V̈-Com™ Increases Comfort and May Decrease Adverse Effects with Positive Airway Pressure Therapy

Suggesting a Diminished Role for Inspiratory Pressure in Treating Uncomplicated Obstructive Sleep Apnea

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Abstract

For 30 years, much focus in treating obstructive sleep apnea (OSA) with positive airway pressure (PAP) therapy has been increasing inspiratory PAP (IPAP) to maintain therapy and reducing expiratory PAP (EPAP) for comfort. First, bilevel PAP devices, then expiratory PAP (EPAP) reduction algorithms, and later mask resistance compensation algorithms were introduced, but this concept of IPAP > EPAP has not improved adherence and review of the literature suggests that this focus on IPAP may be misguided. Reducing EPAP decreases both pharyngeal cross-sectional area and wall stiffness which increases inspiratory resistance and effort, potentially increasing arousals and work of breathing (Analogous to drinking through a thinner straw with more collapsible walls). Our hypothesis was that reducing IPAP below EPAP (similar to early PAP devices) may improve comfort and decrease adverse effects. Since no current PAP device can reduce IPAP below EPAP, we developed the V-Com™ as a novel way to reduce IPAP and test our hypothesis.

Independent testing found 98% of new PAP patients (n=46/47) preferred the comfort of lower IPAP with the V-Com™ in their PAP circuit and felt more confident about using PAP such that 83% (n=39/47) were willing to pay $35 extra out of pocket for the V-Com™. 77% of long-term PAP users also preferred the lower IPAP with the V-Com™. Pressure intolerance during PAP titration polysomnogram was relieved with the V-Com™ in 91% (n=31/34) of patients.

The V-Com™ did not significantly affect therapy (P90/95% pressure), but did significantly improve usage time, leak, and residual index with auto-titrating PAP (n=61) in long-term PAP users. In fact, the V-Com™ reduced leak in 88% (n=54/61) of long-term users. The V-Com™ reduced two adverse effects of PAP therapy as evaluated in 400 consecutive titration polysomnograms: (1) the V-Com™ reduced the need of chinstraps for mouth openings by 85% (n=53/62) and (2) the V-Com™ resolved treatment emergent central sleep apnea (TECSA) in every occurrence (n=9/9).

These results that reducing IPAP with the V-Com™ improves comfort yet preserves therapy and likely reduces adverse effects should cause sleep medicine providers to rethink our approach to PAP therapy, particularly in regards to IPAP, and consider letting all new patients experience the V-Com™ in their circuit and decide what feels most comfortable to them.

Contents

Executive Summary

For 30 years most CPAP device advances have been focused on maintaining inspiratory positive airway pressure (IPAP) and reducing expiratory pressure (EPAP). Beginning with Bilevel PAP (BPAP) in 1990, then expiratory pressure reduction algorithms in 2003, and later mask resistance compensation algorithms around 2010, the thought was higher IPAP would maintain therapy and lower EPAP would decrease adverse effects. Yet none of these measures has been clearly shown to improve therapy or adherence. In fact, the opposite may be true regarding adverse effects. Having IPAP > EPAP may lead to increased leak, central sleep apnea, possibly aerophagia, and certainly increased risk of rebreathing CO_2. Since BPAP was released, we can find no report of testing IPAP less than EPAP. In fact, no currently marketed device can lower IPAP below EPAP, and therefore testing would not be simple.

Lowering EPAP, particularly end-expiratory pressure (EEP), compromises therapy. Reducing EEP reduces pharyngeal cross-sectional area (CSA_p), which dramatically increases inspiratory resistance, duty-cycle, and effort, thus increasing intraluminal collapsing forces. Increased inspiratory effort potentially increases arousals and work of breathing. Reducing EEP also reduces end-expiratory lung volume (EELV), which increases pharyngeal wall compliance (less stiffness), making it more likely to collapse. Supplying additional IPAP above EPAP in an attempt to offset this compromised airway might be prudent if lower EPAP improved outcomes, but that has not occurred. Despite all the other advances in technology, PAP adherence is still poor.

This IPAP > EPAP concept has potentially led to a widespread misunderstanding that IPAP is the best therapy for hypopneas, partly because hypopneas are principally an inspiratory event. The most effective treatment of hypopneas is sufficient EPAP to optimize CSA_p and minimize the inspiratory obstructing forces. Optimizing CSA_p decreases inspiratory effort and work of breathing. Sufficient EPAP also decreases pharyngeal wall compliance (increases stiffness) which further stabilizes the airway during inspiration. This IPAP > EPAP concept also fails to account for the viscoelastic properties of the pharynx. It is possible that the Starling resistor model has led to some of this misunderstanding. Higher IPAP is only necessary because the airway was destabilized by lowering EPAP.

Our hypothesis was by supplying sufficient EPAP (and EEP) to stabilize the upper airway, IPAP could be reduced below EPAP to maintain therapy and make the initial PAP experience more natural (lower inspiratory pressure) and more comfortable. In addition, we hypothesized that reducing IPAP below EPAP might decrease common adverse effects such as leak, treatment emergent central sleep apnea (TECSA), and possibly aerophagia. Since no current PAP device can be set with IPAP less than EPAP, we added a set amount of non-compensated resistance (V-Com™ device) to the circuit to reduce IPAP and principally maintain EPAP.

To evaluate the comfort of reduced IPAP with the V-Com™, a large regional medical equipment company performed independent testing and found 98% (n=46/47) of new CPAP patients felt more comfort with V-Com™ in their circuit and believed the V-Com™ would make them more

likely to use CPAP. In addition, after experiencing the V-Com™, 83% (n=39/47) were willing to pay $35 extra for the V-Com™ in their circuit.

We found 77% of long-term PAP users (n=52/67; survey response 67%) who experienced the V-Com™ for 4 nights preferred having the V-Com™ in their circuit long term. Pressure intolerance during PAP titration polysomnogram was relieved with the V-Com™ in 91% (n=31/34) of patients.

In evaluating possible effects on therapy and auto-titrating algorithms, we found the V-Com™ did not significantly affect P95%/90% pressure (therapy), but significantly improved residual index, leak and usage time (n=61 total), 23 using ResMed AirSense 10 or 11, 21 using Philips DreamStation II, and 17 using React Health Luna II). In fact, 88% (n=54/61) of long-term users had decreased leak with V-Com™ in their PAP circuit. In addition, bench testing showed that the V-Com™ does not affect the operation of expiratory pressure release algorithms (C-Flex+ [Philips] and EPR [ResMed]), does not affect CO_2 exhaust or increase the risk of rebreathing in the PAP circuit, and does not adversely affect oxygen therapy when combined with PAP therapy.

Preliminary data from 400 consecutive titration polysomnograms suggests that the V-Com™ reduced the need for a chinstrap in the event of oral leak/mouth opening in 85% (n=53/62) of patients and resolved 100% (n=9/9) occurrences of TECSA. In addition, we have numerous anecdotal reports of decreased aerophagia. The V-Com™ is a class 1 device for comfort and these preliminary results are not a therapeutic claim. Much more study is needed.

In regard to comfort, sufficient evidence may already exist for widespread use. If an intervention (V-Com™) is available, which adds comfort for a difficult to tolerate therapy (CPAP) and does not adversely affect that therapy and has minimal cost, it seems all new patients should be exposed to that intervention to see if they prefer the comfort. Long-term adherence trials will be interesting, but from the above data, it appears that patients preferring the V-Com™ in their PAP circuit is sufficient evidence for use.

About the Authors

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Disclosures

Both Dr. Noah and Dr. Hete have ownership interest in SleepRes, LLC, which manufactures the V̈-Com™.

Ms. Chafin has no conflicts to disclose.

1. The History of Increasing IPAP greater than EPAP

1.1 Beginning with Bilevel PAP

For 30 years, manufacturers of continuous positive airway pressure (CPAP) devices for the treatment of obstructive sleep apnea (OSA) have been focused on maintaining inspiratory positive airway pressure (IPAP) for therapy and reducing expiratory pressure (EPAP) for comfort and increased adherence. Prior to that however, the first commercial CPAP devices had much lower inspiratory pressures and higher expiratory pressures and still maintained therapy,[1] but some patients complained of difficulty exhaling. In 1990, Respironics (now Philips) first separated IPAP and EPAP and created the first bilevel PAP (BPAP).[2] Their thought was the forces leading to airflow obstruction were higher during inspiration, and by increasing IPAP, they could reduce EPAP for comfort and increase adherence. Increasing IPAP permits a reduction in EPAP, but after 30 years, the evidence for BPAP improving adherence is weak at best.[3,4] Potentially billions of dollars have been wasted switching patients to BPAP when continuing CPAP may have had the same outcome.[3] BPAP was a major advancement for noninvasive ventilation, but evidence suggests not for OSA, and the payers finally stepped in and said enough.

Increasing IPAP greater than EPAP has not only failed to improve efficacy or adherence[3] but has led to a common misunderstanding of the therapy for OSA. While realizing that EPAP is the therapy for complete airway obstructions (apneas), many in the field believe IPAP is the best treatment for partial airway obstructions (hypopneas). BPAP was introduced to lower EPAP for improved adherence, not to suggest IPAP was superior therapy for hypopneas.[2] IPAP alone cannot provide therapy; only EPAP can prevent apneas.[2-5] Merely lowering EPAP increases flow limitation[6] and IPAP must be increased above the CPAP level to compensate, generating a higher peak pressure in the system. In fact, BPAP has been shown to decrease upper airway stability.[7]

As we will discuss below, reducing EPAP, particularly end-expiratory pressure (EEP), reduces pharyngeal cross-sectional area (CSA_p)[7,8] either directly or potentially by reducing end-expiratory lung volume (EELV),[9,10] and this reduction in CSA_p extends into inspiration.[7] Reducing CSA_p exponentially increases inspiratory resistance (Darcy-Weisbach equation in Appendix 1), requiring increased inspiratory effort and causing increased inspiratory collapsing forces. Flow limitation from decreased CSA_p increases inspiratory duty-cycle (inspiratory time),[11] inspiratory effort leading arousals[12,13] and work of breathing (WOB).[14] Decreasing EELV also increases the therapeutic pressure required to prevent obstruction[15] and increases pharyngeal wall compliance, making the walls “floppier” and more vulnerable to flow limitation.[9,10,16] In other words, the increased IPAP with BPAP is only necessary because the upper airway was destabilized by reducing EPAP.[7,8] Optimizing EPAP minimizes the obstructing forces and effort during inspiration and best stabilizes the airway, rendering higher IPAP unnecessary.

Actually, CSA_p changes little during inspiration.[17] It may be best to think of the pharyngeal airway as a straw. Reducing EPAP reduces the diameter of the straw, requiring more effort and lower intraluminal pressure leading to inspiratory obstruction, and reducing EPAP makes the walls of the straw flimsier and even more likely to obstruct or collapse. The strategy behind BPAP to treat OSA would still be prudent if reducing EPAP had improved adherence as initially hoped.

Before Sullivan et al. introduced CPAP to treat OSA in 1981,[18] airway obstruction was thought to occur in response to inspiratory forces,[19] but in 1983, it was first found that EPAP alone could treat not only apneas but hypopneas (desaturations without apnea),[20] and that upper airway resistance (UAR) increased during expiration before inspiration.[21] This increase in expiratory UAR was later found to progress in the breaths preceding an obstructive event[22] and likely correlates with the progressive decrease in CSA_p found at end-expiration in the breaths preceding an obstructive event.[23] Increased IPAP can reduce hypopneas,[2,5] but sufficient EPAP to stabilize the pharyngeal airway at end-expiration, by increasing CSA_P and decreasing UAR, appears to prevent inspiratory obstruction regardless of higher IPAP.

Despite substantial evidence otherwise, sometime after the introduction of BPAP, it seems the focus left expiratory forces and returned to inspiratory forces proposed in the 1970s.[19] Possibly the observation that hypopneas are mainly an inspiratory phenomenon contributed to this misunderstanding that hypopneas are best treated by IPAP.[24] We have interviewed numerous pioneers in the field to try to elucidate how this incorrect thinking returned and continued. Several suggested the focus on IPAP > EPAP gained steam from the large home ventilation market that BPAP opened. IPAP > EPAP provides pressure support (PS), which augments ventilation and decreases the work of breathing (WOB) for patients with poor lung mechanics.

Without evidence we can find, it is commonly thought that IPAP > EPAP also decreases WOB for patients with normal/near normal lung mechanics. However, the opposite is more likely true. As discussed below, reducing EPAP and CSA_p increases inspiratory resistance and effort which increases WOB (Darcy-Weisbach equation in Appendix 1). Again, consider the straw analogy or think of trying to wean a ventilator patient with a small endotracheal tube. The patient may fail weaning because of increased WOB.

Financial incentives may have had some role in the persistence of IPAP > EPAP since manufacturers have substantially higher margins with BPAP over CPAP and medical equipment companies have much higher reimbursement. However, a provider (usually without financial gain) had to write a prescription for the more expensive device. Sleep medicine providers script the device which they believe will be most helpful and most cost efficient for their patient. BPAP was ordered because the provider believed it provided better therapy and/or adherence that was worth the markedly increased cost. The question is where is the evidence to support this believe and to support IPAP is superior therapy for hypopneas?

Though the evidence for BPAP in OSA is weak, it has helped many individuals with OSA and is certainly a major milestone in our field. The inventers of BPAP revolutionized noninvasive ventilation (particularly in nonhospital settings) and provided great science to the field of sleep

medicine. It is interesting that their initial BPAP titration protocol from 1990[2] with IPAP > EPAP is still the basis for the American Academy of Sleep Medicine (AASM) BPAP titration guideline recommended today.[25]

1.2 Expiratory pressure reduction algorithms got us further off track

While manufacturers may have profited from BPAP, they were clearly motivated by true belief in IPAP > EPAP when they later added IPAP > EPAP to CPAP devices. In 2003, Respironics released an expiratory pressure reduction algorithm (C-Flex) for CPAP devices based on previous work by Juhasz et al. [26] Respironics' resulting huge increase in market share led ResMed and other manufacturers to quickly add similar algorithms. Basically, most CPAP devices on the market became bi-level with IPAP > EPAP, though the PS is limited to 1-3 cmH_2O for most devices. Again, like BPAP, the expiratory "relief" of IPAP > EPAP has not clearly demonstrated an increased long-term adherence,[27] and is potentially decreasing efficacy.[28]

1.3 The peak of IPAP obsession: Mask compensation algorithms

The IPAP > EPAP belief among manufacturers strengthened to the point that around 2010 Philips, who just acquired Respironics, introduced mask compensation algorithms to further maintain IPAP, and other manufacturers again quickly followed. Each mask on the market has a different resistance and this resistance varies further depending on the cushion size. This information is in the package insert of the mask. In general, full-face masks have minimal resistance, and nasal masks have slightly more, but nasal pillow masks have considerable resistance, especially the smaller cushion sizes.

Many PAP devices now have a setting for the type of mask so that the device can compensate for the resistance in the mask. The higher the resistance, the more compensation required to maintain IPAP. Selecting the setting for a nasal pillow will further increase IPAP attempting to compensate for the drop in inspiratory pressure over the mask resistance. These algorithms may also reduce EPAP to compensate for increased EPAP (back pressure) developing in the pharynx during expiration.

The main fallacy of these algorithms is this continued obsession with maintaining IPAP despite evidence, but also that some manufacturers only provide compensation for their own masks. Using a ResMed mask with a Philips device may further increase IPAP and using a Philips or Fischer-Paykel mask with a ResMed device may decrease IPAP. There is also tremendous difference in resistance between ResMed's different nasal pillow cushion offerings, but there is only one setting.

Therapy is the pressure delivered to the pharynx and lung, not that delivered to the face. There is also the resistance of the nasal passage which behaves similarly. This is partly why nasal masks require less pressure for therapy than oronasal masks.[29-31] If you are going to compensate for

the increased resistance in a nasal-type interface over an oral mask, why not compensate for the nasal passage? While the resistance of a nasal pillow cushion (and the nasal passage) will drop the inspiratory pressure in the pharynx, that same resistance will increase the expiratory pressure for improved therapy but realize the pressure changes are flow-dependent.

These mask compensation algorithms fixated on IPAP have taken away part of the advantage of nasal pillow masks, increased the use of full-face masks, and have possibly worsened adherence. The small opening in the nasal pillow cushion increases the velocity of gas against the nasal mucosa (jetting). The resistance inherent in the small opening creates pressure drop and thus lowers that velocity for comfort, but the mask compensation eliminates this comfort. Even more, these algorithms were added without any evidence we can find showing improved therapy or adherence, pointing again to the prejudicial bias towards IPAP > EPAP in the field.

We suggest you test these algorithms on yourself using a nasal pillow mask. Experience the same pressure setting with the full-face mask setting selected then the nasal pillow mask setting (X2 and X1 on a Philips device). We have not found one person who preferred the nasal pillow setting.

2. IPAP greater than EPAP may have More Adverse Effects than CPAP

2.1 Summary

The hope that IPAP > EPAP would decrease adverse effects has not panned out. In fact, the opposite is likely true. IPAP > EPAP increases the risk of rebreathing CO_2, and possibly increases treatment-emergent central sleep apnea (TECSA), aerophagia, leak, and mouth openings.

2.2 Reducing EPAP increases risk of rebreathing carbon dioxide (CO_2)

Reducing EPAP increases the risk of rebreathing CO_2. Exhaust flow (intentional leak) and clearance of CO_2 from the PAP circuit is principally dependent on EPAP, not IPAP. The exhaust flow may be determined from the pressure-flow curve in the mask's package insert, which warns providers of CO_2 rebreathing at lower pressure settings. Increasing EPAP increases clearance of CO_2 and increases the safety in the PAP circuit.

2.3 Higher IPAP may increase treatment emergent central sleep apnea (TECSA)

IPAP > EPAP provides PS which can augment tidal volumes and lead to central apneic events.[32,33] TECSA is more commonly associated with BPAP with PS than CPAP[34] and with expiratory pressure reduction algorithms,[35] presumably from the small PS generated from the algorithms. We recently found the prevalence of TECSA during an in-lab titration study with expiratory pressure reduction (C-Flex+ at 3) to be 2.5% (n=10/400) compared to 0% (n=0/400) without expiratory pressure reduction turned on, again suggesting TECSA is more common with IPAP > EPAP. We also found that the V-Com™, which reduces IPAP below EPAP, resolved TECSA in all 10 cases (one case occurred during REM sleep and 9 in stage 2 sleep), further suggesting that IPAP > EPAP may be responsible. It may be that TECSA is very rare and only made more common by IPAP higher than EPAP. It may be no coincidence that expiratory pressure release algorithms were first introduced in 2003 and TECSA, initially called complex sleep apnea, was first described two years later.[36]

2.4 Higher IPAP may increase aerophagia (air swallowing)

Just as IPAP > EPAP increases the pressure gradient for airflow into the lungs, IPAP > EPAP increases the pressure gradient for airflow into the esophagus. Aerophagia, as an adverse effect to PAP therapy, is the development or worsening of abdominal distension, bloating, heartburn,

belching and flatus in response to PAP therapy. Aerophagia is more common with an oronasal mask than a nasal mask,[37] likely because pharyngeal IPAP is higher with an oronasal mask because of the lower resistance. Higher IPAP increases airflow into the esophagus (depending on the competence of the upper esophageal sphincter), and an incompetent lower esophageal sphincter allows esophageal air to exit into the stomach. This is likely why aerophagia is more common in patients with gastrointestinal reflux disease.[38] We have multiple anecdotal reports of lowering IPAP < EPAP with the V̈-Com™ reducing aerophagia symptoms and are currently formalizing a trial.

2.5 Higher IPAP may increase unintentional leak and mouth openings

IPAP > EPAP likely increases the risk of unintentional leak. The potential for leak increases as the pressure in the circuit increases.[39] BPAP may allow a lower EPAP and mean airway pressure[2] but increasing IPAP above the therapeutic CPAP level increases the peak pressure in the circuit. We recently found that the V̈-Com™ resolved mouth opening and oral leaks thus removing the need for a chinstrap in 85% (n=53/62) of patients with mouth opening during in-lab titration (see below). V̈-Com™ reduces IPAP while preserving EPAP and reduces leak and mouth openings, which further suggests that IPAP > EPAP increases the likelihood of leak.

3. The Science behind Reducing IPAP below EPAP

3.1 Brief review

Figure 1 shows a tracing from a 1986 study by Strohl and Redline with inspiratory pressure approximately 40% less than expiratory pressure, yet without respiratory events.[1] Because some patients complained of difficulty exhaling with these early devices, BPAP was introduced hoping a reduction in EPAP increased adherence.[2] Despite weak evidence for BPAP improving adherence[3,4] and no evidence we can find for IPAP > EPAP being superior therapy for OSA, many in the field still believe maintaining IPAP is a priority for therapy and that IPAP is the best treatment for hypopneas. It is interesting that no literature can be found in which IPAP below EPAP was tested for comfort and no current BPAP can even be set with IPAP below EPAP to easily test the concept.

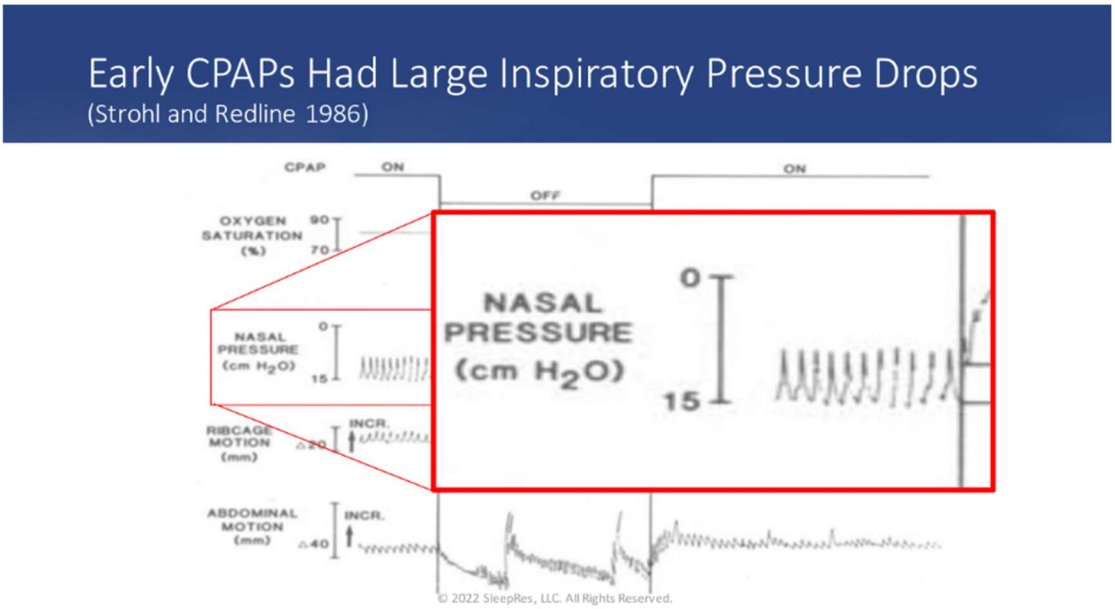

***Figure 1**: Enlargement of tracing from a 1986 study by Strohl and Redline with inspiratory pressure approximately 40% less than expiratory pressure.*

Supplying sufficient EPAP minimizes inspiratory resistance and obstructing forces as well as increases EELV, which increases pharyngeal wall stiffness. Again, think of the pharynx as a straw. Reducing EPAP is like trying to breathe through a thinner straw and one with more flimsy walls wanting to collapse. In addition, this focus on IPAP fails to account for the viscoelastic nature of

the airway and accompanying time delay with changes in CSA_p. We should discuss these three elements in more detail.

3.2 Sufficient EPAP optimizes CSA_p and minimizes inspiratory forces and need for IPAP

The inspiratory UAR across the pharynx increases roughly by the fourth power of the diameter of the CSA_P (Darcy-Weisbach equation in Appendix 1), meaning small decreases in CSA_P at end-expiration create large increases in inspiratory resistance, which in turn requires increased inspiratory pressure gradient (inspiratory effort) to overcome, which subsequently causes much lower intraluminal pressure and increased likelihood of obstruction. Resistance to flow in the pharynx acts like an orifice plate and length of the pharynx becomes less relevant. Appendix 1 presents the derivation from Darcy-Weisbach of how the pressure gradient (inspiratory effort) necessary to maintain inspiratory flow (and tidal volume) is inversely proportional to the average diameter of the obstructing segment of the pharynx. If obstruction is in more than one location then the pharynx would function as multiple orifice plates in a series and the resistances would be additive.

It is not the intent of this paper to discuss the multiple mechanisms proposed in reduction of CSA_p during expiration, but to address the consequences of decreased end-expiratory CSA_p. The marked increase in UAR with small decreases in CSA_p increases inspiratory effort, which can lead to arousals without flow limitation (respiratory effort-related arousals, RERAs).[12,13] By maintaining the same V_t, WOB must increase ($WOB = \Delta P \times V_t$).[13] As UAR further increases, either inspiratory effort leads to an arousal or flow limitation occurs. Once flow limitation develops, either inspiratory duty-cycle (inspiratory time) or respiratory rate must increase to maintain minute ventilation ($\dot{V}_m$)[11]. Both of these will increase WOB. For increased inspiratory duty-cycle, maintenance of the respiratory rate necessitates that exhalation be active, which requires additional work. For increased breath rate, assuming $\dot{V}_m$ remains constant, more effort per unit time is required, thus increasing WOB.

This concept that IPAP > EPAP decreases WOB can only be true after EPAP has been optimized to minimize UAR. Otherwise, it is like weaning a ventilator patient with too small of an endotracheal tube.

It is EPAP that determines end-expiratory CSA_P[7,8] which extends into inspiration, [7] likely by virtue of the viscoelastic nature of the pharyngeal wall constituents (see below). Optimal EPAP minimizes inspiratory resistance, inspiratory effort, and the inspiratory forces leading to airflow limitation. Increased IPAP is only required if EPAP is reduced to suboptimal levels where the airway is destabilized. IPAP alone does not provide therapy and can only reduce hypopneas.[2,5] IPAP provides no assistance to CSA_P at end-expiration,[5-8] the critical time to stabilize the airway.[5-8,17]

The concept of IPAP less than EPAP may be viewed in the context of critical closing pressure of the pharynx (P_{crit}), which relates to the therapeutic CPAP pressure.[40] Figure 2 was adapted from

Horner[41] where pharyngeal volume (y-axis) is plotted against P_{crit} (x-axis) and the slope of the line is pharyngeal wall compliance (wall stiffness). As pharyngeal volume increases (with increased CSA_p), the x-intercept or P_{crit} becomes more negative, which means there is more capacity to permit greater breathing effort without incurring apneas. We can thus see from Figure 2b and 2c, increasing pharyngeal volume and decreasing pharyngeal compliance both reduce the incidence of apneas by reducing P_{crit}.

Just as there is a P_{crit} for complete obstruction at the x-intercept where pharyngeal volume is presumed to be "0," there is also a critical pressure at some greater pharyngeal volume for partial obstruction (hypopneas and snoring). We will call that pressure P_{crit-o} for the critical obstructing pressure inducing a hypopnea, represented as horizontal line "o" in Figure 2. As pharyngeal volume increases from increased EPAP, P_{crit-o} or the "o"-intercept becomes more negative. Optimizing EPAP stabilizes the upper airway allowing lower IPAP for therapy.

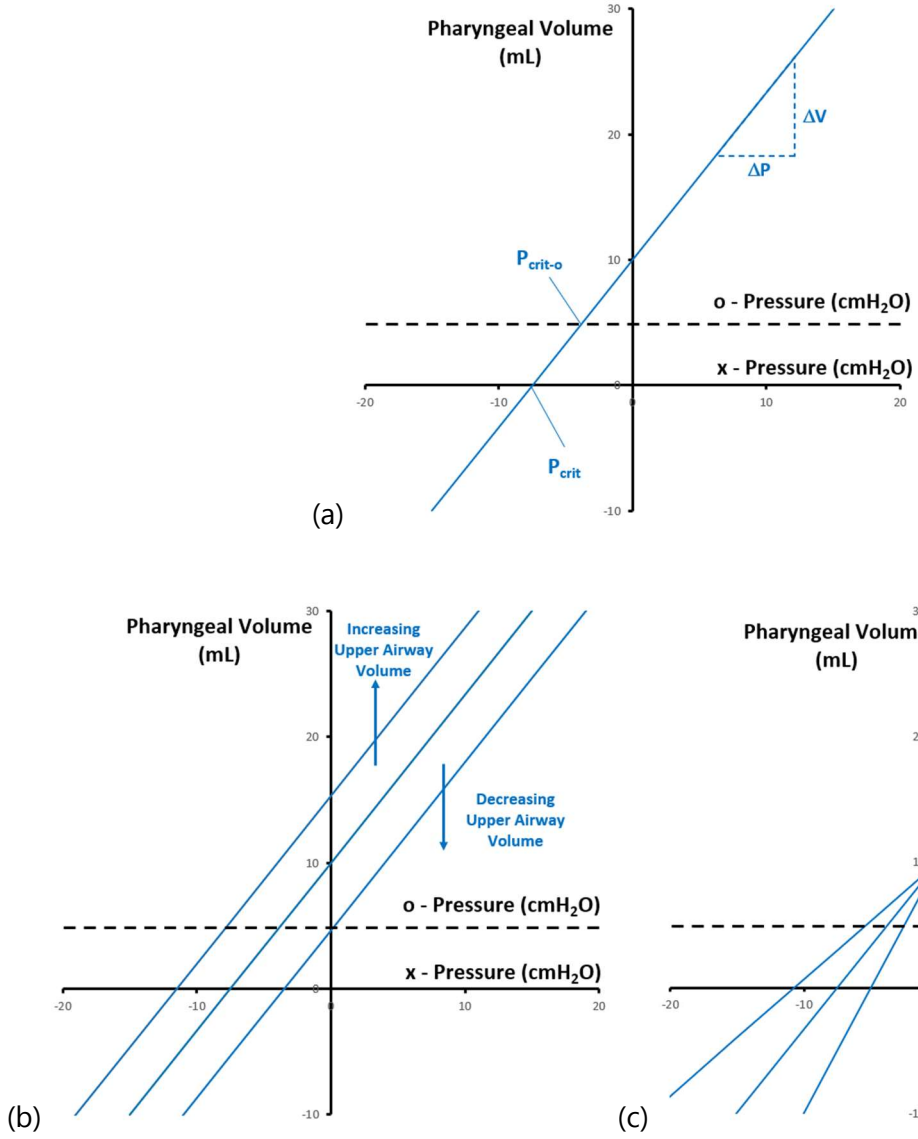

***Figure 2**: Diagrams based on Horner. Observing the first, 2(a), the vertical axis is pharyngeal volume, which more accurately can be thought of as cross-sectional area. The horizontal axes include the x-axis, where the intersection point represents the critical pressure, P_{crit}, and the o-axis represents the intersection point represents the critical hypopneic pressure, P_{crit-o}. Figures 2(b) and 2(c) illustrate the effect of changing pharyngeal volume and pharyngeal wall compliance, resp., on both P_{crit} and P_{crit} .*

3.3 EPAP, not IPAP, increases end-expiratory lung volume and tracheal traction

In 1984, Hoffstein et al., found CSA_p in patients with OSA was dependent on EELV,[9] and in 1990, Series et al., using an iron lung, found pharyngeal resistance varied with passive changes in EELV.[16] Later Heinzer et al. also used an iron lung to manipulate EELV and found that the therapeutic CPAP pressure could vary as much as 12 cmH_2O (4.8+/-0.7 to 17.1+/-1.0 cmH_2O) depending on EELV.[15] Then they later found they could reduce the apnea-hypopnea index by roughly half without any PAP by merely increasing EELV.[42]

The understanding of increased EELV increasing tracheal traction and decreasing pharyngeal wall compliance (increasing wall stiffness) has been well established for decades.[43] As lung volume increases moving downward in the chest, tracheal traction increases pulling down and stiffening the pharyngeal airway. This wall stiffening decreases P_{crit} (stabilizing the airway), which has been found to vary inversely with EELV, specifically $\Delta P_{crit} / \Delta EELV$ = -2.0+/-0.2 cmH_2O/L (p-value < 0.001).[44]

Returning to Figure 2 with pharyngeal volume on the y-axis, P_{crit} on the x-axis, and P_{crit-o} on the horizontal line "o," the slope ($\Delta V/\Delta P$) represents the pharyngeal wall compliance or wall stiffness. Decreasing slope (decreasing wall compliance) and increasing wall stiffness generates a more negative P_{crit} and more negative P_{crit-o}, thus stabilizing the airway and reducing the likelihood of obstruction.

Thus, it is optimal EPAP, particularly EEP, that has two actions to decrease P_{crit}: (1) by increasing pharyngeal volume or CSA_p (increasing the y-intercept) the x (P_{crit}) and o (P_{crit-o}) intercepts become more negative, and (2) by increasing EELV and decreasing pharyngeal compliance (reducing slope of $\Delta V/\Delta P$), both the x and o intercepts (P_{crit} and P_{crit-o}) are further reduced (made more negative). IPAP has neither action.

However, some IPAP may be necessary to maintain increased EELV. In a separate study, Heinzer et al., using a two-way valve to allow sub-atmospheric inspiratory pressures, found that EPAP alone did not increase EELV (other than that expected from the compressibility of the gas).[45] This would be expected if expiration in this model was forced. Braga et al., using an expiratory resistance device in the nares generating nasal EPAP (nEPAP), found the flow-dependent nEPAP increased EELV.[46] This finding seems unlikely since flow-dependent nEPAP peaks in early expiration and is absent at end-expiration, so what would be the mechanism to increase EELV?

The role of EELV in OSA is often under-emphasized. It should be noted that supine position[47,48] and sleep onset[49] both reduce pharyngeal wall stiffness by decreasing EELV and diaphragmatic

activity (which reduces EELV), respectively. Obesity and male sex both decrease EELV and have reduced pharyngeal response to increased EELV,[44,47,49] which may partly account for the increased prevalence of OSA in these populations. Abdominal compression using a pneumatic cuff to decrease EELV increased pharyngeal collapsibility in obese males with OSA.[50] It is EPAP, not IPAP, that compensates for the reduced EELV associated with obesity, male sex, supine position, and sleep onset.

Oral appliances, upper airway surgery, and hypoglossal nerve stimulators (HNS) do not increase EELV, which partly explains their reduced efficacy compared to CPAP, particularly in obese patients. Even in patients with supine predominant OSA where an oral appliance or HNS are thought to have a greater chance for success, Joosten et al. found EELV to be an important "triggering factor" for OSA in this group.[51] The lack of EPAP increasing EELV and pharyngeal wall stiffness is a major limitation to these alternate therapies for OSA. However, Kent et al. recently introduced neurostimulation of the Ansa cervicalis innervating the infrahyoid strap muscles of the neck to simulate the tracheal traction of increased EELV.[52] The combination of Ansa cervicalis stimulation and HNS appears promising.[53]

To complete the discussion on lung volume and its effect on upper airway obstruction, we must address what happens upon inspiration. While intraluminal forces for airway closure are higher during inspiration, the immediate increase in lung volume above EELV likely compensates and may explain why pharyngeal volume remains mostly stable throughout inspiration.[17] IPAP > EPAP was conceived to counteract the inspiratory pressure drop,[2] but that pressure drop coincides with increased tracheal traction at the initiation of inspiration. Again, increased IPAP is only necessary if EPAP and CSA_p are reduced.

Pharyngeal wall compliance is a dynamic process and the slope in Figure 2 changes throughout the respiratory cycle. The slope decreases (most wall stiffness) during inspiration and is at a maximum (most "floppy") at end-expiration when lung volume is the lowest and the airway is most vulnerable. Therefore, sufficient EPAP is required not only to maintain CSA_P and minimize inspiratory UAR, but to increase EELV to stiffen and stabilize the airway against collapse, particularly in obese patients where EELV is already reduced. Some amount of IPAP may be needed but not above EPAP.

3.4 Pharyngeal viscoelastic properties may extend EPAP effects into the inspiratory phase

This continued focus on IPAP > EPAP may partly exist from the historic approach to pharyngeal collapsibility characterized by the Starling resistor.[54,55] Though simplistic, it describes an ideal scenario, which only considers the upstream pressure and P_{crit} to define maximal flow under flow limitation. More recently, the biomechanical tube law has been applied to the pharyngeal airway to account for the varying locations and mechanisms for collapse.[56,57] Collapsing of biomechanical conduits often involves the development of longitudinal folds,[58] which is much

more complex than that represented in the Starling resistor model and is beyond the scope of this work.

The point is the viscoelastic nature of the pharyngeal airway, also called hysteresis, which is inherent in the biomechanics of flexible tubes, likely requires time to change shape and obstruct due to the viscous portion of the viscoelastic property. The Starling resistor model on the other hand, typically uses a purely elastic material, which insinuates an immediate change in CSA_P as intraluminal pressure changes (like volume in a balloon), thus failing to simulate the time delay in CSA_P changes after intraluminal pressure change. The reduced CSA_P and increased resistance that begins during expiration leading to obstruction develops over several breaths.[22,23]

The point to our discussion is that the increased obstructing forces during inspiration have little time to act as lung volume rapidly increases while the viscoelastic nature of the pharynx would likely delay reduction in CSA_P. It thus seems the principal means for the pharynx to obstruct during inspiration is insufficient EPAP to stabilize the airway beforehand.

A possible example of this viscoelastic property and time delay in obstruction may be the nEPAP devices, which have indications for mild-to-moderate cases of OSA and/or snoring.[59] With these devices, inspiration is sub-atmospheric, generating negative pharyngeal pressure, but expiration across the added resistance generates expiratory pharyngeal PAP. This nEPAP is flow-dependent and is maximal at peak expiratory flow but diminishes throughout the remainder of expiration. Most importantly, there is no nEPAP at end-expiration because there is no flow. This is a major limitation to therapy for nEPAP devices but despite sub-atmospheric inspiratory pressures and no EEP and its associated benefits described above, they still have some efficacy for inspiratory events (hypopneas and snoring). This is likely from the time delay of the viscoelastic nature of the pharyngeal airway, which does not fit the Starling resistor model.

3.5 Lung elasticity recoil pressure is increased in patients with OSA

It is interesting that there is less new in the literature in recent years regarding PAP and pharyngeal/lung mechanics. It seems more interest lies in nerve stimulation or other phenotypes of OSA. However, in 2015 Abdeyrim et al. found increased lung elastic recoil pressure in patients with OSA presumably related to the decreased lung volumes and increased UAR.[60] This may yield insight into the expiratory origin of OSA. Could this increased elastic recoil pressure participate in the gradual destabilization of the pharyngeal airway over several breaths?[22,23] It is interesting that in theory, EPAP with increased EELV would likely decrease this elastic recoil pressure, and increased IPAP with reduced EPAP (reduced EELV) and PS seems more likely to augment the recoiling. It is an interesting new concept that needs to be explored.

3.6 Reducing IPAP needs to be investigated

After 30 years of IPAP > EPAP, long-term adherence rates remain poor.[61-63] Our group recently published adherence data (n=3884)[64] comparing patients initiating PAP therapy through an integrated sleep practice (ISP group) vs standard care (control group). By defining adherence as averaging > 4 hours/night for > 70% of nights during the 30 days prior, the ISP group had 71% vs 66% (p-value=0.004) at 30 days, 66% vs 56% (p-value<0.00001) at 90 days, and 52% vs 32% (p-value<0.00001) at 1 year. Nonadherence rates for other chronic disease care are estimated between 25-50% in developed countries worldwide.[65-67]

While our ISP group had 90% more usage during the first year (312 vs 164 minutes; p-value<0.00001), there is still tremendous opportunity for further improvement. There are obviously many factors contributing to poor adherence including difficulty exhaling, but reducing EPAP has clearly not improved usage. There is an optimal EPAP to stabilize each airway that patients should adapt to over time. We need to explore elsewhere. Maybe after 30 years we should explore reducing IPAP.

4. The Science behind the V̈-Com™

4.1 IPAP less than EPAP returns after decades

Based on the evidence presented above, we hypothesized that supplying sufficient EPAP (and EEP) to stabilize the upper airway, IPAP could be reduced below EPAP to reduce inspiratory flow and mean airway pressure for comfort and still maintain therapy. The above evidence suggested that lower IPAP might make the initial PAP experience more natural (lower inspiratory pressure) and more comfortable. Certainly, maximizing EPAP and CSA_P should reduce inspiratory effort. In addition, we hypothesized that reducing IPAP below EPAP might decrease common adverse effects such as leak, TECSA, and possibly aerophagia. Since no current PAP device can be set with IPAP less than EPAP, we had to invent a way to reduce IPAP and principally maintain EPAP.

The easiest solution to test this hypothesis was adding a set amount of non-compensated resistance to the circuit between the PAP device and the exhaust port in the mask. The V̈-Com™ (released June 2022) is a small amount of resistance added into the PAP circuit (1.7 cmH_2O at 50 L/min). Earlier prototypes had slightly more resistance (2.1 cmH_2O at 50 L/m). Adding non-compensated resistance to a PAP circuit is not a new occurrence or phenomenon but purposely adding a specific amount to provide comfort is novel.

The resistance in the PAP circuit is changed unknowingly every day in medical equipment offices and sleep labs by changing masks, hoses, filters, and cushion sizes. Depending on the amount of resistance change and the location of the resistance change (before or after the exhaust port), both the therapy and experience for the patient may change considerably. In our experience these changes in circuit resistance are usually not accounted for in managing patients, yet doing so could provide much benefit to patients. As discussed above, many PAP devices attempt to compensate for the resistance of the elements in the circuit (e.g., mask compensation algorithms), but most devices sold in the US only compensate for masks by the same manufacturer and a single cushion size, and this compensation was added mainly to further increase/maintain IPAP and reduce EPAP.

4.2 V̈-Com™ reduces IPAP and inspiratory flow to improve comfort

The V̈-Com™ is a known addition of resistance to reduce IPAP for improved comfort while preserving EPAP, which does not appear to affect therapy adversely based on data presented below. The V̈-Com™ takes advantage of the parabolic shape of the pressure-flow curve with turbulent flow (Figure 3). Note at high flow there is considerable pressure drop, but at low flow, pressure drop is minimal. The V̈-Com™ adds specific resistance that the PAP device does not know is present in the circuit and therefore cannot compensate by further increasing IPAP.

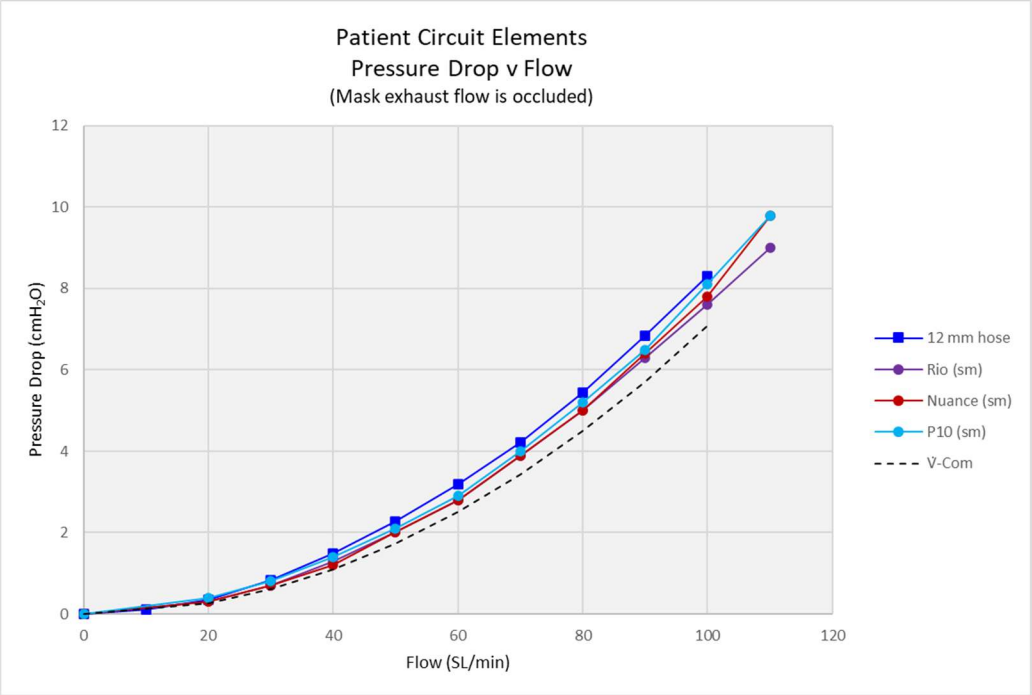

Figure 3: *Pressure-flow curve of V-Com™, 12 mm circuit hose, and 3 nasal pillow masks with small cushions. At high flow (during inspiration) a large pressure drop occurs (reducing IPAP). At low flow (during expiration) minimal pressure drop occurs (preserving EPA*

In Figure 4 there are 3 flows in a PAP circuit: Circuit flow coming from the PAP device, the patient flow (either inspiratory or expiratory), and exhaust flow exiting the circuit through the exhalation valve into the room. During the inspiratory phase on PAP, the circuit flow across the V̇-Com™ is high and includes the patient inspiratory flow plus the exhaust port flow in the mask (Figure 4a). The high flow across the V̇-Com™ during inspiration causes a large pressure drop (Figure 3), thus reducing IPAP.

During expiration, there is no patient flow crossing the V̇-Com (unless there is inadequate exhaust flow and potentially rebreathing of CO_2) and much of the exhaust flow is the patient's expiratory flow so the circuit flow from the device across the V̇-Com™ is minimal (Figure 4b). Minimal circuit flow means minimal pressure drop preserving EPAP and therapy. The V̇-Com™ reduces pressure during the inspiratory phase but provides very little pressure effect during the expiratory phase.

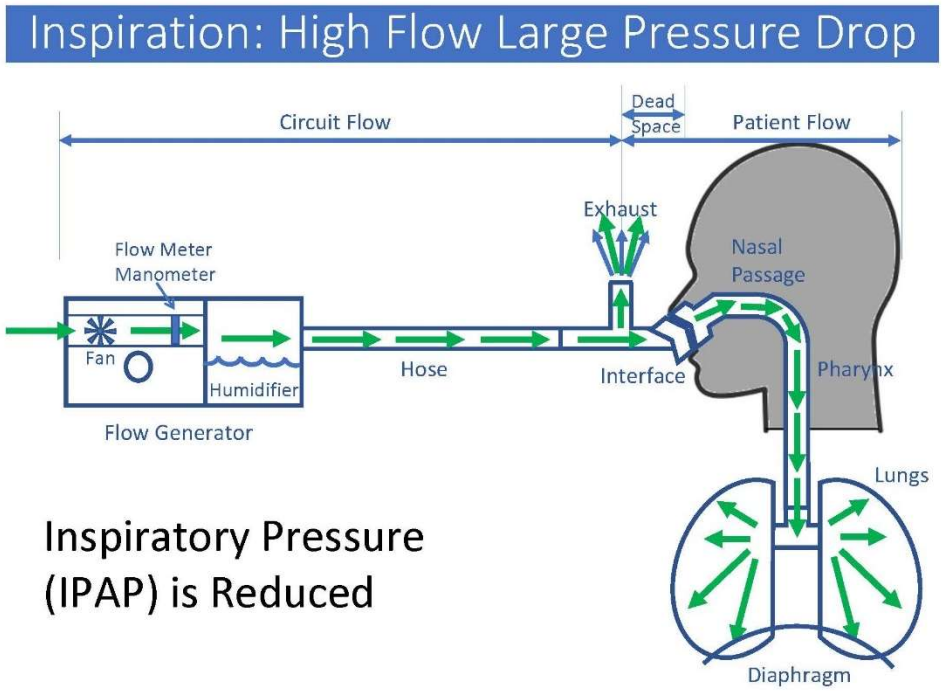

Figure 4a: *Pressure-flow curve during inspiratory phase.*

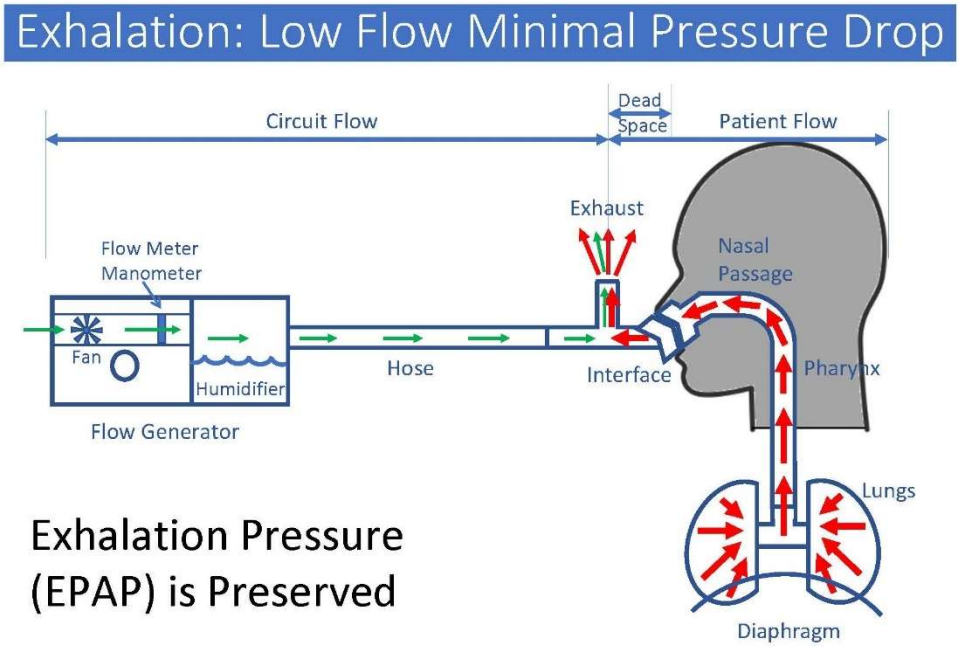

Figure 4b: *Pressure-flow curve during expiratory phase.*

4.3 Managing the flow-dependent pressure drop

As with all resistant elements of the PAP circuit, pressure drop is flow-dependent. Taller patients with higher inspiratory flow rates will experience greater pressure drop, and when trying the V-Com™, patients should breathe easy with their eyes closed as if they are trying to fall asleep. Many patients when first trying CPAP are anxious and take large breaths. This amplifies the expiratory resistance of the PAP circuit without the V-Com™. With the V-Com™ in the circuit. if patients take large enough breaths out of anxiety and blow past the exhaust port, they could experience increased resistance, and it is important for any person beginning PAP therapy to be coached to breathe easy.

Patients on higher PAP pressures will have exhaust flow much greater than expiratory flow and thus will have more flow over the V-Com™ during expiration. This circuit flow during expiration will cause expiratory pressure drop (reduced EPAP). Patients on fixed-pressure settings may need adjusting 0.5-1.5 cmH_2O higher. If the patient is in auto-titrating mode, the device should compensate. For patients requiring higher pressures, it is usually best to use a mask with a lower exhaust flow. This will reduce noise, humidity lost in the room, blowing on bedpartner, and potential pressure drops in the circuit.

We have been asked about using a bacteria filter as a resistor, but there are problems with using a bacteria filter. First, the resistance of the filter varies with the moisture content and can be dangerous. As moisture content increases, the risk of rebreathing CO_2 increases. Second, the resistance of a bacteria filter is also flow-dependent, but linear, not parabolic. There would be greater pressure drop at low flows and less pressure drop at higher flows. Finally, the cost would be exorbitant. Bacteria filters are not cleanable and should be replaced daily.

5. Summary of Clinical Data behind V̈-Com™

Note: Data presented below is part of multiple submissions for publication in process or part of the V̈-Com™ Quality Manual System

5.1 Comfort data

5.1.1 98% of new CPAP patients felt more comfort and are more likely to use CPAP with the V̈-Com™ and 83% were willing to pay extra for the V̈-Com™

To evaluate patient's perception of comfort, a large regional durable medical equipment (DME) company in the midwestern US conducted a trial without relationship, involvement or financial support from SleepRes, LLC (except SleepRes, LLC provided a box of 50 packaged V̈-Com™ samples for the trial). Using a single office in a large metropolitan area and a single respiratory therapist (RT) with a set protocol, the DME's goal was to obtain comfort information from 50 consecutive patients either presenting for new setup of CPAP, or for mask refitting. Each patient in the trial experienced CPAP at their prescription pressure using the same interface both without and then with the V̈-Com™ in the circuit. Patients were then asked 3 questions regarding their experience:

1) Which CPAP circuit felt more comfortable to you, with or without the V̈-Com™?
2) Do you believe the V̈-Com™ in the circuit would make you more likely to use your CPAP?
3) Would you be willing to pay $35 extra out of pocket to have the V̈-Com™ in your CPAP circuit?

From 9-6-2022 through 11-25-2022, 47 patients experienced their PAP circuit without, then with, the V̈-Com™ during new CPAP setups in the same office by the same RT. Because of the additional time required to educate and enroll participants in the study, patients were only recruited on days when the RT had four or less new setups on their schedule.

The results were as follows:

1) 98% (n=46/47) felt CPAP was more comfortable with the V̈-Com™
2) 98% (n=46/47) believed they were more likely to use CPAP with the V̈-Com™
3) 94% (n=39/47) were willing to pay $35 extra out of pocket to have V̈-Com™ in their CPAP circuit

5.1.2 V̈-Com™ was preferred by 77% of long-term PAP patients

To examine potential adverse effects for V̈-Com™'s Quality Management System (QMS), 101 patients from a large community-based sleep medicine practice were recruited to examine the V̈-Com™ in the circuit in regard to effects on auto-titration algorithms (P90/955 pressure), usage

time, leak and residual index (AHI). Initially, 61 were recruited to obtain therapy data, then later an additional 40 more were recruited. Patients with excellent adherence (> 6 hours/night) and no complaints with therapy were recruited to use the V̈-Com™ in their circuit for four nights. Download data was compared for four nights before (without V̈-Com™) and four nights with the V̈-Com™ as the only variable. Results are below under therapy data.

Each of the 101 participants were asked to give a written description of their experience with the V̈-Com™ during the 4 days of use. Of the total, 67% (n=67/101) responded and 77% (n=53/67) elected to continue use of the V̈-Com™ in their CPAP circuit long term.

This was an unexpected finding. We initially believed that patients who had habituated to CPAP would have become tolerant of the higher inspiratory flow and pressure with CPAP and not prefer the V̈-Com™ in their circuit. This was true in 23% of respondents, but 77% of long-term users who responded chose to keep their V̈-Com™ in the circuit indefinitely.

5.1.3 V-Com™ improves pressure tolerance during in-lab CPAP titration

During collection of titration PSG data from June 2022 – February 2023 for TECSA and oral leak, sleep technologists were also allowed to add a V-Com™ to the PAP circuit of a patient with pressure intolerance to the point they were about to abort the titration study. During the time period of the study, sleep technologists identified 34 patients with such pressure intolerance. The V-Com™ alleviated the pressure intolerance such that the titration study could continue and be completed in 91% (n=31/34) of those patients.

5.2 Therapy data

5.2.1 V̈-Com™ reduces IPAP without increasing respiratory events

The University of Utah Sleep|Wake Center studied several patients assessing the effect of the V̈-Com™ device by performing home sleep testing using a pressure tap at the mask. Figure 5 shows the V̈-Com™ is decreasing inspiratory pressure (IPAP) yet the expiratory pressure (EPAP) is maintained, and no increased respiratory events were noted with the V̈-Com™ in the circuit. Thus, effective therapy was maintained despite the decrease in IPAP. They also noted that the patients had less leak, but this is a small case series.

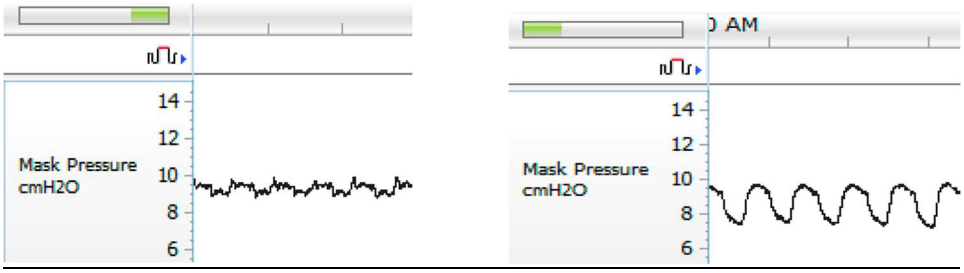

Figure 5: *Mask Pressure During Respiratory Cycle without V-Com (left) and with V̈-Com (right)*

5.2.2 V-Com™ did not affect auto-titration algorithms, usage time, unintentional leak or residual index (AHI)

The University of Utah performed independent review of the data from 61 patients from a large, community-based sleep medicine practice examining the effect of the V-Com™ in the circuit in regards to effects on auto-titration algorithms (P90/955 pressure), usage time, leak and residual index (AHI). Patients with excellent adherence (> 6 hours/night) and no complaints with therapy were recruited to use the V-Com™ in their circuit for four nights. Download data was compared for four nights before (without V-Com™) and four nights with the V-Com™ as the only variable. From Table 1 we can see that the P95%/90% pressure was not significantly changed. The usage time significantly increased and leak and AHI significantly decreased. Thus, therapy was not adversely affected and possibly improved. More specifically, with the V-Com™ in their circuit 88% of patients had decreased leak, 69% had decreased residual index (AHI), and 64% had increased usage.

Parameter	Participants	No V-Com	Std. dev	V-Com	Std. dev	Outcome w/ V-Com**	% Improved by V-Com™
P95%/90% Pressure (cmH_2O)	n=61	11.23	2.82	11.33	3.01	No difference	N/A-
AHI (events/hour)	n=61	2.15	2.37	1.79	1.75	Improved (p-value<0.04)	69% (n=42/61)
Leak (L/min)	n= 43*	12.06	9.50	8.00	7.27	Improved (p-value<0.0001)	88% (n=38/43)
Usage (hours)	n=61	7.27	1.33	7.54	1.43	Improved (p-value<0.03)	64% (n=39/61)

*****Leak data from Reach Health/3B devices was not available. One ResMed patient had leak of 120 L/min without V-Com™ (obviously from hose disconnect or error) and was removed.
******Differences AHI, Leak and Usage are significant based on ANOVA analysis.

Table 1: *Effect of V-Com on P95/P90 pressure, residual AHI, leak, and usage time.*

In this study, we were not able to obtain leak data from the React Health/3B devices because leak was not available from the specific QR code used to collect the data. Regardless, like the ResMed and Philips devices, the residual index was reduced. The V-Com™ is a known addition of resistance to improve comfort, which does not appear to adversely affect therapy and may improve therapy based on current data.

5.3 V̈-Com™ decreased adverse effects associated with PAP therapy

5.3.1 V̈-Com™ reduced the need for chinstraps in 85% (n=53/62) of 400 consecutive patients undergoing titration polysomnogram (PSG)

Our hypothesis was that higher inspiratory pressure (IPAP) was more likely to cause mouth opening and leak. From 6-21-2022 to 9-22-2022 400 consecutive titration polysomnograms (excluding BPAP and ASV/AVAPS titration studies) were performed and data collected. A protocol was established at three sleep centers (15 beds total) that during titration, before a chinstrap was to be applied to a patient for oral leak/mouth openings, a V̈-Com™ should be added to the circuit prior. The chinstrap was indicated (based on sleep technician assessment) in 16% (n=62/400) of titrations and V̈-Com™ was introduced first in all 62 cases. The V̈-Com™ avoided the need for a chinstrap in 85% (n=53/62) of cases, despite therapy pressure being further increased after the V̈-Com™ in many of these titration studies. It should be noted that in each of these titrations, C-Flex+ was utilized at setting 3.

This data suggests that V̈-Com™ may reduce the use of chinstraps and further suggests that oral leak/mouth openings may be related to higher IPAP and improved by reducing inspiratory pressure. Combining this data with the decreased leak data from above suggests that leak is more associated with inspiratory pressure, particularly when IPAP is greater than EPAP.

5.3.2 V̈-Com™ resolved treatment emergent central sleep apnea (TECSA) in 100% (n=9/9) of patients developing TECSA during 400 consecutive titration PSGs

Our hypothesis was that TECSA resulted from augmented tidal volumes (V_t) and increased $\ddot{V}_m$ from PAP therapy, particularly when IPAP greater than EPAP provides PS. While increased loop gain is likely involved, there must be some increase in $\ddot{V}_m$ to reduce $ETCO_2$ below the apneic threshold. It is noteworthy that TECSA (complex sleep apnea) was first described in 2005,[36] which was 2 years after the introduction of expiratory pressure reduction algorithms in 2003 and these algorithms have been reported to increase the occurrence of central sleep apnea (CSA).[35]

From 6-21-2022 to 9-22-2022, which included 400 consecutive titration polysomnograms (excluding BPAP and ASV/AVAPS titration studies), a protocol was established at three sleep centers (15 beds total) that in each instance of TECSA occurring during CPAP titration, a V̈-Com™ should be placed in the patient's CPAP circuit and the titration should continue. Among the 400 titration studies, TECSA was identified 15 times or in 3.75% (n=15/400) of studies using the criteria of CSA index > 5 events/hour over the time interval beginning at the time of the first event. Cases were not considered to be TECSA if CSA was observed during the diagnostic PSG or diagnostic portion of a split study. No evidence of Cheynes-Stokes breathing, history of CSA or heart disease, or narcotic use could be present.

Detailed review of each case suggested that in 5 of the cases, the central apneic events occurred mostly after arousals during fragmented sleep (despite a CSA index > 5). In addition, 1 case of TECSA was clearly REM-related, which is reported[68] but rare. Nine cases remained in which no explanation was found for their CSA (which all occurred during stage 2 sleep) other than the central events began during initiation of CPAP therapy for an incidence of 2.3% (n=9/400). In each of the 9 cases, introduction of the V̈-Com™ into the circuit resolved the CSA (reduced CSA index < 5 events/hour). The V̈-Com™ also resolved the CSA in the other 6 cases initially identified but later excluded.

During each of the 400 consecutive CPAP titrations over 3 months, C-Flex+ was utilized at setting 3. Then C-flex+ was turned off in all 3 sleep centers (15 beds total) and titration studies were monitored beginning 10-22-2022 until 400 CPAP titration studies occurred. Only 1 case of potential TECSA was identified during the 3-month time period without C-Flex by a sleep technologist and review found CSA present during the diagnostic portion of the study and that the patient was on narcotics. Thus, no cases of TECSA were discovered among the 400 consecutive titration PSGs.

The finding of 9 cases (potentially 15 cases) of TECSA over 3 months with expiratory pressure reduction (small PS) engaged and no cases over the similar circumstances further suggests these algorithms, which produce small amounts of PS, may participate in the occurrence of TECSA. The finding that the V̈-Com™, which reduces IPAP yet maintains EPAP, resolved each occurrence of TECSA, further supports our hypothesis that TECSA occurs at least partly in response to augmented V_t and $\ddot{V}_m$ associated with PAP therapy.

5.3.3 V̈-Com™ may reduce aerophagia (air swallowing) and machine noise

Our hypothesis was that aerophagia was likely increased by IPAP > EPAP with resulting small amounts of PS, and that by reducing IPAP below EPAP, aerophagia symptoms may improve. Since the release of the V̈-Com™ in June of 2022, we have received numerous anecdotal reports of the V̈-Com™ reducing symptoms related to aerophagia when introduced into the circuit. Some of these anecdotal reports occurred among the 101 patients enrolled in our therapy evaluation trial, yet most occurred randomly from patients adding the V̈-Com™ to their circuit and other providers informing us of the finding. We are currently organizing a formal trial.

5.4 Safety data

5.4.1 V̈-Com™ does not affect the operation of expiratory pressure reduction algorithms

Experiments were conducted to identify the effect of the V̈-Com™ on expiratory pressure release algorithms in both ResMed AirSense 10 and Philips DreamStation 2 PAP devices according to the schematic in Figure 6. The presence of the V̈-Com™ caused the IPAP pressures to decrease as compared to the non-V̈-Com™ condition, but during the expiratory phase, there was no

change in EPAP when the V̈-Com™ was added. Thus, there was no effect on expiratory pressure release in either device.

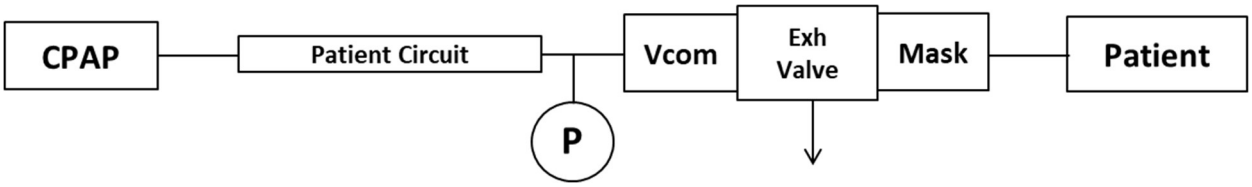

***Figure 6**: Schematic for expiratory release experiments.*

5.4.2 V̈-Com™ does not affect CO_2 exhaust or rebreathing in the PAP circuit

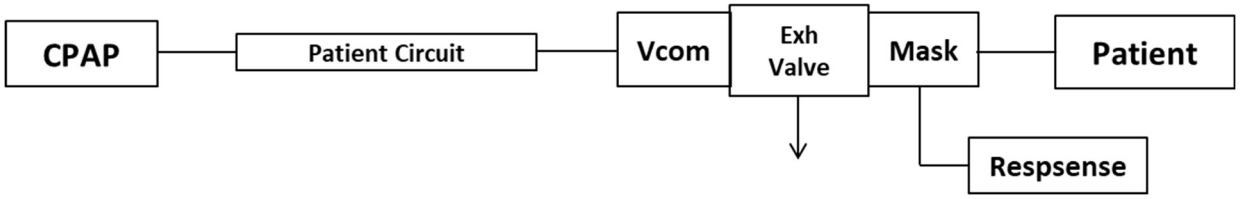

***Figure 7**: Schematic for CO_2 experiments. Note that Respsense is a capnography monitor from Nonin.*

5.4.3 V̈-Com™ does not adversely affect oxygen therapy combined with PAP therapy

Experiments were conducted to identify the effect of the V̈-Com™ on FIO2 in spontaneously breathing patients on oxygen therapy according to the schematic in Figure 8. The FIO2 without the V̈-Com™ was recorded to be 25.5% for both nasal pillow and full-face masks without the V̈-Com™ present. After the V̈-Com™ was added, both masks registered FIO2 values around 26%. Patient FIO2 increased slightly (0.5%) when the V̈-Com™ was added to the circuit. We attribute this to the fact that during the inspiratory phase, there is less oxygen leaking from the system due to the lower drive pressure that drives flow from the exhalation valve, reducing the amount of oxygen lost from the circuit.

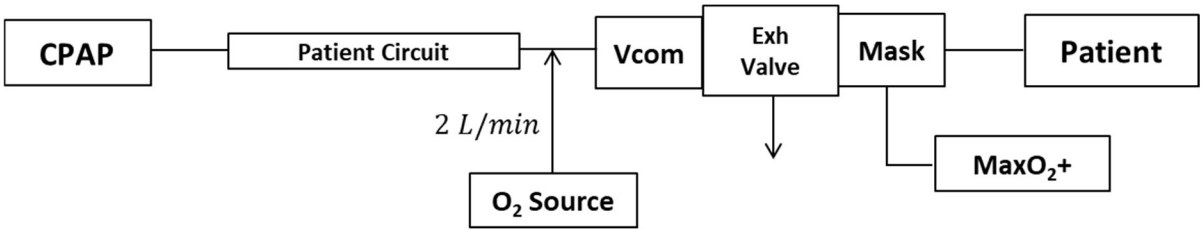

***Figure 8**: Schematic for FIO2 experiments. Note that the MaxO2+ is an oxygen analyzer from Maxtec.*

6. Appendix 1: Darcy-Weisbach Equation and Application to Pharyngeal Physiology

- Pressure is a gradient of mechanical energy and in our case is transmitted to surfaces by a fluid (air). It acts equally perpendicular to all surfaces it contacts.
- Pressure has many units but in respiratory medicine, cmH_2O are used.
- Pressure is a potential and does not itself transfer mass (air molecules), but must be present in order for mass to be transferred.
- Flow ($\dot{V}$ or Q) is volume over time (think of it as the number of molecules of air over time), and is given in L/min.
- For flow to occur, pressure must first be present. The quantity of flow is dependent on the resistance, which is defined primarily by the cross-sectional area of the flow path
    - As cross-sectional area goes to 0, flow goes to 0 and resistance becomes infinite
    - As cross-sectional area becomes large, flow gets large also, and resistance goes toward 0
- Flow resistance in the pharynx acts like an orifice plate, which means flow is turbulent and the length of the pharynx can be ignored, giving the following relationship among pressure, flow and resistance
- For flow through an orifice,

$$\Delta P = RQ^2$$

$$R = \frac{c}{d^4}$$

where c includes numerical constants and various gas properties and d is the orifice average diameter

- Pressure drop becomes

$$\Delta P = c\frac{Q^2}{d^4}$$

- Work of breathing is the product of pressure and volume
    - Pressure is generated by diaphragmatic effort
    - Volume is the quantity of gas accumulated during the inspiratory phase but because of metabolic need, the volume must be held constant through time

- For a given minute volume, WOB is directly proportional to pressure

$$WOB = \Delta P \times V \longrightarrow \Delta P \propto \frac{1}{d^4} \longrightarrow WOB \propto \frac{1}{d^4}$$

- Start with diameter of 20 mm and assume the required flow results from a pressure generated of 5 cmH_2O
- **For the same flow**, the following reductions in diameter and resulting pressure need and WOB change would be:

Diameter (mm)	Pressure (cmH_2O)	WOB Factor
20	*5.0*	*1.0*
18	7.6	1.5
15	15.8	3.2
12	38.5	7.7

Table 2: *Model describing the required elevated pressure and multiple on work of breathing (WOB Factor) associated with reducing airway diameter.*

- The high pressures at the bottom of the table are the physical requirement to maintain the same minute volume under the given resistance, but in reality, such restriction may result in flow limitation instead, and pressure would not rise to those levels.

7. Appendix 2: Additional Frequently Asked Questions

1. Does V-Com™ require a prescription?

   The answer is no. V-Com™ is not a therapy but an accessory to PAP therapy and is only indicated for use in a PAP circuit. To use a V-Com™ as indicated, an individual must be on PAP therapy, which is a prescribed therapy. No separate prescription for a V-Com™ is necessary.

2. How long does a patient need to wear the V-Com™?

   The length of time will vary among patients (like training wheels on a bike). Over weeks (or months), patients develop tolerance to the peak flows and pressures of PAP therapy. Once a patient can easily tolerate the peak flows and pressures of PAP therapy, the V-Com™ device may be removed from the circuit.

   However, since beginning short trials with long-term PAP users, we are finding many participants wish to keep and use their V-Com™ indefinitely. V-Com™ not only reduces inspiratory pressure and thus flow, but it "softens" the inspiratory flow curve, and many patients are preferring that experience. V-Com™ also appears to decrease unintentional leak and mouth openings, which also improves the experience and possibly the therapy. There are also numerous reports that V-Com™ reduces the noise from the device which has led to bedpartners requesting the V-Com™ in the circuit.

3. What about using V-Com™ in patients on fixed pressure settings?

   For patients who have been prescribed a fixed pressure on a PAP device and have a V-Com™ device added to the circuit, a clinician may consider increasing the set fixed pressure by the pressure drop of the exhaust flow (found in the package insert of the interface). For example, if the exhaust flow of the patient's mask is 30 Lpm at the fixed pressure, V-Com™ may decrease patient pressure by 0.6 cmH_2O between breaths. The clinician may wish to increase the fixed pressure by 0.5-1.0 cmH_2O or just observe and follow.

4. Is the cost of V-Com™ economical?

   Considering the cost of sleep testing (both home sleep apnea test [HSAT] and polysomnogram), office visits, the PAP device, interface, and other supplies, the V-Com™ device, by increasing comfort, may be the most cost-effective part of treatment. If a patient cannot tolerate the PAP device, all the costs of diagnosis and treatment were a waste of money and time. Also, those patients who fail CPAP therapy will be presented with the much higher cost of an oral appliance or the exorbitant costs of surgery. The V-Com™ device is a tremendous value for patients prescribed PAP therapy.

5. How do patients clean the V-Com™?

   The V-Com™ is cleaned using soap, water, and a small brush. Specific cleaning instructions are detailed in the package insert. V-Com™ is single patient, multi-use.

6. Does V-Com™ affect the function of bilevel PAP (BPAP) for noninvasive ventilation (NIV)?

   The answer is that V-Com™ minimally affects BPAP. Because V-Com™ has more effect on inspiratory PAP (IPAP) than EPAP, we expected V-Com™ to reduce the level of pressure support (PS) [PS = IPAP – EPAP]. However, our testing showed little change (< 1-2 cmH2O) in PS (IPAP 20 and EPAP 10) with V-Com™ in the circuit. With BPAP, the level of PS is usually titrated to a target tidal volume (V_t). To minimize the effect of V-Com™ on the target V_t, place V-Com™ in the circuit before titrating the level of PS. Note that V-Com™ has not yet been tested in adaptive servo ventilation and average volume-adjusted pressure support breathing circuits.

7. Will V-Com™ help someone acclimated to PAP therapy?

   Yes, but not necessarily. V-Com™ was indicated for individuals initiating or struggling with PAP therapy. However, we have had many patients acclimated to PAP therapy want to try the V-Com™ and subsequently preferred the experience with V-Com™. Partly for the softened inspiratory flow, partly for the decreased leak, partly for believing they felt better the following morning with the V-Com™, and partly for the decreased noise from the device, many long-term PAP users have chosen to add a V-Com™ to their circuit. We were not expecting this prior to launching the V-Com™. We have subsequently broadened the indications for use to provide inspiratory comfort to any patient on CPAP, APAP, and BPAP.

   Someone who has become very comfortable with the pressures and flows of their PAP therapy without the use of a V-Com™ may not enjoy a V-Com™ being added to their circuit. The softening of inspiratory flow and pressure by V-Com™ will be a change in experience that they may not prefer. This has been the experience of some long-term users who do not want the V-Com™ in their circuit. However, there have also been those users who did not prefer the V-Com™ at their current pressure, but after being re-titrated to a higher pressure, appreciated the comfort of the V-Com™ at the higher setting.

   V-Com™, like training wheels on a bike, was mainly designed for individuals beginning or having difficulty with PAP therapy to get them experiencing the benefits of PAP therapy faster and easier. However, the majority of long-term PAP users we included in our trials chose to leave the V-Com™ in their circuit after the trial. They preferred the V-Com™ experience. We have also found since the release that most patients starting PAP therapy with the V-Com™ are choosing to continue with the V-Com™ long term.

8. How should I breathe with a V-Com™ in my PAP circuit?

   You should breathe the same as you do without a V-Com™ in your PAP circuit. No change. However, we find many patients do not understand how to breathe on a PAP circuit in general. When beginning PAP therapy (putting on the mask and turning the PAP device on) you should be lying in bed, relaxed, ready to fall asleep. Your respiratory rate (RR) should be slow, and your breath size (V_t) should be smaller. You should focus on breathing that way. It may help you fall asleep.

   PAP circuits are not designed for a larger V_t and higher RR associated with activities or even anxiety. Increased V_t and RR cause two main problems:

   a) Increased perception of resistance in the circuit on both inspiration and expiration. This can be particularly true with extra resistance in the mask.

   b) Increased likelihood of CO_2 rebreathing by overloading the exhaust flow.

   When first trying PAP therapy, many individuals are apprehensive and unknowingly increase both their Vt and RR, which makes the experience, even with a V-Com™ in the circuit, less desirable. These individuals need to relax and breathe easily as if they are falling asleep to best experience PAP therapy and the comfort of V-Com™.

9. If you remove V-Com™ from your PAP circuit, should you discard your V-Com™?

   We recommend keeping your V-Com™. After cleaning and drying your V-Com™ per the instructions, place your V-Com™ in its heavy duty, resealable plastic package and store with your PAP equipment/supplies. In the future, your PAP therapy (pressure setting) may require changing and your V-Com™ device may be required again. If the V-Com™ is showing signs of wear, then discard it.

10. Would every new patient on PAP therapy benefit from having V-Com™ in their PAP circuit?

    For most patients the answer is yes, but not every patient will require a V-Com™. Just like training wheels on a bike. Training wheels would help almost every child ride sooner, but not every child needed them in order to learn to ride.

    There is a small subset of patients with COPD, hypoventilation, and even morbid obesity where the higher IPAP is necessary for treatment. If the V-Com™ is to be included in the circuit, the clinician must account for the decrease in IPAP > EPAP.

    A major problem with PAP therapy is that the majority of prescriptions are written for an APAP range of 4 (or 5) cmH_2O to 20 cmH_2O, yet the average and most common pressure required is 12 cmH_2O (this is from a database of >8000 consecutive patients and excluding those patients that required > 20 cmH_2O and were prescribed BPAP). Few patients require <7 or >18 cmH_2O. During PAP therapy set-up (and demonstration), most patients are tried at 5-6 cmH_2O, yet more than half may require 12 or more

cmH2O. These patients may have a very difficult experience in the middle of the night and stop therapy.

To improve early acceptance of PAP therapy, which has been shown to increase long-term adherence,[57] new patients should experience higher pressure (8-12 cmH_2O minimally) during set-up. Have them breathe slow and easy, tightening their chest and abdominal muscles to learn to resist the pressure and control the flow. Once they can accomplish that, then place the V̈-Com™ in the circuit. They will see the ease in breathing the V̈-Com™ immediately adds. The comfort and tolerance they experience with the V̈-Com™ will give them confidence in this critical beginning of therapy, especially in the case that they require higher pressures.

V̈-Com™ will increase early tolerance across a patient population, and early tolerance has been shown to increase long-term adherence.[61,69]

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