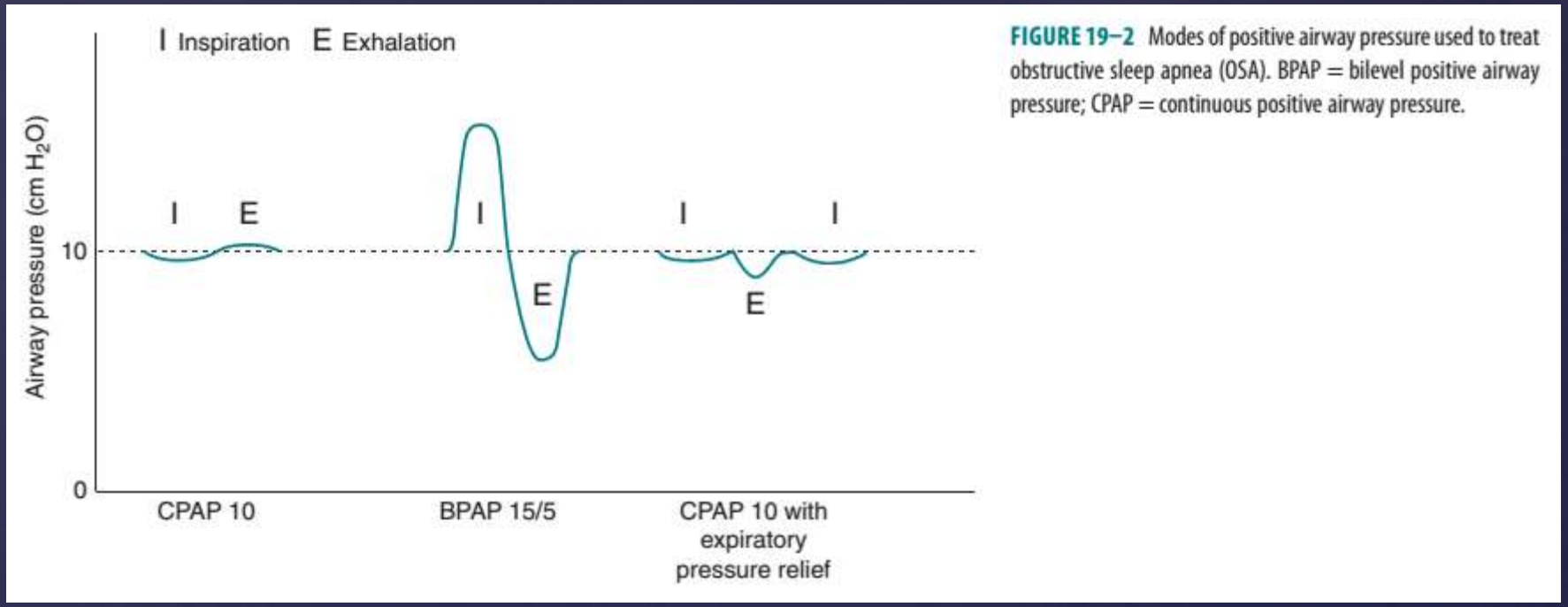


FIGURE 19–2 Modes of positive airway pressure used to treat obstructive sleep apnea (OSA). BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

Fundamentals of sleep medicine by Richard B Berry. Chapter 19. Elsevier

EPR™

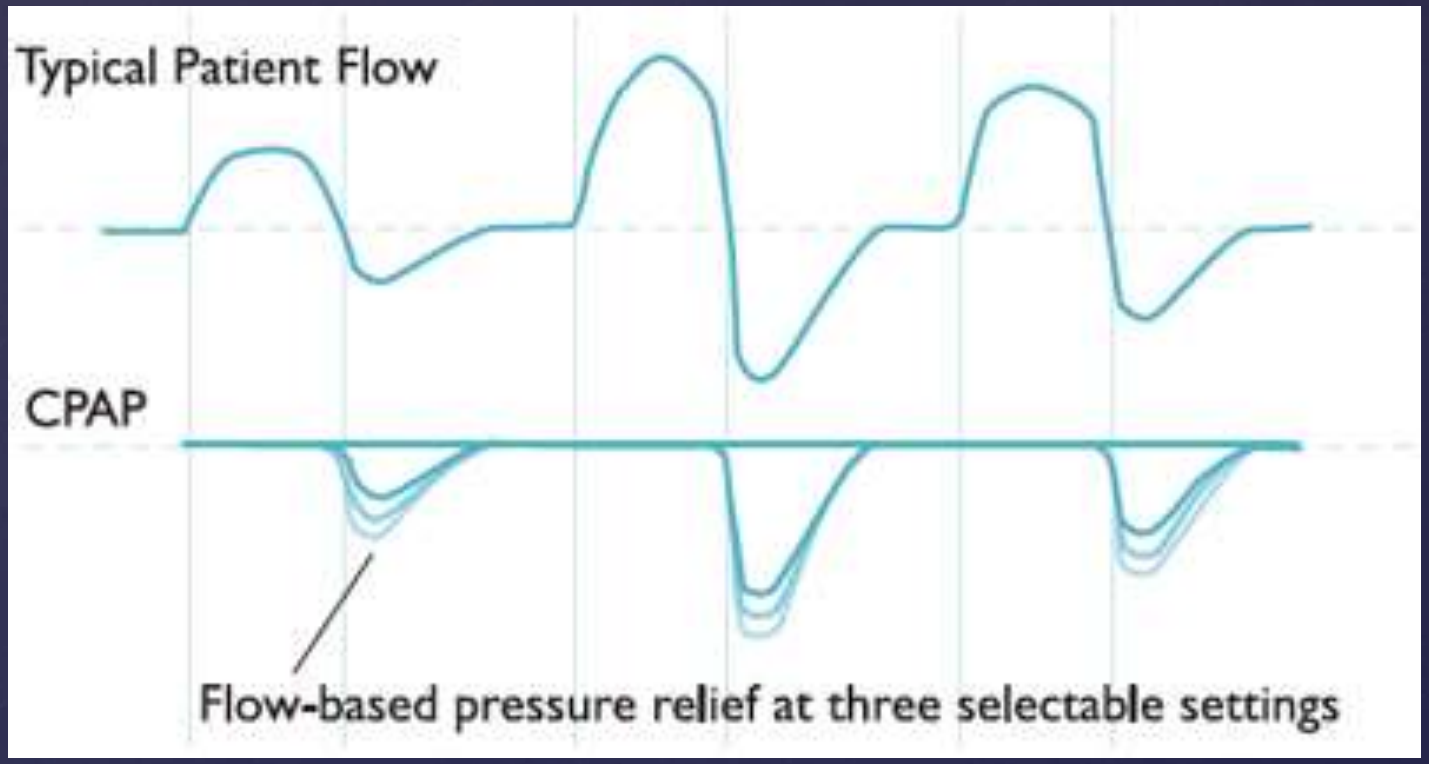
- EPR™ (ResMed) – expiratory pressure relief
- When patient exhales, machine detects and allows pressure drop. *Mild* (1cm of water) *moderate* (2cm) and *maximum* comfort (3cm) pressure drop can be set
- *Ramp or full control* : the EPR pressure drop can be set for full time of sleep or only during the early stages of sleep when patients are alert and experience maximum difficulty in sleeping with CPAP

http://www.resmed.com/us/assets/html/device_epr/epr.html?nc=patients

Flex technologies

- Digital auto-trak and sensitivity™ technology.
- It has an algorithm that tracks each breath and detects the onset of inspiration and expiration – even in the presence of mask leak
- Response then occurs by providing an adaptive pressure relief when the patient needs it.

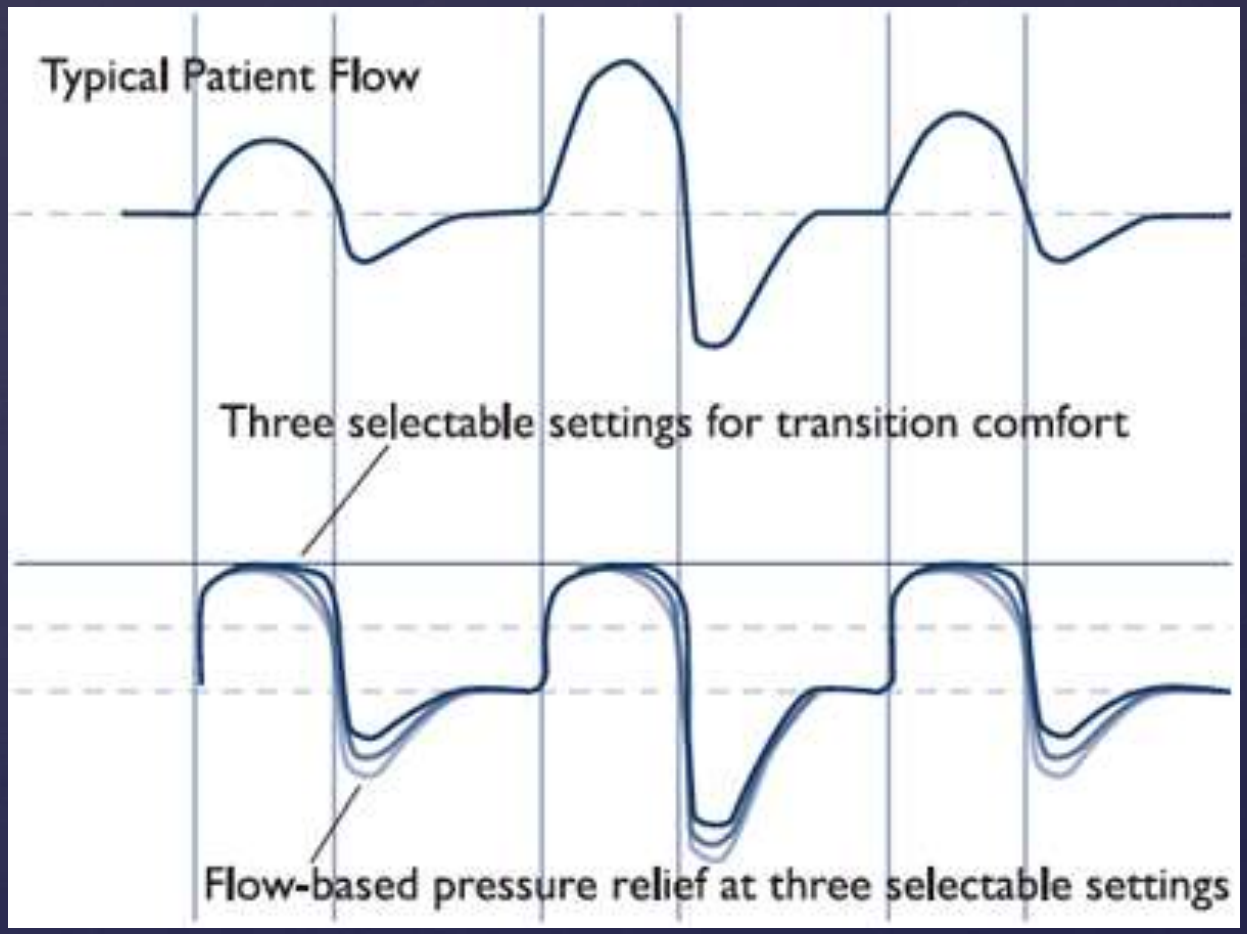
C Flex ™



Pressure relief occurs at beginning of exhalation and returns back to CPAP level before next inspiration. The level of pressure relief varies based on the patient's expiratory flow and which of the three C-Flex settings has been selected.

Cflex.respironics.com

C Flex+ TM



C-Flex+ softens the pressure transition from inhalation to exhalation to provide additional comfort in fixed-CPAP mode

Cflexplus.respironics.com

Bi Flex™

- Aims to make BiPAP therapy more comfortable
- Pressure relief at three possible points

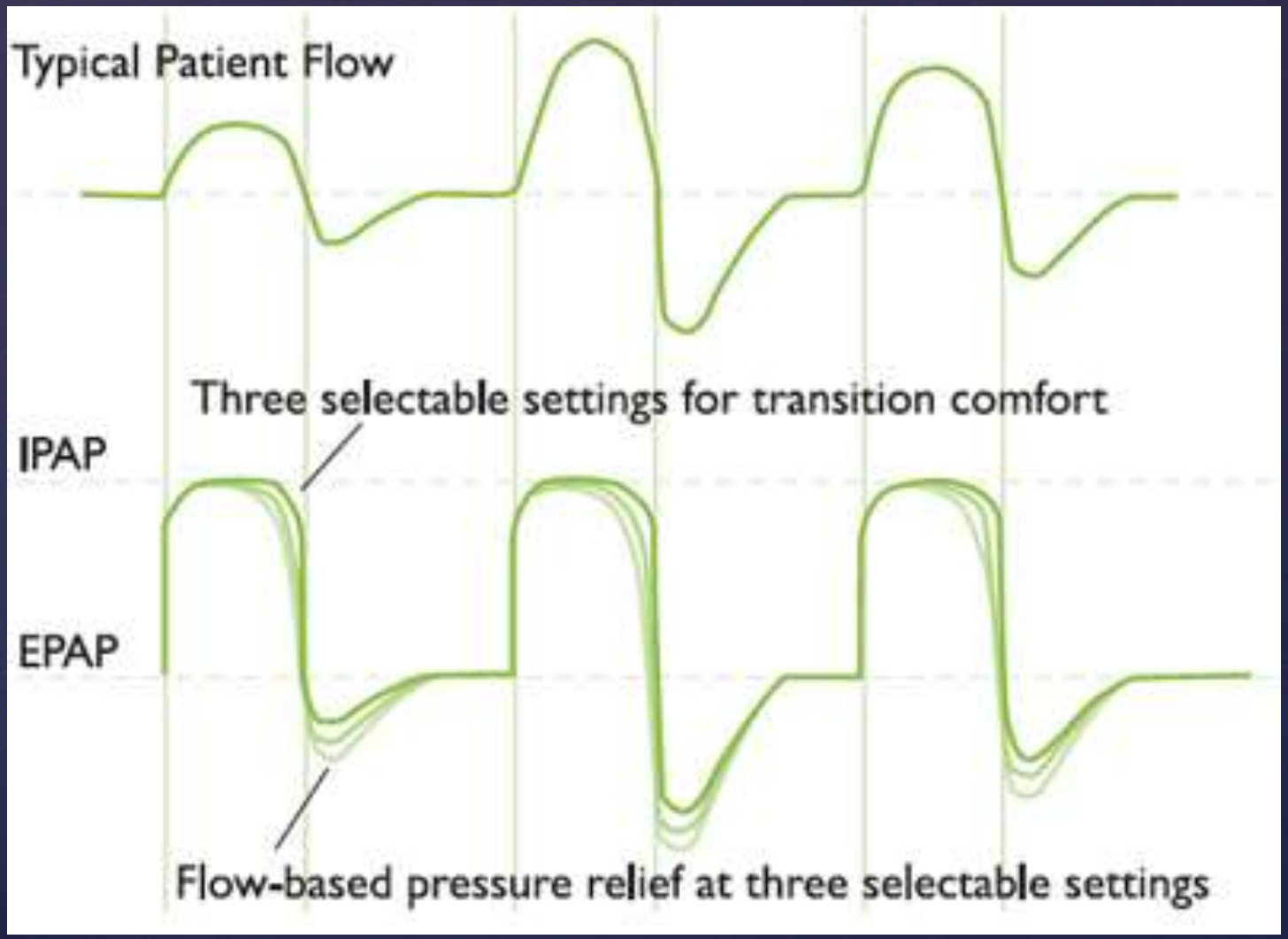
  transition from exhalation to inhalation

  transition from inhalation to exhalation

  during exhalation.

Biflex.respironics.com

Bi Flex™



Biflex.respironics.com

C Flex vs. CPAP

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Alioa et al Chest 2005	Controlled clinical trial NIH study – grants from Respironics	CPAP naïve OSA by PSG 89 patients 64 men 25 women	C flex vs. CPAP in mod to sev OSA	Functional outcomes and subjective sleepiness similar in both groups	Improved adherence over 3 months
Nilius et al Chest 2006 Oct	Prospective Randomized Cross over design	52 naïve OSA patients	PR CPAP vs. CPAP (Pressure relief)	Compliance not assessed AHI, arousal all improvements similar	Comparable effectiveness
Mulgrew AT et al Sleep breath 2007	Cross over trial	15 patients with PSG titrated OSA Either APAP with Cflex or CPAP standard	CPAP vs, APAP with C flex	Treatment efficacy Patient preference	Similar efficacy – equally efficacious Patient preference better than CPAP

C Flex vs. CPAP

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Wenzel et al Pneumonolgie 2007	Prospective Randomized Single blind Cross over trial	20 OSA	C flex vs. conventional CPAP Followed up C flex for 3 yrs	C flex. CPAP equivalent in PSG improvement	90% more comfortable with C flex 3yrs adherence 84.2% in C flex
Marshall et al Sleep breath 2008 Nov	RCT	Severe OSA 19 patients	CPAP vs. C flex for 4 weeks	ESS subjective sleepiness, better in CPAP Objective tests similar	Trend towards better compliance in C flex Needs large study
Leidag et al J physiol pharmac 2008 Dec	Double blind Randomized cross over trial	30 OSAS patients 12 drop outs from this 30	CPAP vs. C Flex	No difference in compliance and leakage	But significantly more persons preferred C flex ?reason ? No of patients

C Flex vs. CPAP

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Dolan et al Sleep breath 2009	Multi site Single blind RCT	138 men 46 women Average AHI 51	CPAP vs. C Flex followed up to 180 days	Trend towards greater hours of usage with C flex Comparable benefit in sleepiness	C flex- better comfort Adherence and symptoms similar
Pepin et al Chest 2009 Aug	Multicenter Double blind RCT	218 new OSA patients	108 CPAP vs. 110 C flex for 3 months	Compliance Side effects Comfort	No difference Low compliers to CPAP had better acceptance to C flex
Bakker et al Sleep 2010 Apr	Double blind parallel arm RCT	76 sev OSA	C flex vs. CPAP	Sleep quality QoL, reaction time, treatment comfort all were similar Compliance similar	No increase in compliance over CPAP None appeared to be superior
Chihara et al Sleep 2013 Feb	RCT Cross over A flex and C flex groups crossed over at 3 month. APAP group switched over to A flex for 3 months	93 new OSA	APAP 31 patients APAP with C flex 31 APAP with A flex 31	Adherence and quality of life and sleep at 3 months and 6 months	Adherence significantly better in APAP with C flex APAP with A flex better than APAP in adherence when crossed over

Pressure modification for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea (Review)

Six studies, 218 participants

Figure 8. Forest plot of comparison: 4 CPAP with expiratory pressure relief versus fixed CPAP, outcom 4.1 Machine usage (hours/night) - 1st arm/parallel studies.

	C-Flex PAP			Fixed CPAP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Dolan 2008	6.23	0.98	92	6.05	1.04	92	98.4%	0.18 [-0.11, 0.47]
Marshall 2008	4.7	2.9	9	3	2.1	10	1.6%	1.70 [-0.60, 4.00]
Total (95% CI)			**101**			**102**	**100.0%**	**0.20 [-0.09, 0.49]**

Heterogeneity: Chi² = 1.65, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 1.38 (P = 0.17)

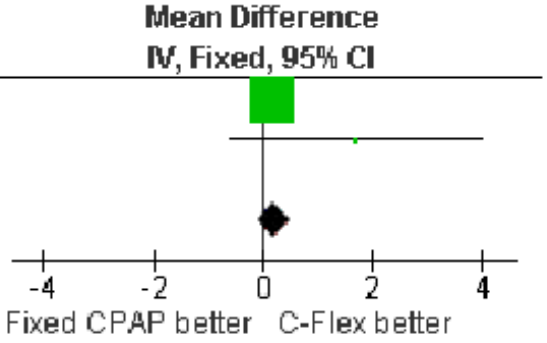
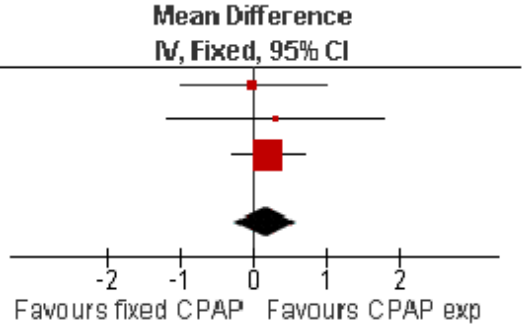


Figure 9. Forest plot of comparison: 3 CPAP with expiratory pressure relief versus fixed CPAP, outcome: 3.2 Machine usage (hours/nt) - cross-over studies.

			C-Flex PAP	Fixed CPAP		Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI
Gfüllner 2007	-0.01	0.5102	18	18	18.5%	-0.01 [-1.01, 0.99]
Modrak 2007	0.3	0.755	26	26	8.4%	0.30 [-1.18, 1.78]
Wenzel 2007	0.2	0.2563	20	20	73.1%	0.20 [-0.30, 0.70]
Total (95% CI)			**64**	**64**	**100.0%**	**0.17 [-0.26, 0.60]**

Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Empirical CPAP therapy

- In patients waiting for PSG. Is there a role?
- Long waiting for diagnostic PSG – other possible alternatives include home testing and empirical trial of CPAP therapy

Empirical CPAP therapy

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Senn O et al Chest 2006	Prospective	76 patients sent for sleep study	CPAP trial of 2 weeks vs. PSG	Diagnostic accuracy of CPAP trial 58% had AHI>10/h	Adherence to CPAP >2h/night and wish to continue rx predicted OSA with Sens 80% Spec 97% PPV,NPV - 98%,78%
Skomro RP et al Can Resp J 2007	Retrospective	183 patients with high suspicion of OSA	Arbitrary pressure CPAP therapy	OSA was present in 91% of patients on trial 40% received suboptimal pressures	Adherence to CPAP trial >2h/ night predicted OSA with Sens 82% Spec 41% PPV,NPV 92%,22%
Masa et al AJRCCM 2004 Dec	Prospective randomized trial	360 patients 12 weeks follow up	Standard CPAP titration group Auto adjusting group Predicted formula and domiciliary pressure adjustment	Improvement in AHI and ESS similar in all 3 groups	These can be alternatives for Standard lab PSG. Potential to save cost and time

APAP (Auto titrating PAP)

- These devices have inbuilt microprocessors for detection and treatment of OSA events
- Self-adjusting, automatic, smart CPAP or Auto-PAP
- Serve as an alternative to lab testing for OSA
- Achieves lower mean pressure than CPAP, hence claimed to have better adherence

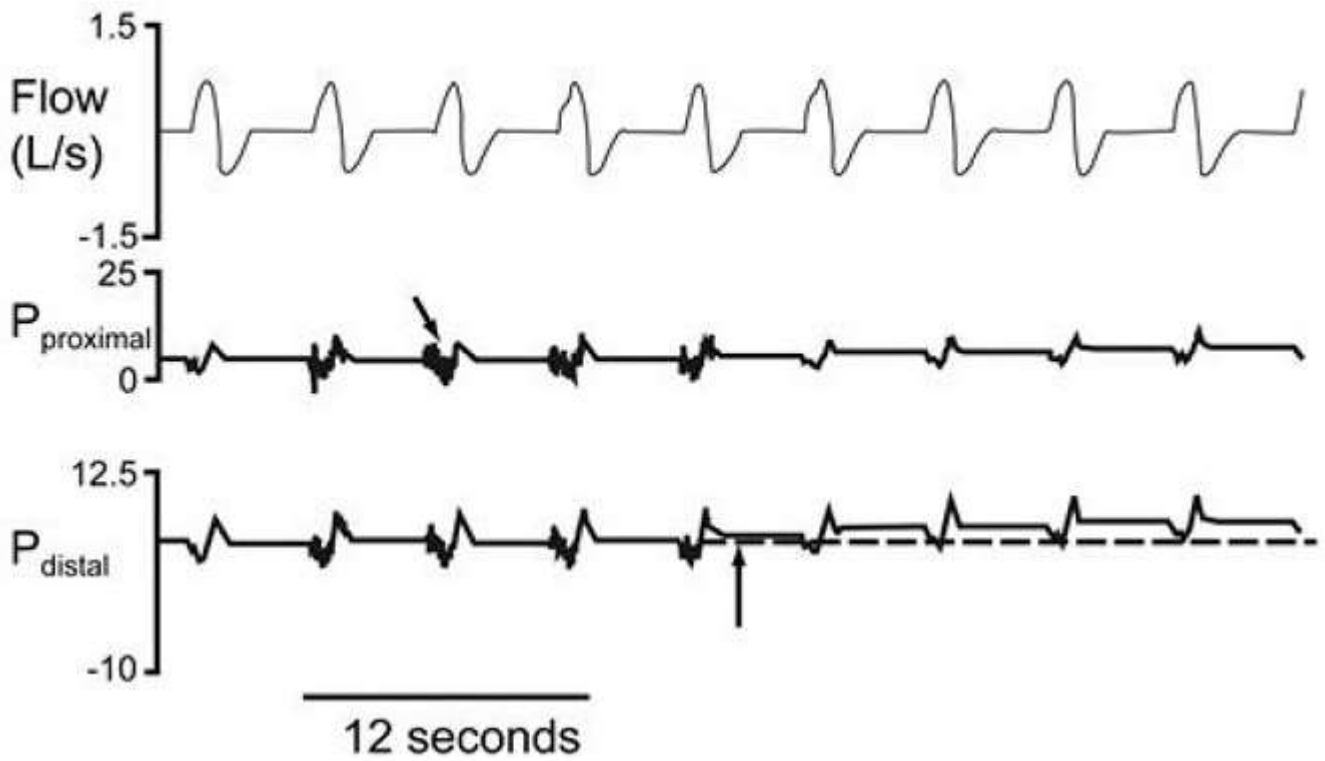
Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

APAP (Auto titrating PAP)

- First generation autoPAPs detected vibrations produced by snoring and thereby titrated the PAP accordingly
- Later generation devices are able to detect apnea, hypopnea or inspiratory flow limitation or inspiratory flow contour

Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

APAP (Auto titrating PAP)



Bench-study testing of an auto-titrating positive airway pressure (auto-PAP) device that was subjected to snoring mimicked by a built-in loudspeaker (saw-tooth like oscillations in pressure [shorter arrow]). The auto-PAP device detects the snoring and responds by an increase in airway pressure, measured by 2 pressure transducers located distal and proximal to the auto-PAP device (P_{distal} and $P_{proximal}$). The longer arrow depicts the point in time when the auto-PAP begins to respond, whereas the complete pressure response to the one

Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

APAP vs. CPAP

Reference	Study Design	Patients	Interventi on	Outcome	Remarks/ conclusions
Ayas et al Sleep 2004 March	Meta analysis of 9 trials	282 patients		No significant advantage in reducing AHI or ESS Mean pressure across night decreased by 2.2cm in APAP Adherence was not improved with APAP as compared to CPAP	APAP a/w significant reduction in mean pressure requirement APAP not be routinely recommended in v/o cost May be advantageous in certain situations like home titration

APAP vs. CPAP

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Xu T et al Sleep breath 2012 Dec 16	Meta analysis of 19 trials	845 patients	APAP vs. CPAP for ***treatment***	Non significant trend towards better AHI and outcomes with APAP apart from improvements in compliance, preference and architecture	APAP over CPAP in mild improvement in compliance Patient preference and sleep architecture
Gao et al Sleep breath 2012 June	Meta analysis of 10 trials	849 patients	APAP vs. CPAP for ***titration***	AHI & ESS improvement is as effective as in CPAP Acceptance & compliance of treatment not different in the two	APAP titration as effective as manual titration
Ip et al Syst Rev 2012	Meta analysis of 24 RCT	APAP vs. CPAP for ***treatment***		Compliance and ESS better in APAP But objective outcomes not measured Minimum oxygen saturation 1.3% more in CPAP	Short follow up studies Patients with Comrbidities excluded in trials

Is APAP better?

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Drummond et al Arch bronch 2009	Prospective	98 mod to sev OSA Treated with APAP after titration	Before at 9 days and 6 months of APAP therapy ***Hs CRP, IL 6*** measured	No significant reduction in inflammatory markers both after short (9 d) and long term therapy (6mth)	
Paruno et al Chest 2007 May 131	Randomized prospective controlled trial	31 newly diagnosed severe OSA	APAP vs. CPAP for for treatment after standard CPAP titration	Glucose Insulin CRP SBP,DBP All decreased in CPAP	CPAP better than APAP in CV outcomes Only CRP reduction was similar
Karasulu et al Lung 2010 Aug 188	Prospective study done on two nights 1 week apart	40 naïve patients	HR variability in OSA patients	Respiratory events were comparable in APAP vs. CPAP However not HR variability	HRV improved in CPAP than APAP

Is APAP better?

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Marrone et al Clin Exp Hypertens 2011	Prospective parallel, non randomized	9 OSA with APAP 8 control on CPAP	Nocturnal urinary catecholamine 24h ambulatory BP before and 2 months after treatment	APAP and CPAP similar	Reduction in nocturnal sympathetic activity with rx for OSA (both APAP and CPAP)
Bakker et al Sleep Breath 2011 Sep	Randomized single blind cross over trial	12 severe OSA patients	CPAP or APAP for 4 nights f/b 4 nights wash out	CV outcomes at baseline, post washout and after each treatment arm Non invasive measures of arterial stiffness – Augmentation index and central BP	Augmentation index (non invasive measure of arterial stiffness) was lower in CPAP group than in APAP though not statistically significant

Is any APAP better than the other?

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Hertegonne et al Respiration 2008	Double blind Randomized Cross over trial	50 OSA patients diagnosed by overnight PSG	Two devices based on inspiratory flow limitation ResMed Spirit (RS) Respironics REMstar (RR)	Primary- AHI Secondary- snoring index Pressure profile Sleepiness score	Similar RR provided better AHI at lower pressure levels ?clinical relevance

Pressure modification for improving usage of CPAP machines in adult OSA (cochrane review)

Auto CPAP vs. CPAP 30 studies 1136 patients

*a statistically significant difference in ***machine usage*** of 0.21 hours/night was observed in favour of auto-CPAP from cross-over studies

*parallel group studies did not identify a statistically significant difference between pressure modes in ***Epworth Sleepiness Scores***, but there was an overall reduction of 0.64 units with cross-over studies

*More participants preferred auto-CPAP to fixed CPAP where this was measured

Smith I, Lasserson TJ. The Cochrane database of systematic reviews. 2009(4):Cd003531.

Short comings of APAP

- Detects apneas only (does not differentiate central/complex vs. obstructive). Hence may paradoxically worsen PAP induced complex/central apneas
- However newer device which are based on sensing upper airway impedance can differentiate between them effectively (Forced oscillatory technique or measuring compliance changes following rapid injection of air)

Forced oscillation technology based APAP

- FOT measures upper airway impedance
- It has the ability to assess whether upper airway is open or closed**
- FOT based APAP vs. lab PSG based CPAP in a RCT involving 38 patients*
- Both were comparable in reducing AHI and subjective sleepiness at 6 weeks*

*Galetke et al. Sleep Med 2009; 10(3):337-343

**Ficker JH. Biomed Tech (Berl). 2003; 48(3):68–72

Newer Auto-PAP

- Can identify Cheyne stokes respiration (by detecting breath to breath variation in flow)
- Identify hypoventilation (by measuring V_T and V_E using calibrated flow sensors)
- Measure airway resistance of upper and lower airways (Forced oscillation techniques)

Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

BPAP

- In unselected patients, no advantage noted over CPAP
- Patients complaining of difficulty in exhaling with CPAP or who complain of bloating of abdomen on CPAP seem to benefit from BPAP

BPAP

- Useful when there is concurrent obstructive or restrictive lung disease
- Hypoventilation syndromes
- Not tolerating CPAP therapy
- Pressure relief systems available to dampen the steep rise when machine switches from IPAP to EPAP

BPAP

Reference	Study Design	Patients	Intervention	Outcome	Remarks/ conclusions
Blau et al Sleep breath 2012 Sep	Prospective double blind RCT	35 CPAP naïve mod to sev OSA patients	18 CPAP 17 Auto level pressure relief BPAP	Decrease in AHI after 3 moths similar in both groups	As effective as CPAP
Gentina et al Sleep breath 2011 Jan	Pilot study to assess Auto BPAP with pressure relief	35 patients, who were non compliant i.e. <4h/d for >70% nights in last 3 months	Auto bilevel device for 10 wk, and PSG at ten weeks	Significant improvement of daytime sleepiness, compliance, functional outcome score at 10 weeks	In patients with poor tolerance to CPAP this may be an option

Bilevel PAP vs. CPAP (from cochrane review)

Six studies and 285 participants

Bilevel PAP vs. CPAP -------no difference was observed (4 studies) (p 0.77)

Smith I, Lasserson TJ. The Cochrane database of systematic reviews. 2009(4):Cd003531.

Proportional assist ventilation

- Also called as proportional pressure support (Drager™)
- In PSV constant pressure support is provided, whereas here the pressure support also varies with the patient effort. More pressure support with increased patient efforts
- All breaths are spontaneous, as in PSV
- No preset pressure, volume and flow goals (in invasive PAV), but safety limits of pressure and volume can be set
- Minute ventilation in PSV is increased by increasing V_T and not RR (unlike PSV)

PAV –pros and cons

- Better V-P synchrony
- Increases tidal volume with effort
- Limitations – Need to quantify elastic properties of lung before setting the ventilator
- As lung mechanics are not constant, frequent monitoring and settings modification required
- These shortcomings are presently taken care of by software that can detect changes in lung mechanics

Proportional assist ventilation

Reference	Study Design	Patients	Interventions outcomes	Results	Conclusion
Dolmage et al CHEst 1997	Prospective controlled study, random order in PFT lab	Ten severe COPD (FEV1 29%)	Submaximal exercise-cycling(50-70%) 1.Baseline 2.PAV 3.PAV+CPAP 4.CPAP 5cmH2O 5.Sham	Dyspnea measured Only PAV+CPAP was found superior to sham	PAV+CPAP provided ventilatory assistance during cycle exercise sufficient to increase the endurance time
Ambrosino et al ERJ 1997	Effect of PAV nasal on exercise capacity in chronic vent failure	30 COPD 12 kyphoscoliosis	PAV set at 80% of patients volume and flow assist calculated based on elastance & resistance of patient's lung	ABG and dyspnoea (VAS) at baseline and 60mt after PAV	PAV well tolerated Improves gas exchange and exercise capacity
Gay et al AJRCCM 2001	Randomized controlled trial	Acute respiratory failure 23 NIV PSV 23 NIV PAV	Mortality Intubation rates Reduction in RR Refusal rate Complication rate	Similar Similar Better in PAV Lesser in PAV Lesser in PAV	PAV, PSV similar efficacy. PAV better tolerated

Proportional assist ventilation

Reference	Study Design	Patients	Interventions outcomes	Results	Conclusion
Serra et al Thorax 2002	Randomized control study PSv vs. PAV	12 patients of advanced cystic fibrosis and chronic resp failure	PSV 12cmH2O mean PAV set to patient's comfort Ventilatory pattern Transcutaneous blood gases Diaphragm EMG	Improved ventilation Reduced CO2 and reduced diaphragm load with both PSV and PAV than baseline unsupported	***Both PSV, PAV well tolerated improve all parameters*** from baseline
Hart et al Thorax 2002 nov	PAV and PSV comparison in chronic respiratory failure	Stable awake neuromuscular and chest wall deformity 15 patients (3 excluded later)	PAV vs. PSV compared in these aspects: O2 saturation Transcut CO2 MV Tidal volume RR Diaphragm EMG	All physiologic parameters similar, except ***Diaphragm unloading and greater symptomatic benefit with PSV*** than PAV	Tolerance to PAV may be compromised in these patient population and PSV may be better
Wysocki et al Crit care Med 2002	Prospective 'Crossover Randomized study	12 COPD with hypercapnic acute respiratory failure	Baseline CPAP f/b NIV PSV or NIV PAV	Arterial pH, pCO2 similar improvement Tidal volume variability more in PAV	***Similar unloading*** of respiratory muscles with NIV PAV and ***better comfort than PSV***

Proportional assist ventilation

Reference	Study Design	Patients	Interventions outcomes	Results	Conclusion
Porta et al Chest 2002	Randomized controlled physiologic study	11 COPD 7 restrictive chest wall disease Randomise to PSV or PAV (pressure of 2-4cmh2o)	Breathing pattern, MV, lung mechanics During spontaneous (baseline) and after PAV or PSV	More time spent for setting PAV Tidal volume variability was greater with PAV Both PAV and PSV increased tidal volume to similar extent, but was more than spontaneous breath	In chronic ventilatory failure ***PAV not superior to PSV in unloading insp muscle***s or increasing MV or tidal volume ***NO diff in V-P synchrony***
Winck et al Chest 2004	Crossover Randomized	4 COPD 10 restrictive chest wall disease with hypercapnia (chronic CO2 >55)	PAV vs. PSV 5 consecutive nights, with 2 days washout period inbetween	Nocturnal SpO2, ABG before after rx Subjective symptoms (VAS)	Similar tolerance ***Similar effectiveness in reducing CO2*** & symptom improvement PAV- less oral & nasal dryness but high alarm noise

Proportional assist ventilation

Reference	Study Design	Patients	Interventions outcomes	Results (PSVvs PAV)	Conclusion
Fernandez-vivas et al Intensive care medicine 2003	Prospective Randomized trial	117 acute respiratory failure 59 PSV 58 PAV	Frequency of intubation Mortality Mean stay	37% vs. 34% 29% vs. 28% Similar Comfort (VAS) better in PAV Intolerance (15% vs. 3.4%)	***PAV more comfortable***, less intolerance, rest ***similar to PSV***
Varellman D Crit Care Med 2005	Randomized trial	12 acute respiratory failure	PAV, PAV+ATC,PSV in random order	Tidal volume and end expiratory lung volume increased in all modalities similarly	***Newer modalities not superior to PSV in unloading inspiratory muscles*** or improving cardiovascular demand
Rusterholtz et al Intensive care med 2008	Prospective Multicenter Randomized Trial	36 adults with pulm edema, RR>30, oxygen req >10L/mt despite furosemide Rx	Full face mask CPAP – 10cmH2O (n 19) vs,. PAV 5-6cmH2O (n 17)	MI and mortality similar Failure (37% CPAP vs. 41% PAV) Physiologic parameters similar	***PAV not superior to PS***V in pulmonary edema

Proportional assist ventilation

Reference	Study Design	Patients	Interventions outcomes	Results	Conclusion
Moderno et al Respir Med 2010	To assess exercise capacity in IPF patients on using PAV	10 IPF patients	Cardpulm exerc testing Submaximal exer test (60%) With CPAP and PAV	PAV > CPAP in performing exercise test Improved arterial O2 and subjective breathlessness improved in both	Improvement in ***exer tolerance, dyspnea in IPF patients using PAV***
Dreher M Respir Med 2010	PAV's effect on exercise endurance in obese	18 male obese patients	With and without PAV Exercise endurance Dyspnoea Blood gases Limb discomfort noted	PAV improved all parameters Exercise duration increased by 31%	Overall prolongation in ***exercise endurance and reduced dyspnea in obese patients***
Alexopoulov et al Int care med 2013	Randomized crossover physiologic study	14 patients Majority(87.5%) had COPD acute exarcebation	PAV+ vs. PSV	PAV+ reduced V-P dyssynchrony Greater sleep fragmentation in PAV+	PAV+ better V-P synchrony but ***FAILED to improve sleep quality***

Proportional assist ventilation-conclusion

- PAV may be better tolerated than PSV
- PAV similar in effectiveness in patients with chronic respiratory failure due to obesity, cystic fibrosis, RCWD (restrictive chest wall diseases)
- Larger trials are needed
- No strong evidence to favour one modality over other (PSV and PAV)

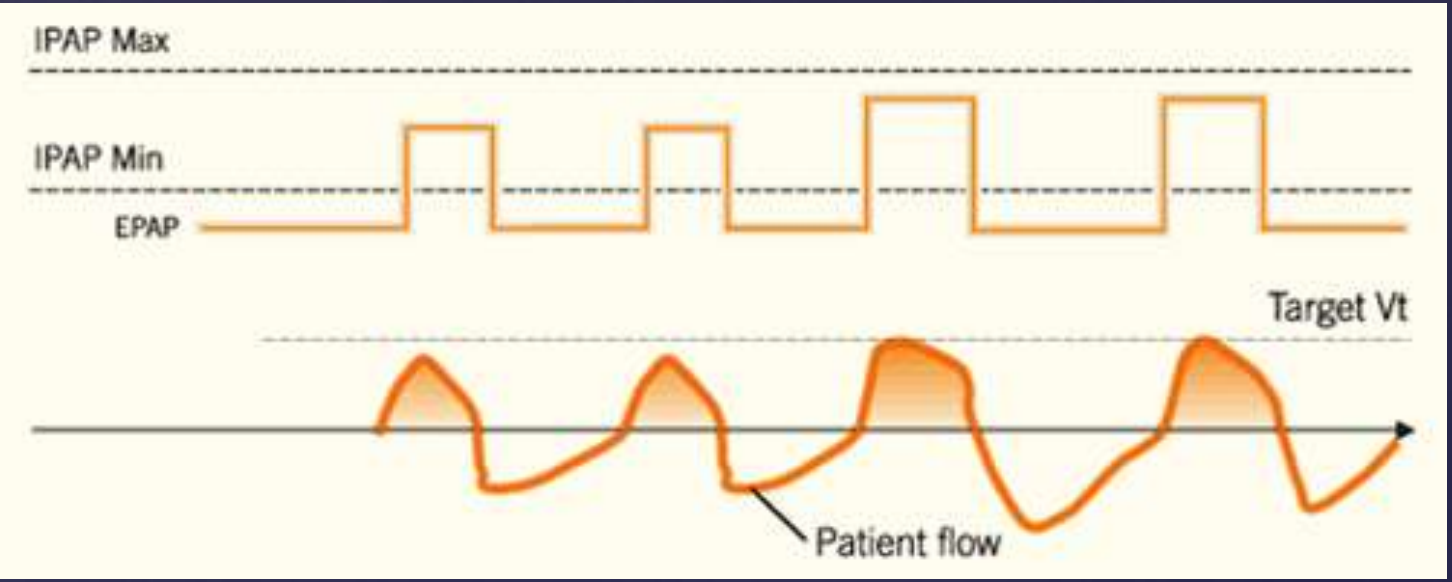
Volume targeted pressure support (VT-PSV)

- Newer hybrid mode
- Guarantees minimum tidal volume by varying inspiratory airway pressure support
- Ensures maintenance of adequate ventilation despite dynamic changes in respiratory mechanics during sleep

Volume targeted pressure support (VT-PSV)

- Bilevel NIV mode used commonly provides a constant pressure, and may not deliver adequate tidal volume with changing pulmonary mechanics, as during sleep.
- Initial small trail showed greater reduction in nocturnal CO_2 when compared to Bilevel NIV [*Storre et al. Chest 2006;130:815e21]*

VT PSV – (AVAPS™)



Patients expiratory tidal volume monitored every breath and pressure support varied accordingly

Volume targeted pressure support (VT-PSV)

- Further trial showed that benefit was offset by distorted sleep architecture due to AVAPS [*Janssens et al Respir Med 2009;103:165e72]*

AVAPS

Reference	Design	Interventions	Outcome	Results	Remarks
Crisafulli et al Lung 2009 sep-oct	Single blind randomized Cross over trial	9 stable hypercapnic COPD patients, two 5 days period of PSV vs. AVAPS	ABG Comfort (VAS) Percieved sleep efficiency	VAS and ABG improvement was similar. Sleep efficiency better with AVAPS	
Storre et al Chest 2006 sep	Prospective RCT	OHS patients not responding to CPAP 10 patients mean BMI 41 6wks BPV S/T with or without AVAPS	Ventilation pattern Gas exchange Sleep quality HRQoL	Significant difference in transcutaneous CO2 reduction between BPV S/T vs. AVAPS Rest parameters similar	AVAPS better in reducing transcutaneous CO2 further than BPV S/T
Murphy et al Thorax Aug 2012	Two center Single blinded RCT	50 patients with BMI >50 23 PSV 23 AVAPS completed at 3 months	Primary-day time $PaCO_2$ at 3 months Physical activity HRQoL	No difference	Suggests that AVAPS may enhance daytime activity and promote weight loss

ASV

- Adaptive servo ventilation is a variant of BPAP that was designed to treat Cheyne Stokes breathing
- It stabilizes breathing patterns such as CSR, complex sleep apneas
- VPAP adapt SV (ResMed), BiPAP auto SV (Respironics)
- BiPAP auto SV has a within breath adjustment capability, and targets 90% of the previous MV

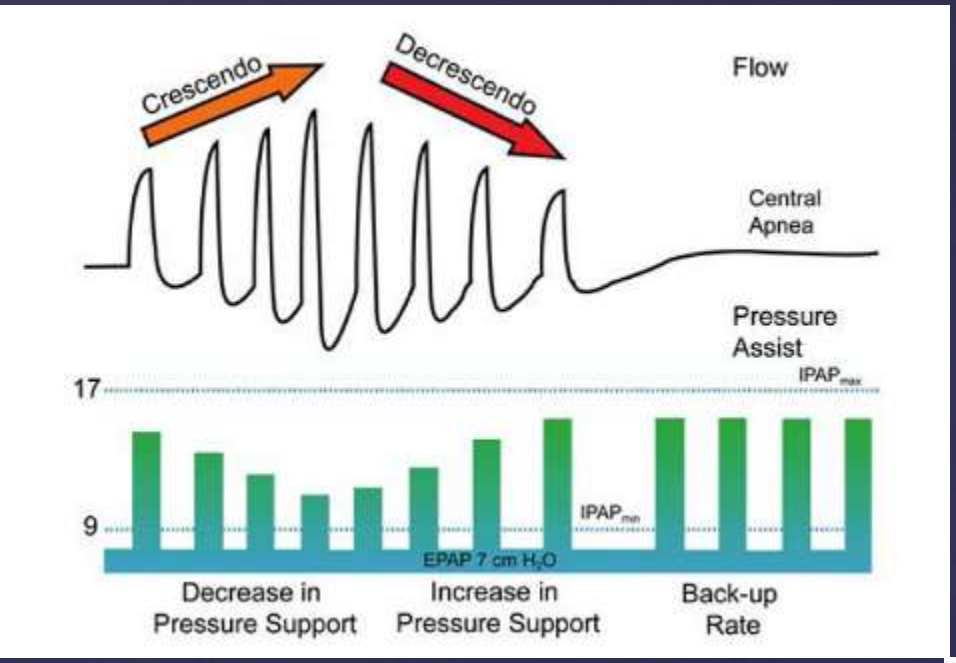
How to set ASV?

- Set *EPAP* at level required to abolish obstructive sleep apneas/hypopneas
- EPAP is generally not increased beyond 15 cmH_2O especially in patients with heart failure and central apneas so as to avoid hypotension that occurs due to the reduction in venous return

How to set ASV?

- IPAP is determined by the device algorithm, between the pre-specified $IPAP_{min}$ and $IPAP_{max}$ (Not >30cmH_2O)
- A *back up rate* is to be set. Generally 2 breaths less than the resting RR when the patient is awake. Titrated further if central apneas increase

Adaptive servo ventilation



Principles of operation of servo ventilation. The air flow tracing depicts a classical crescendo (orange arrow) and decrescendo (red arrow) pattern of Cheyne-Stokes respiration, followed by an ensuing central apnea. The servo-controlled automatic adjustment of the inspiratory positive airway pressure [I PAP] level is inversely related to the changes in peak flow over a moving time window. Specifically, during the crescendo pattern of peak flow rates (orange arrow) the pressure assist (or I PAP) level decreases in order to dampen the rise in inspiratory peak flow rate (or tidal volume). Conversely, during the decrescendo pattern of peak flow rates (red arrow) the pressure assist (or I PAP) level increases in order to dampen the fall in inspiratory peak flow rate (or tidal volume). Therefore, the servo system dampens the inherent oscillatory behavior of the patient's breathing pattern and smoothes respiration. During a central apnea, however, the device backup rate kicks in and ventilates the patient (right side of the figure). The maximum and minimum IPAP ($IPAP_{max}$ and $IPAP_{mjn}$) are set at 17 cm H_2O and 9 cm H_2O (dashed blue lines). The expiratory positive airway pressure (EPAP) is set at 7 cm H_2O. During any given breath the pressure assist or pressure support is equal to the IPAP minus the EPAP.

Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

Adaptive servo ventilation

Servo system thus dampens the oscillatory pattern of breathing and smoothens respiration

Antonescu-Turcu A, Parthasarathy S. Respiratory care. 2010;55(9):1216-29.

Adaptive servo ventilation

Reference	Details of the study and conclusions
Morgenthaler et al Sleep 2007 Apr	ASV better than NPPV in patients with CSA/CSR, mixed apnoeas and complex sleep apnoeas
Ramar K J clin sleep med 2012 Oct	ASV effective in Rx of complex sleep apnoea due to CHF and chronic opioid use
Allam et al Chest 2007	Retrospective study. ASV effective in complex sleep apnoeas and CSA syndromes resistant to CPAP
Kasai T Circ Heart Failure 2010	31 CHF patients CPAP vs. ASV. In coexisting OSA + CSA/CSR ASV is better than CPAP
Su et al Sleep breath 2011 Dec	42 sev OSA patients Rx with autoPAP for 1 mth had residual sleepiness. ASV is effective in improcing symptoms and ESS in these patients

Adaptive servo ventilation

Reference	Details of the study and conclusions
Joho et al J card fail 2012 Oct	ASV improved muscle sympathetic nerve activity and cardiac function assessed by echocardiography in 32 patients with NYHA II III HF and CSA
Randernath et al Chest 2012 Aug 142	70 patients of OSA coexistent with CSA/CSR, hypertension, CAD, NYHA II,III randomized to CPAP and ASV. Respiratory disturbances, desaturations and arousal improved in similar fashion. Central apnea/hypopnoea index and BNP improved significantly in ASV group
D Elia et al J card Vasc Med 2013 Apr	Study on 17 patients. Comparison of HR, HR variability with holter were doe before and after ASV. ASV beneficial in CSA as well as improves HRV by reducing sympathetic tone
Dellweg et al Sleep 2013 Aug	RCT of 30 patients who developed complex sleep apnea during CPAP. ASV is more effective than NPPV in this situation

ASV beneficial on LVEF

A meta-analysis of six trials doe before and after ASV treatment in

LVEF, showed ASV to be significantly better

Aurora RN, et al. Sleep. 2012;35(1):17-40.

ASV – proven benefits

- When ASV added to standard heart failure therapy – improves sleep disordered breathing, LVEF, Pro BNP and cardiopulmonary exercise testing parameters *Eur H J 2008;10:6(581-586)*
- ASV reduces early morning hypercapnic cerebral vascular reactivity (thereby possibly stroke risk) *Sleep 2007 ;30 : 648-652*

ASV – proven benefits

- ASV reduces re-hospitalisation in CHF with CSR. *J of Cardiac Failure 2011;17:9*
- ASV improves cardiac sympathetic activity in heart failure patients with breathlessness at 6 months of therapy. *J of Card Failure 2011; 17:9*
- ASV improves hemodynamic parameters on angiography. *Eur Heart Journal 2011*

Trilevel ASV (SOMNOventCR™)

Trilevel ASV: Three different pressure levels used over one respiratory cycle

IPAP provides inspiratory support, helps in ventilation by determining tidal volume

EPAP is varied from a low level (at the beginning of expiration) to a higher level at the end of expiration

Oldenburg O, et al. Sleep medicine. 2013;14(5):422-7.

Trilevel ASV – pilot study

- It is a combination of Auto-PAP and ASV
- Two week treatment in patients with coexisting OSA, CSA and periodic breathing was proven to be effective

Randerath WJ, et al. Sleep medicine. 2009;10(8):898-903.

Trilevel ASV for treatment of central and mixed sleep apnea in chronic heart failure patients

CPAP – though was beneficial in many parameters, failed to show a mortality benefit in the large CANPAP (Canadian continuous positive airway pressure trial) in heart failure patients with Cheyne Stokes respiration

Though the post-hoc analysis showed increase in transplant free survival in these patients on CPAP, further modalities for treatment are needed

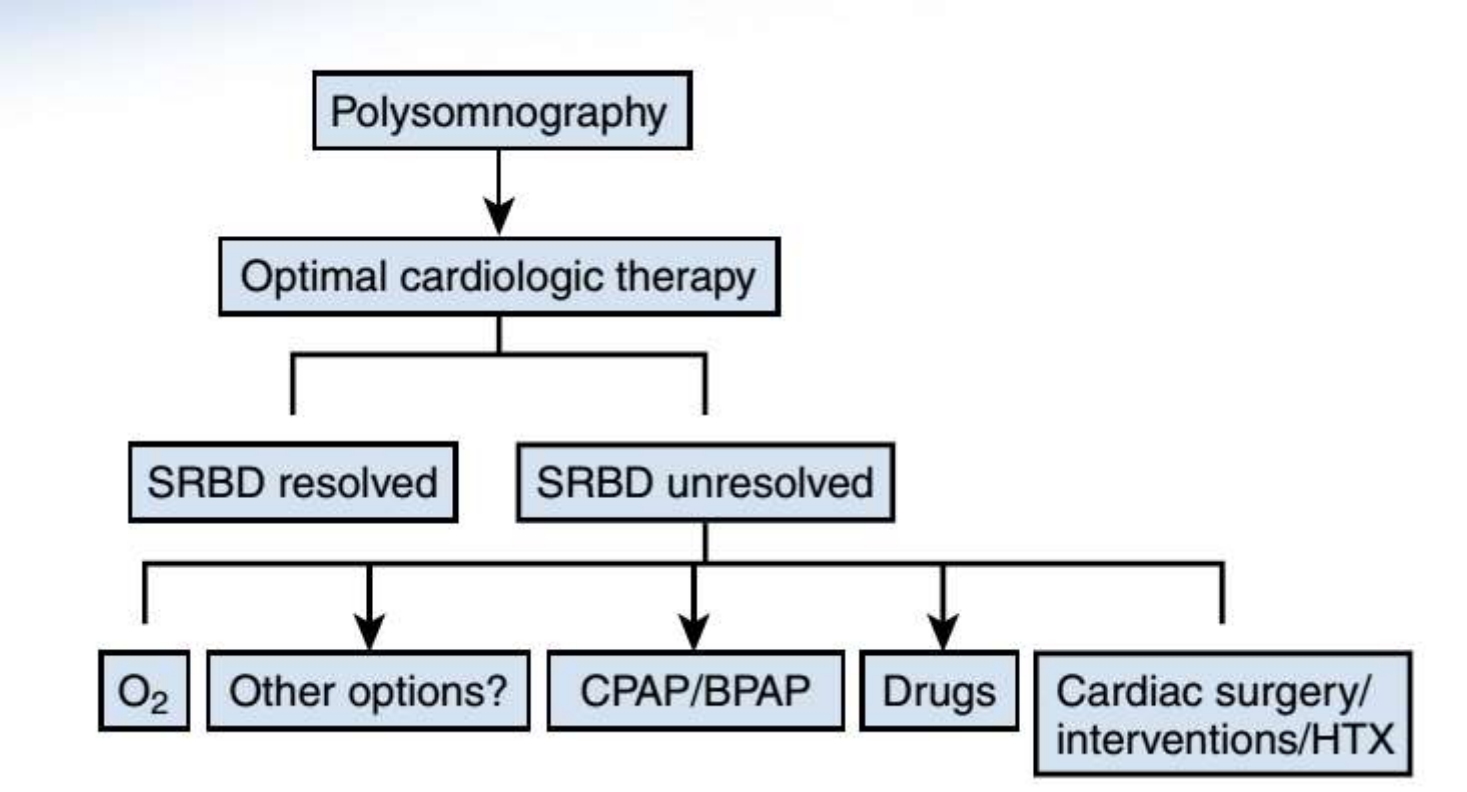
Study done on 38 patients with HF, elevated BNP, mod to severe SDB (AHI > 15/h) with combined obstructive and central effects

Oldenburg O, et al. Sleep medicine. 2013;14(5):422-7.

- Most data are extrapolated from study on CSA in patients with CHF
- Hence no clear evidence of NIV in other forms of CSAs
- For e.g. primary CSA – only 51 patients in the included trials and no data regarding use of CPAP, BPAP, S,T or ASV. The little available evidence is for zolpidem, acetazolamide, triazolam and carbon dioxide
- But still an OPTIONAL recommendation given for use of CPAP in primary CSA

Aurora RN, et al. Sleep. 2012;35(1):17-40.

Therapy in central breathing disorders



Randerath JW. Chapter 19. central and mixed sleep related breathing disorders

Summary

Disease	NIV
OSA AHI > 15 or AHI >5 with other risk factors	CPAP
OSA + COPD (overlap syndrome)	CPAP if not tolerated, BPAP
CSA	Treat heart failure, try O_2, then CPAP if fails or not tolerated BPAP, ASV
Complex sleep apnoeas	ASV or BPAP (less effective)