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"How I do it": Home Non-Invasive Ventilation in COPD

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Title: "How I do it": Home Non-Invasive Ventilation in COPD

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Abbreviations

ATS	American Thoracic Society
AVAPS/iVAPS	Average / Intelligent Volume Assured Pressure Support
BMI	Body Mass Index
BUR	Back-up Rate
COPD	Chronic Obstructive Pulmonary Disease
CTS	Canadian Thoracic Society
EPAP	Expiratory Positive Airway Pressure
ERS	European Respiratory Society
EFL	Expiratory flow limitation
FEV_1	Forced expiratory volume in 1 second
IPAP	Inspiratory Positive Airway Pressure
LT-NIV	Long-term Non-Invasive Ventilation
LTOT	Long-term Oxygen Therapy
MPV	Mouthpiece Ventilation
NIV	Non-Invasive Ventilation
PCO_2	Partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
PS	Pressure Support
RT	Respiratory Therapist
$TcCO_2$	Transcutaneous carbon dioxide
Ti	Inspiratory time
QoL	Quality of life

Abstract

There is increasing evidence that long-term NIV (LT-NIV) can improve outcomes in individuals with severe, hypercapnic COPD. Though the evidence remains uncluear in some aspects, LT-NIV appears to be able to improve patient-related and physiological outcomes like dyspnea, FEV_1, PCO_2, and also reduce rehospitalizations and mortality. Efficacy is generally associated with reduction in PCO_2. To achieve this, an adequate interface (mask) is essential, as are appropriate ventilation settings that target the specific respiratory physiology of COPD. This will ensure comfort, synchrony and adherence that will result in physiologic improvements. This article briefly reviews the newest evidence and current guidelines on LT-NIV in severe COPD. It describes a true case who benefitted from the therapy. Finally, it provides strategies for initiating and optimizing this LT-NIV in COPD, discussing high-pressure NIV, optimization of triggering and control of inspiratory time. As demand increases, clinicians will need to be familiar with this therapy, to reap its benefits, as inadequately adjusted LT-NIV will not be tolerated or effective.

1. Introduction

COPD is a major cause of morbidity and the third-leading cause of death worldwide[1] . With progressive disease, chronic hypercapnic respiratory failure may occur, which is associated with a 1-year mortality of 17-30%[2-5]. Hospitalization due to hypercapnic exacerbation is associated with 11% in-hospital mortality and 49% 2-year mortality[6].

The benefits of non-invasive ventilation (NIV) in acute exacerbations are well-established[7-10]. For chronic use in the home setting, older systematic reviews found no evidence of benefit but identified higher baseline CO_2, higher pressures and longer daily NIV use as predictors of greater CO_2 reduction[11]. Recent randomized controlled trials have changed the landscape in the field. However, practice had been variable, from higher proportions of patients with COPD in ventilation programs in European countries[12-14] to few across Canadian provinces[15] , and generally few chronically hypercapnia COPD patients receiving home NIV in the United States[16] . Hence, experience with long-term NIV (LT-NIV) is highly heterogeneous among pulmonologists. Varying ventilation targets[17], rapid technological advances with different ventilation modes, diverse settings and nomenclature between manufacturers, and the multitude of parameters on NIV devices resulting in wide range of possible prescriptions, all make NIV a complex therapy that may be challenging to implement.

The purpose of this review is to summarize the current data and guidelines on LT-NIV in COPD and provide a practical approach to its initiation.

2. Evidence for LT-NIV in COPD

Randomized controlled trials of NIV in COPD published prior to 2010 largely failed to demonstrate benefits on physiologic, functional or patient-reported outcomes, reduction of hospitalizations or survival[11,18]. One exception was an Australian trial comparing LT-NIV with long-term oxygen therapy (LTOT) or LTOT alone which found improvement in mortality with LT-NIV after a mean follow-up of 2.21 years[4]. However, there was worsening of certain quality of life (QoL) parameters, which hampered widespread support for LT-NIV in COPD[19].

In parallel, work done in Europe generated increasing evidence that LT-NIV could result in improved outcomes, if settings were adjusted targeting obstructive COPD physiology and with specific CO_2 reduction goals, termed “high-intensity” ventilation[20-22] . While the exact definition of high-intensity NIV remains somewhat contentious, it is primarily the high pressure rather than

a high back-up rate that is the most relevant parameter[23,24]. Using this type of strategy, Kohnlein et al. demonstrated markedly improved survival with LT-NIV in stable hypercapnic COPD patients[5], with improved QoL. The mean inspiratory (IPAP) and expiratory (EPAP) pressures were 21.6 and 4.8 cmH_2O respectively, with back-up rate (BUR) 16.1/min. This trial included participants with $PaCO_2 \geq 52$ mmHg (mean 58 mmHg) and showed reduction, but not normalization of daytime $PaCO_2$, and improvement in oxygen saturation and FEV_1. Murphy et al. studied patients who remained hypercapnic (mean PCO_2 59 mmHg) 2-4 weeks following hospitalization for exacerbation requiring acute NIV, and who met criteria for LTOT[25]. Using mean IPAP and EPAP of 24 and 4 cmH_2O, respectively, they demonstrated delayed time to readmission, reduced readmission rate and improved QoL. There was no improvement in mortality but many control patients eventually crossed over to active treatment, and there were few deaths. Conversely, another trial also including hypercapnic (mean PCO_2 approximately 59 mmHg) participants post exacerbation did not demonstrate benefit of NIV on readmissions or death[26], using mean IPAP and EPAP 19 and 4 cmH_2O, respectively. It has been suggested this resulted from inclusion of participants randomized as early as 48 hours after discontinuation of acute NIV, who may not have been chronically hypercapnic, since reduction of PCO_2 in the control group mirrored that in the NIV group in the first 3 months. Variable results across modern trials highlight that LT-NIV benefits very specific COPD patient populations; the positive trials define the indications and target populations.

Real world data, notwithstanding potential biases, have helped understand the impact of LT-NIV in North America. Retrospective single center studies demonstrated good adherence[27], improved event-free survival with LT-NIV post discharge[28] and marked reduction in re-hospitalizations with a multimodal intervention including LT-NIV[29]. Using Medicare data, it was demonstrated that in patients with COPD and chronic respiratory failure, LT-NIV was associated with reduced all-cause mortality, hospitalizations, and ER visits[30,31], with benefit on mortality and reduction in Medicare expenditures restricted to those with hypercapnia[16].

3. Clinical Practice Guidelines

The European Respiratory Society (ERS)[32], American Thoracic Society (ATS)[33] and the Canadian Thoracic Society (CTS)[34] have recently published guidelines that agree there is a role for LT-NIV in chronic stable hypercapnic COPD, but recommendations are weak, with very low

to moderate certainty evidence. LT-NIV is suggested following acute hypercapnic respiratory failure requiring acute NIV, provided the patient remains hypercapnic after resolution of the acute episode. The ATS and CTS recommend re-evaluation after 2-4 weeks. All three guidelines specify that NIV should aim to normalize or at least significantly reduce hypercapnia. The ERS and CTS found no evidence to preferentially support auto-adjusting modes and recommend fixed pressure modes. The ATS suggest evaluating patients for obstructive sleep apnea (OSA), at a minimum with a questionnaire (very low certainty evidence). There remain many unanswered questions regarding implementation of LT-NIV in COPD, including the need to better identify patients most likely to benefit, develop strategies to initiate and optimize LT-NIV, and clarify management of obese hypercapnic COPD patients, especially given high obesity rates in North America including in COPD[27].

4. Case Study

A 57-year-old male was referred for optimization of home NIV in December 2021. He was a former smoker of 35 pack-years, who quit 1 year prior, with body mass index (BMI) 25 kg/m^2, FEV_1 0.6L (19% predicted), on optimal bronchodilator therapy and LTOT. He had multiple hospitalizations for hypercapnic respiratory failure over the 2 years prior, with maximal venous $PvCO_2$ 136 mmHg, requiring NIV acutely several times and intubation once. His arterial blood gas 3 years prior showed pH 7.4 and $PaCO_2$ 59 mmHg.

This patient would have likely benefitted from earlier implementation of home NIV, which may have prevented re-hospitalizations and intubation.

He had been started on nocturnal NIV at the referring center using an oronasal mask, in spontaneous-timed (ST) mode as per parameters used during his last admission: IPAP 16 cmH_2O, EPAP 10 cmH_2O, BUR 12/min, rise time 300 ms, inspiratory time (Ti) minimum 0.8 sec and maximum 1.6 sec, high trigger sensitivity and medium cycling sensitivity.

These parameters are not optimal due to low IPAP and low driving pressure (Δ=IPAP-EPAP). It is unclear why the EPAP was relatively high but this was comfortable for the patient. The rise time should be faster, Ti maximum lower and cycling sensitivity high for earlier cycling from IPAP to EPAP (cf below).

Despite symptomatic improvement, he was briefly re-hospitalized with P_VCO_2 102 mmHg. Upon discharge, parameters were modified remotely by his home care respiratory therapist (RT) to IPAP 19 cmH_2O, with fastest rise time. The patient reported good subjective sleep quality with NIV. A few days later, a routine follow-up P_VCO_2 taken at home was 119 mmHg.

The driving pressure remained low in the context of COPD. Note that P_VCO_2, while convenient, is not recommended as it is not a reliable estimate of P_aCO_2.

IPAP was gradually increased remotely to 25 cmH_2O, with Ti max 1.3 sec. About 9 months after starting NIV, an overnight oximetry on NIV and O_2 at 3L/ minute showed mean SpO2 95% ,and SpO_2 <90% during0.8% of the night. His daytime transcutaneous CO_2 ($TcCO_2$) taken in the outpatient clinic was 58 mmHg. Supplemental oxygen at night was reduced.

Excessive O2 supplementation may result in CO_2 retention. O_2 should be titrated to maintain SpO_2 not higher than 92% at rest.

EPAP was decreased to 8cmH2O and Ti range to 0.8 – 1.1 sec, but an attempt at increasing IPAP was not tolerated. Overnight $TcCO_2$ showed a mean of 54mmHg, fluctuating depending on leak (incompletely controlled). Due to increasing daytime NIV use, mouthpiece ventilation (MPV) was added to help with dyspnea during daily activities. It allowed the patient to do some work in his garage, for which he was grateful. About 24 months after starting NIV, he remains at home with no further hospitalizations despite exacerbations requiring antibiotic and corticosteroid treatment.

Despite imperfect CO_2 control, the patient was stabilized and re-hospitalizations have to date been averted.

5. Approach to home NIV in COPD

5.1. Initiation setting

There is no agreed-upon optimal initiation location. The ATS suggests *against* titrating NIV in the sleep laboratory due to concerns regarding cost, delay, safety of achieving rapid normocapnia over a single night and proficiency of personnel in such titrations[33]. European studies used initiation in hospital, often in specialized ventilation units, over days, with progressive acclimatization and optimization[5,17,25]. This is not currently possible in most North

American centers. However, parameters used and tolerated during an acute exacerbation can be a useful starting point. Titration performed while admitted for an acute exacerbation is practical, but chronic hypercapnia should be confirmed before starting LT-NIV and parameters reassessed based on ventilation goals.

Home initiation has been studied as an alternative to in-hospital initiation[35]. The protocol required multiple home visits and daily calls from a specialized nurse, remote monitoring of ventilator and overnight $TcCO_2$ data, and lasted a median of 7 days . Technical difficulties affected $TcCO_2$ measurements in a significant proportion of patients. This protocol was non-inferior to hospital initiation, cheaper and safe (patients with unstable cardiac comorbidities or heart failure were excluded). This highly resource-intensive protocol is promising but would likely require further optimization and adaptation to local realities.

In our experience, NIV initiation often takes place in the outpatient setting, utilizing a combination of resources, ideally specialized RTs, available in clinic and at home. Clinic visits may include discussions regarding NIV potential benefits and challenges with shared decision-making regarding initiation, training on equipment, and interface selection. A daytime NIV trial may be performed, starting at low pressures and increasing pressures as tolerated during quiet wakefulness. Alternatively, initiation may be performed directly at home, utilizing trained home care or medical equipment providers.

Close follow-up in the initial period after starting NIV is important. Trained staff (ideally an RT) should follow-up within days to provide support and optimize interface and ventilation comfort. This could be done remotely, including for parameter adjustments (for non-life support devices)[35], providing there is adequate connectivity. New mask trials, if needed, should be done in person. The extent to which this is done by home care or equipment companies versus clinic staff may vary based on local resources. Physician follow-up should occur within weeks to assess adherence, comfort and PCO_2 [arterial, capillary or $TcCO_2$] to inform further parameter adjustments. We suggest targeting reduction of daytime PCO_2 by $\geq$20%, or to <48 mmHg if possible[5]. Adjustments can then be completed targeting nocturnal gas exchange[25] based on overnight $TcCO_2$ or oximetry, remembering the latter will not be reliable regarding hypoventilation in patients on LTOT. This type of outpatient protocol may take longer to reach optimal parameters than hospital-based initiation but may constitute a lesser burden on patients and healthcare resources.

188

189 5.2.Mask choice:

190 The choice of mask is crucial for initiation and adaptation to LT-NIV, and is a key issue for the
191 majority of NIV users and caregivers[36]. Oro-nasal interfaces appear to be most frequently used[36],
192 possibly because of oro-nasal mask use during hospitalizations. Additionally, very dyspneic
193 patients may be unable to breathe exclusively through their nose, precluding use of a nasal
194 interface. However, nasal masks should still be considered, as they cover a smaller facial area,
195 hence are less prone to leaks, and might be easier to apply. A chin strap can help counter mouth
196 leak[37] for patients able to use one. Nasal masks also have less potential for exacerbating upper
197 airway obstruction [38,39] but this has not been studied in the context of NIV.

198 To improve adherence, the chosen mask must be comfortable and easy to handle. Patients
199 applying their mask independently must be able to do it easily and quickly if dyspneic. If
200 experiencing difficulty lifting arms up to the head, strategies should be developed to limit
201 required movement during mask application. A well-fitting mask can determine adherence by
202 minimizing uncomfortable pressure points, and preventing leaks which can be bothersome, cause
203 asynchrony, reduce effectiveness of ventilation and introduce errors into reported ventilation.

204

205 5.3.NIV Parameters

206 Pressures

207 Achieving significant PCO_2 reduction is the main goal of NIV, along with resting of the
208 diaphragm and accessory muscles. Using bilevel NIV, this typically requires high driving
209 pressures (IPAP >18 cm H2O) to overcome high airways resistance present also in inspiration in
210 severe COPD. This results in larger tidal volumes, allowing adequate alveolar ventilation in the
211 context of increased dead space, and lower respiratory rates to help reduce hyperinflation[22]. In a
212 naïve patient, IPAP can be started at 12 cmH_2O, and increased empirically to maximal tolerated,
213 aiming a normalizing PCO_2[22]. Pressures up to 42 cmH2O have been reported[40], though values
214 above 30 cmH2O are unusual. While IPAP may need to be gradually increased to allow patient
215 adaptation, it has been shown that adherence is better with higher compared to lower pressures,
216 in addition to improved PCO_2, dyspnea and FEV_1[21].

217

Volume assured pressure modes (AVAPS/iVAPS), with or without auto-EPAP, can be a good option for auto-titration or for long-term use. However, mask leaks must be controlled for device algorithms to function properly. They appear to be equivalent with respect to efficacy to fixed PS modes[41,42], though some evidence suggests auto-EPAP can be superior regarding PCO_2 control and symptoms[43,44]. A starting target tidal volume of 6-8 mL per kilogram of ideal body weight can be used, with subsequent adjustment to optimize PCO_2 and comfort. The set minimal IPAP should be sufficiently high to ensure the target volume is reached through support provided primarily by the device rather than patient-generated effort.

The EPAP has traditionally been set at low values in non-obese COPD patients. A level of 3-5 cmH_2O should be used to start (devices limit minimum EPAP of 3-4 cmH_2O to prevent re-breathing in a single limb passive circuit). However, higher EPAP may be needed to correct upper airway obstruction[45], and can be titrated during polysomnography or using an auto-EPAP mode. EPAP can also help match intrinsic positive end-expiratory pressure (auto-PEEP), reducing triggering effort and asynchrony[46]. However, auto-PEEP cannot easily be measured. There is some evidence that higher EPAP may also correct expiratory flow limitation (EFL) by "stenting" the airways during expiration[46] which could improve comfort and reduce hyperinflation. NIV devices with self-adjusting EPAP targeting EFL exist, but are not widely available, and require further study. Manual adjustment optimizing patient device triggering and comfort remains necessary.

Back-up rate & Trigger sensitivity

Effective triggering is important for optimal synchrony, to minimize work of breathing and for comfort[12]. In addition to optimizing mask fit and EPAP, this can be achieved by adjusting trigger sensitivity in many devices, starting with medium. Initial high-intensity protocols included high BUR to control ventilation and minimize patient effort[47]. However, it has been shown that with adequate pressures, a high BUR does not provide further benefit or unloading of respiratory muscles [23]. In the US, obtaining a device for COPD with a BUR often requires either prescribing a ventilator, or "failing" a spontaneous bilevel device. For less severe patients, starting without a BUR may be reasonable. For more severe patients, obtaining a device with a BUR is advisable. When utilizing a BUR, we suggest starting at 12/min and titrating up only after optimizing

pressures, triggering, and Ti/cycling. Overly aggressive BUR may exacerbate patient-ventilator asynchrony (e.g. glottic closure)[48] and promote intolerance.

T_I and Cycling Off

Longer expiratory time helps reduce hyperinflation in COPD, hence a shorter Ti (Figure 1) is beneficial provided ventilation remains adequate. Delayed cycling off (returning from IPAP to EPAP)[49] can lead to asynchrony during flow-based cycling modes like bilevel S or ST, and VAPS (Figure 2). Cycling off should therefore be set at high sensitivity (earlier). Uncontrolled leaks may prevent synchronized cycling. Pressure (assist) control (PC / PAC) modes, where the T_I is fixed for all breaths, can be useful to remedy these problems. For bilevel S or ST and some VAPS modes, many devices allow limits on T_I on spontaneous breaths (min/max Ti); device-triggered breaths have a fixed Ti. We suggest a Ti min and max starting range of 0.5 - 1.0 sec.

Rise time

Patients with COPD often have "air hunger". A rapid pressure rise from EPAP to IPAP provides high flow when inspiration is triggered, reducing work of breathing[50]. This also allows reaching target IPAP faster and higher delivered volume for a given T_I.

Ramp up and Ramp down:

Bilevel devices may have a "Ramp up" feature allowing pressures to increase progressively when started. This can help when high IPAP is difficult to tolerate. Yet if pressures are too low, this may be uncomfortable and result in uncontrolled hypoventilation[51], hence this should be applied judiciously and followed-up.

Some COPD patients experience prolonged dyspnea upon stopping NIV in the morning, termed deventilation syndrome[52]. It can be remedied by adjusting parameters and improving synchrony[52]. Some devices now also include a "Ramp down" feature where pressures decrease gradually for an intended smoother transition to spontaneous breathing, but no clinical data are available on this feature.

5.4.Comorbidities

A significant proportion of COPD patients also have OSA, obesity, or another restrictive condition such as kyphoscoliosis. OSA can be corrected by adapting EPAP. However, the literature is scant on how to approach other parameters in the context of mixed obstructive and restrictive syndromes. While NIV for restrictive conditions also requires high IPAP, one would typically use longer T_I, slower rise time and delayed cycling off. Our practice is typically dictated by the primary spirometric abnormality. In a patient with milder COPD with a primarily restrictive syndrome, we chose parameters targeting the restriction. Adjustments are made as needed to optimize comfort, synchrony and gas exchange.

5.5. Monitoring

Monitoring of symptoms and daytime PCO_2 are key elements providing the clinician with feedback regarding NIV effectiveness. Overnight gas exchange should be assessed[53]. Oximetry is frequently used but difficult to interpret with supplemental oxygen. Overnight home $TcCO_2$ is useful[54] but remains technically challenging, expensive, and not widely available in North America. Device recordings (either via manual "download" or cloud-based remote monitoring) can help ascertain adherence, interface adjustment (leak), and more detailed ventilation outcomes[55]. Importantly, download data, such as tidal volume and minute ventilation, are inaccurate in the face of significant leak.

6. Applications beyond night-time use

Very dyspneic patients may benefit from NIV extension into the daytime. This can be achieved using the same settings as for sleep, e.g. during a rest period, but favoring a nasal mask to allow easier speech. Open circuit mouthpiece ventilation (MPV)[56] allows more freedom, mobility and improves ability to communicate. Commercial home ventilators now have dedicated MPV modes and circuits. Hand-held portable devices have been shown to improve dyspnea and walking distance[57], but can be heavy and impractical.

7. Conclusions

Data are accumulating, suggesting home LT-NIV in patients with hypercapnic severe COPD can improve clinical and patient-related outcomes, when the parameters are adapted to COPD physiology. Many questions remain regarding patient selection and implementation. COPD

patients bring a different set of challenges compared with other populations requiring home NIV. Pulmonologists will inevitably be faced with increasing demand that will require locally adapted protocols and care pathways to optimize delivery of this therapy.

Table:

Table. Principles of mask selection and application

Always confirm mask fit with NIV on
Lift the mask to inflate the air cushion, before tightening the headgears
Use the minimum tension required on the headgear
Always try the mask in the position it will be used
Verify that the patient can apply the mask correctly and without excessive effort
Clean the mask daily to remove the film left by skin sebum

Figure legends:

Figure 1. Main Elements of a Bi-level NIV Device -Supported Breath.

From Selim BJ, Wolfe L, Coleman JM, 3rd, Dewan NA. Initiation of Noninvasive Ventilation for Sleep Related Hypoventilation Disorders: Advanced Modes and Devices. *Chest* 2018; 153: 251-265.

Figure 2. Cycling threshold affects the duration of respiration. A: Normal respiratory mechanics. The cycle setting is 25% of peak inspiratory flow. Cycling is ideal, as indicated by the fact that the inspiratory flow decreases to the 25% cycling level at the end of the patient's neural inspiratory time (T_I). B: Obstructive respiratory mechanics. The change in the inspiratory flow curve leads to the 25% level being reached later, well after the end of the neural T_I. The duration of delayed cycling is represented by the excess T_I. Increasing the cycle setting to 60% of peak inspiratory flow corrects this problem, and cycling occurs at the end of neural T_I. Insp = inspiration. Exp = expiration.

From Gentile MA. Cycling of the mechanical ventilator breath. *Respir Care.* 2011;56(1):52-60

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335 Figure1 . (Permission will be required: Selim et al. *Chest* 2018; 153: 251)

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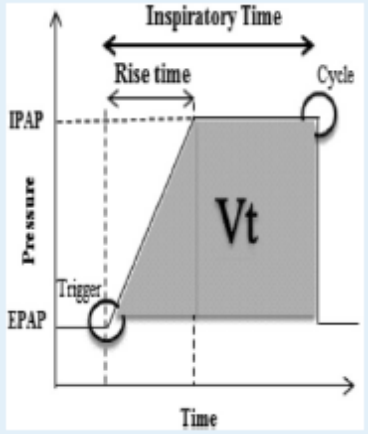
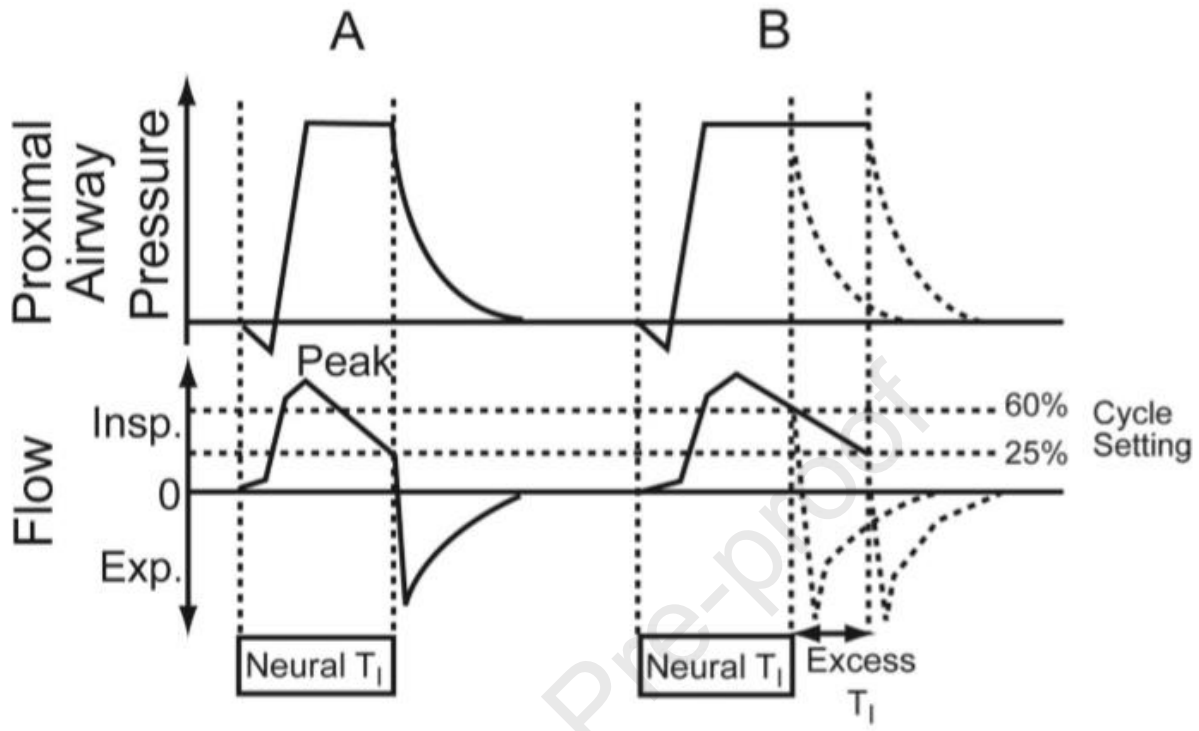


337 Figure 2, (Permission will be required; From Gentile, Respir Care 2011)



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