Robert C. Basner
Sairam Parthasarathy *Editors*

Nocturnal Non-Invasive Ventilation

Theory, Evidence, and Clinical Practice

Springer

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Editor's Preface

"Nocturnal noninvasive ventilation": the term, rightly, is at once compelling and confusing; the current state of the art reflects this. Imperative indeed is the need for better appreciation of the background and theory of noninvasive ventilation, and its optimal application both awake and in sleep. For the art and science of noninvasive ventilation is a "black box" even among the most well-taught and intuitive of our clinicians and researchers, particularly when the "nocturnal" imperatives (usually, read "sleep") are considered, or at least should be considered. What is the history of such ventilation, what is the current biologic and clinical evidence base, and what are the lessons of these for current standards of practice of this critical health-care modality? What are the clinical conditions and medical settings which should, and must, be met with noninvasive ventilation (e.g., acute or chronic hypoventilation syndromes and settings in which hypoventilation and cardiorespiratory status can be improved or at least sustained); in which physiologic state is such ventilation best applied (e.g., awake, asleep, and both); how is such ventilation optimally applied (e.g., interface, settings, and mode), and how best assessed for accuracy (e.g., bedside clinical and blood gas monitoring of the patient, polysomnography) acutely, and chronically (e.g., objective tracking systems)?

This volume is novel in its design and purpose: to be a readable, intelligible, precise, comprehensive, and authoritative single textbook encompassing the most current clinical and theoretical knowledge base necessary to understand the clinical imperatives and optimal practice of this most noble and important aspect of our medical profession and encounters; to inform and stimulate clinicians and researchers to optimally work out the investigational demands of the field of noninvasive ventilation in 2015 and well beyond; and to allow us to apply the modality of noninvasive ventilation for the optimal benefit of a critically ill and a most vulnerable population.

And, to allow the "black box" of nocturnal noninvasive ventilation to be opened, and to remain so.

New York City, 2015 Robert C. Basner, M.D.

Contents

1 "Nocturnal" Noninvasive Ventilation: An Overview 1
Robert C. Basner

2 Negative Pressure Noninvasive Ventilation (NPNIV): History, Rationale, and Application 27
Norma MT Braun

3 Nocturnal Noninvasive Ventilation in Heart Failure 73
Sogol Javaheri and Shahrokh Javaheri

4 Nocturnal Noninvasive Ventilation in Obesity Hypoventilation Syndrome 83
Amanda Jane Piper and Carly Ann Hollier

5 Nocturnal Noninvasive Ventilation in Neuromuscular Ventilatory Disorders 113
Brian Palen and Joshua O. Benditt

6 Nocturnal Noninvasive Ventilation in Children 135
Rakesh Bhattacharjee and David Gozal

7 Nocturnal Noninvasive Ventilation and Adjuncts in Disorders of Breathing Control 163
Robert Joseph Thomas

8 Noninvasive Positive Pressure Ventilation: Systems for Tracking Adherence and Efficacy 209
Patrick J. Strollo and John M. Coleman

9 Use of nNIV in Obstructive Sleep Apnea: Modes, Flexes, and More 235
Jeremy A. Weingarten

10 Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure 247
Christopher R. Gilbert and Philippe Haouzi

Index 271

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Chapter 1
"Nocturnal" Noninvasive Ventilation: An Overview

Robert C. Basner

Introduction

Noninvasive ventilation (NIV) represents a ventilatory support strategy employed without the use of endotracheal intubation or tracheostomy, which should be considered in several clinical settings:

- Patients with chronic *awake hypoventilation* and/or breathing control disorders or diatheses
- Patients with acute, or acute on chronic, *awake hypoventilation* and/or breathing control disorders or diatheses
- Patients with awake *hyperventilation* disorders; most importantly, heart failure and cerebrovascular disorders with associated Hunter-Cheyne-Stokes breathing [1]
- Patients with primary *sleep apnea* (e.g., obstructive sleep apnea (OSA), and certain types of central sleep apnea) *not* typically or clinically associated with awake ventilatory disorders

"Nocturnal" NIV (nNIV) as ventilatory support for chronic hypoventilation syndromes, the major focus of this text, has a distinguished history [2]. Use of such therapy has become increasingly more informed, and similarly more complicated, as knowledge and experience regarding sleep breathing control and function and disordered breathing in sleep have accrued, and modes, technologies, and methodologies for delivering NIV, and tracking adherence and efficacy of its use, have progressed. At the same time, expertise and scientific rationale in, and for, the use of NIV, nocturnal and otherwise, paradoxically remain under-accumulated, under-appreciated, under-taught, and typically unempirically applied in clinical practice.

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Consider current characteristic nomenclature for the discipline: “Nocturnal” is not synonymous with “sleep” in the context of using NIV. “Nocturnal” may refer to NIV applied to an awake patient at night (e.g., after admission for an acute on chronic worsening of hypercapnic respiratory failure) as well as to the actual sleep state. “Nocturnal” also invokes circadian pulmonary function physiology and outcomes, particularly in regard to airway patency and resistance, not necessarily associated with the sleep state [3, 4]. “Sleep” itself is a physiologically heterogeneous state of existence, and can occur in the day (diurnal) or the night (nocturnal) in a patient with ventilatory compromise or diathesis, and is a state which, day or night, represents physiologic challenges to breathing that the awake state does not [5]. In non-rapid eye movement (NREM) sleep, dependence on metabolic control of breathing, with virtual loss of voluntary and behavioral control, is associated with a state of decreased chemosensitivity and central neural output compared with awake (i.e., decreased “drive to breathe”), and is permissive of respiratory periodicity and associated sleep-related hypopnea and apnea, particularly in those patients with disorders of abnormal ventilatory control and response. Alveolar hypoventilation compared with awake, associated with such changes in drive to breathe as well as unfavorable chest wall, abdominal, and diaphragm ventilatory mechanics, and increased upper airway resistance and associated breathing workload, is characteristic of NREM sleep. In contrast, rapid eye movement (REM) sleep is associated with neural inhibition of postural muscles including those of the ventilatory and upper airway muscles, including accessory ventilatory muscles, along with erratic and reduced respiratory neuromuscular output and response [5, 6]. These, combined, predispose to central and obstructive apnea, and severe and prolonged alveolar hypoventilation and hypoxemia, the latter likely from a combination of hypoventilation and ventilation–perfusion mismatch, in REM sleep.

Considering such physiologic sleep-related challenges to ventilation, patients who have ventilatory challenge and/or demonstrated insufficiency (primarily as defined as arterial hypercapnia) awake, either from (1) restrictive physiology including obesity, abnormal chest wall configuration, diaphragm mechanical disadvantage, paresis, or paralysis; (2) and/or outright abnormal central nervous system (CNS) drive and/or chemoreceptor response; and/or (3) upper and/or lower airway obstructive diathesis or disorder appear to be particularly at risk for severe disordered breathing in both NREM and REM sleep. A particular patient may in fact be affected with more than one such physiologic challenge, such as patients with chronic obstructive pulmonary disease (COPD) and patients with primary neuromuscular disorders (NMD), in whom abnormal ventilatory drive may be coupled with disadvantageous diaphragm and airway mechanics. Sleep physiology ideally informs a need for considering, clarifying, and distinguishing “nocturnal” (i.e., “sleep”) imperatives in clinical practice.

Further, the use of NIV in sleep ultimately invokes a unique challenge to the clinician: Unlike application of ventilatory assistance to the sedated and/or anesthetized, endotracheally intubated, or tracheostomized patient, or the use of NIV specifically in the awake patient, usually in the acute care setting for acute or acute on chronic ventilatory insufficiency, the efficacy of NIV in sleep by definition invokes

methodologic expertise necessary to maintain optimal sleep continuity and consolidation (with associated decreased diathesis to periodicity of breathing, hypopnea, and apnea) simultaneously with optimal ventilatory support, typically on an ongoing and unmonitored basis [7]. Optimal ventilatory parameters in the unanesthetized and sleeping patient must at all times be adjudicated in the setting of inherent NIV delivery problems via an external nasal or oronasal interface such as air leak, nasal and facial discomfort, aerophagia (and attendant risk of aspiration), and sleep fragmentation. The clinician must also overcome problems regarding achieving a consistent balance between sufficient trigger sensitivity of the ventilator in sleeping patients with impaired ventilatory drive and/or strength, and auto-triggering, each of which may result in patient–ventilator dysynchrony (PVD) and ineffective ventilation in sleep. A consistent balance between achieving an optimal level of ventilatory volume and pressure support, and the accompanying inherent risk for air leak, discomfort, aerophagia, and sleep fragmentation, is imperative.

The term "nocturnal noninvasive ventilation" is abbreviated as "nNIV" in the following overview and describes primarily sleep-associated application of NIV. It will be attempted to specify in this overview and throughout the chapters in this volume when the reference to NIV, "nocturnal" or otherwise, is specifically related to, or not related to, its use in sleep.

Alveolar Hypoventilation: Rationale for nNIV

The clinician ideally should have two potential major goals in mind when considering nNIV for patients with awake ventilatory compromise or diathesis, each goal having physiologic and clinical aspects which interact with the other, not necessarily in a continuum. These are: (1) treat a sleep-associated breathing disorder; (2) provide ventilatory muscle assist and "rest" in sleep, in the absence of a definable sleep-related breathing disorder.

1. Treating a Sleep-Associated Breathing Disorder

Sleep, in imposing the physiologic challenge to ventilation noted above, is associated with specific, treatable *sleep breathing* disorders, in patients *with and without* awake hypoventilation. Such "sleep-disordered breathing (SDB)" in awake hypoventilation disorders is not as easily defined, either methodologically or physiologically, as in other settings such as the primary obstructive and central sleep apneas. Sleep breathing disorders in patients with hypoventilation include such diverse perturbations as: central and obstructive apnea; "hypopnea" (i.e., a discrete period of diminished airflow, primarily associated with increased upper airway resistance, or associated with similarly decreased ventilatory muscle movement without clear manifestation of pathologically increased upper airway resistance); sleep-related hypoventilation, defined and assessed by $PaCO_2$ monitoring [8]; and repetitive or persistent periods of hypoxemia, defined and assessed by a pulse oximeter. Other SDB, less amenable to objective interpretation, includes physiologically

demonstrated increased work of breathing in sleep, typically manifesting as prominent or predominant accessory ventilatory muscle use, chest wall and diaphragm dyssynchrony, and/or outright thoracoabdominal paradox (in patients with awake hypoventilation, e.g., typically seen as thoracic ribcage moving forward with inspiration and abdomen inward as the weakened diaphragm is pulled up with each inspiratory thoracic negative pressure load). Tachypnea with or without such abnormal ventilatory muscle movement, with potential for dead space and therefore ineffective ventilation, is also a common finding in sleep in such a setting.

Treating the recurrent and/or persistent asphyxia, and associated acute cardiovascular and cerebrovascular perturbations and sleep disruption of physiologically defined SDB as above, may in turn be expected to:

- Improve sleep quality and sleep and awake quality of life
- Decrease sleep-related acute morbidity and mortality (e.g., coronary, cerebrovascular, dysrhythmia-related)
- Decrease long-term cardiovascular and pulmonary vascular morbidity (e.g., pulmonary hypertension, left and right ventricular function impairment; systemic hypertension)
- Improve awake and sleep-related perturbed respiratory control and drive

2. Provide Ventilatory Muscle Assist and "Rest" in Sleep

In addition to treating any or all of the above-demonstrated sleep breathing disorders, it has also long been widely hypothesized that, even in the absence of such clearly defined SDB, the clinician may yet, in patients with awake hypoventilation exposed to the neuromuscular and breathing control ventilatory challenges of sleep, use NIV to "rest" the ventilatory system, and thereby improve or at least preserve overall awake and asleep ventilatory muscle strength, ventilatory mechanics, coordination, efficiency, and drive to breathe, and thereby improve chronic awake ventilatory status and symptoms, and/or slow progression of the awake hypoventilatory condition, and/or prevent onset of outright alveolar hypoventilation. Such "resting" of ventilatory muscles by applying NIV to a period of potentially great physiologic challenge to an already taxed respiratory/ventilatory system, even in the absence of a specific breathing perturbation in sleep, has been applied and researched for many years, primarily in disorders with a natural history of progression of ventilatory muscle weakness and/or dysynchrony, for example, COPD, and primary NMDs, including motor neuron disorders, beginning with negative pressure ventilation [9–11], and proceeding to positive-pressure ventilation [12]. Such application has been bolstered by data showing efficacy of nocturnal ventilation via "invasive" ventilation, using tracheostomy-assisted ventilatory support, in reversing effects of severe chronic hypoventilation and cor pulmonale, and improving sleep quality [13].

The distinction between efficacy and outcomes accruing from the application of nNIV to treat a defined disorder of breathing in sleep and to "rest" the ventilatory system in the absence of such SDB has not been well specified in the extant research literature, much of which has in fact not distinguished between the two clinical scenarios, nor the physiologic effects (e.g., improved drive to breathe versus improved

ventilatory muscle strength and mechanics) of treating one versus the other. The expectation of improving chronic awake and asleep hypoventilation by amelioration of SDB-associated blunting of chemosensitivity and ventilatory drive and peripheral motor nerve function has a small amount of specific data support [14, 15], as does the potential of improving awake pulmonary function by treating specific SDB, or increased work of breathing, which is possibly associated with sleep deprivation and/or fragmentation [16, 17].

nNIV: Outcomes

As referred to above, much of the research regarding the physiologic as well as clinical effects of negative and positive-pressure NIV and, for the most part, "nocturnal"—usually sleep-related—NIV has been accomplished, with good reason, in two conditions, which are characteristically associated with awake and asleep hypoventilation and ventilatory failure: the primary neuromuscular weakness and/or restrictive chest wall disorders [18–20] and COPD [11, 19, 21–26]. Although, as noted above, it has been difficult to distinguish physiologically or clinically between improvement in impaired respiratory "drive" [27], improvement in impaired respiratory muscle strength, endurance, and/or improvement in ventilatory mechanics, some data assessing "nocturnal" or "nighttime" NIV in disorders of chronic alveolar hypoventilation indicate improved exercise endurance along with improved nocturnal O_2 saturation parameters [19, 28]. Other data suggest that nNIV may improve abnormal breathing control and "drive" in COPD [21, 29–32] and the neuromuscular weakness/chest wall disorders, particularly since improved sleep-related ventilatory parameters and awake $PaCO_2$ levels can occur without concomitant improvement in pulmonary function mechanics testing [20].

Further, small data sets have both "coupled" beneficial nNIV effect on sleep-related alveolar ventilation with sustained static and functional inspiratory muscle strength and endurance [28], and "uncoupled" parameters of ventilatory muscle strength and function, including arterial blood gas, respiratory static and functional muscle strength and endurance, and pulmonary spirometry; for example, decreasing awake $PaCO_2$ with nNIV applied successfully to address sleep-related hypoventilation does not consistently improve measures of ventilatory or clinical outcomes [18, 20, 28].

Additionally, there is currently an apparent divide between efficacy data in COPD hypoventilation disorders and diatheses and the neuromuscular weakness hypoventilation disorders and diatheses, regarding efficacy of nNIV. For example:

- Much of the data regarding the efficacy of chronic nNIV in improving awake ventilatory parameters in COPD patients have been non-robust at best, or negative, and such non-robustness or absence of awake physiologic and/or clinical improvement generally coincides with the researchers not specifying sleep-related physiologic efficacy of the nNIV regimen either in addressing a specific

sleep-related breathing disorder, or providing effective ventilation (e.g., lowering or stabilizing sleep-related $PaCO_2$), or indeed improving sleep efficiency itself [9, 11, 21, 24, 26, 33–35]. Some of these researchers have specified, in fact, *no* improvement in such sleep or ventilation parameters [26] when awake improvement is not seen.

- When sleep parameters have indeed been assessed and reported on, a lack of efficacy in improving ventilatory parameters in sleep, for example, control of sleep $PaCO_2$ in patients with hypercapnic COPD, has been associated with non-robust awake outcomes such as prolongation of survival [23] and improved quality of life [26]. Conversely, recent randomized controlled available data [36], which do document improved 1-year survival in stable hypercapnic COPD patients using NIV, document the use of the NIV support adjusted to levels to achieve physiologic efficacy of lowering awake $PaCO_2$; whether NIV was used specifically as "nocturnal" (i.e., in sleep) NIV, and whether sleep-related levels of $PaCO_2$ were successfully addressed, is not defined in these data. There is evidence that documentation of sleep-related improvement in ventilation and/or sleep efficiency is associated with improvement in awake ventilatory parameters with nNIV in such patients [22, 25].
- The state of extant research in the use of nNIV in the NMD disorders, such as motor neuron disorder [37], and chest wall restrictive disorders (CWRD), such as kyphoscoliosis, differs importantly from similarly applied COPD data as noted above in two important ways: (1) for NMD and CWRD, data sets are generally small, uncontrolled, and un-randomized; (2) this literature is, however, more specific in documenting efficacy of NIV use *during sleep* [18–20, 28, 38, 39] and more consistently pertains to patients with documented *awake and/or sleep-related hypercapnia*, and/or those who have significant *awake and/or nocturnal respiratory symptoms*. Such relatively small data sets tend to demonstrate both feasibility and efficacy in improving sleep and awake hypoventilation and progressive ventilatory failure in those patients with NMD and/or CWRD who have documented objective or subjective need for it. Progression of awake hypercapnia has been shown to be able to be slowed, or averted, by using nNIV to address documented sleep-related hypoventilation in patients with severe symptomatic congenital neuromuscular weakness and/or chest wall disease, and vital capacity $< 50\,\%$ [40]. Consideration and discussion of options regarding NIV (as well as assisted cough) is considered a quality measure by the American Academy of Neurology [41] in patients with amyotrophic lateral sclerosis (ALS) and "respiratory insufficiency."
- Much of the extant nNIV data specific to motor neuron disorders, and the muscular dystrophies, however, do *not* currently document the presence of awake or sleep ventilatory insufficiency, hypoventilation, sleep apnea/hypopnea, or related symptoms in the patients in whom nNIV is applied which would provide a rationale for directed benefit from nNIV. Further, the majority of data in ALS patients do *not* document physiologic efficacy of nNIV during sleep when prescribed [42, 43]. Some authors, in fact, document *failure of nNIV to improve major sleep or ventilation/oxygenation parameters* [26, 42–45], particularly when

nNIV was applied primarily and essentially arbitrarily for the presence of a low vital capacity or impaired static ventilatory muscle strength rather than addressing a specific sleep breathing disorder or symptom. For example, a randomized controlled trial noted above [44] in patients with moderate to severe Duchenne muscular dystrophy (forced vital capacity (FVC) 20–50% predicted) indicated no improved progression of ventilatory insufficiency ($PaCO_2$, FVC, need for mechanical ventilation), and decreased survival in patients using at least 6 h of nNIV versus controls, when used in the absence of symptoms of SDB or awake hypercapnia.

- Note that utility of nNIV in patients with concomitant OSA and COPD ("overlap syndrome") is a contrasting clinical setting and indication for nNIV which should be considered separately.

NIV: Awake, Sleep, or Both?

Taking into consideration the foregoing discussion, the primacy of "nocturnal" (i.e., sleep) versus awake NIV in the chronic alveolar hypoventilation disorders becomes more problematic when one focuses clinical intent specifically upon the disparate considerations inherent in NIV used "nocturnally" as mentioned above, that is, (1) NIV used to directly address the physiologic imperatives of SDB in these chronic hypoventilation disorders, and (2) NIV used "nocturnally" primarily in a "muscle resting" strategy. It has been considered that, if NIV is to be applied chronically to a patient for a period of hours rather than minutes, sleep offers a unique opportunity to apply such therapy to a patient not otherwise engaged in activities in which such application would represent a significant lifestyle burden, thus being better tolerated in this manner. One also might assume that many patients will better tolerate the physical burden of the mask and pressure when asleep and therefore not conscious of its work. However, in fact, these considerations simultaneously task the clinician and clinical researcher with the burden of assessing whether *awake* use of NIV may be as, or even more, advantageous than "nocturnal" NIV which is applied in the sleeping patient, for this indication. NIV applied awake for "muscle resting" is not, of course, addressing the physiologic burden of sleep-stressed ventilation (e.g., decreased ventilatory responses to breathing control, erratic/inhibited breathing control, impaired ventilatory mechanics), but NIV might be most closely monitored for effect, and most readily adjusted during "awake" settings, thus maintaining meaningful ventilation support for a consecutive period of hours, particularly as regards air leak and interface integrity which can be better monitored by patient and caregivers together when all are awake and aware. Numerous data, including some of the earlier noted, in fact demonstrate efficacy of both positive and negative pressure NIV in chronic hypoventilation disorders during manifestly *awake* sessions to achieve successful ventilatory outcomes such as decreased awake $PaCO_2$ and improved respiratory

muscle strength [9–11, 47]. One prospective case control study directly compared efficacy of awake and "nocturnal" NIV in patients with stable restrictive chest wall and neuromuscular weakness disorders, finding NIV used for 8 h awake equivalent to NIV used for 8 h "nocturnally" (presumably, as described by these investigators, including sleep for some, if not most, of this time) regarding improvement in respiratory parameters including awake $PaCO_2$ [48]. Further, much of the available research data regarding efficacy of NIV, particularly that in patients with COPD, pertains either specifically to awake rather than nocturnal or sleep-related use of the therapy [10, 11, 49] or, as alluded to above, does not in fact clarify whether use was awake- or sleep-related even when the term "nocturnal" or "nighttime" is used. In the recent randomized controlled trial of NIV in stable hypercapnic COPD referenced above [36], sleep versus awake use was, as characteristic of such studies, unspecified and indeed apparently undetermined by the investigators, but it is reasonable to consider that the improved mortality at 1 year, associated with the successful reduction in awake $PaCO_2$ levels targeted with the NIV, was achieved with as much awake as sleep use of the NIV (the investigators do note that patients were encouraged to use the NIV during sleep) given the relatively high inspiratory pressures used which can be considered more characteristic of physiologically efficacious awake versus sleep NIV application.

The above-noted data, successful in the major outcomes cited, highlight the imperative to better determine the role of NIV awake versus sleep ("nocturnal") versus a combination of the two in addressing the chronic hypoventilatory disorders. The latter (a combination of awake and asleep) represents a relatively novel and rational strategy for NIV prescription in awake hypoventilation disorders which do not specifically involve, in a given patient, a clearly treatable disorder of breathing in sleep as discussed above. Such clinical and clinical research considerations directly raise the question as to which patients should undergo polysomnography (PSG) to assess for such sleep-related breathing disorders, and how such testing ties into other awake tests (e.g., arterial blood gas, muscle pressures, spirometry) and symptoms in informing sleep testing and NIV application indications and imperatives. PSG considerations are discussed in more detail below.

The use of nNIV has also been investigated in acute ventilatory insufficiency presentations, primarily in intensive care settings [50–55]. This critical setting for NIV use, including nNIV, is reviewed in detail in this volume in Chap. 10.

nNIV in Disorders Other than COPD and Neuromuscular Weakness

1. Primary "Neurologic" Disorders

In addition to the major entities of neuromuscular and chest wall disorders discussed above, the clinician should also consider similar potential benefit of nNIV in other primarily "neurologic" disorders including:

- Cerebrovascular disorders/cerebrovascular accident (CVA)
- The muscular dystrophies
- Spinal cord disorders such as traumatic spinal cord injury [56, 57] and those associated with Arnold Chiari malformation [58, 59]
- Neuromuscular junction disorders including myasthenia gravis [60–63]
- Polyneuropathies (e.g., peripheral nerve neuropathy)
- Phrenic nerve dysfunction with "isolated" diaphragmatic paralysis [64]
- Guillain–Barré syndrome [51, 53]
- Myopathies such as polymyositis, post-polio syndrome [65, 66], and the glycogen storage disorders

2. "Overlap" syndromes: COPD/OSA and obesity hypoventilation/OSA

The "overlap syndromes," as defined by the presence of OSA in the setting of a separate awake hypoventilation disorder, are emerging as particularly relevant to and compelling in the science and practice of nNIV application, particularly in regard to COPD/OSA overlap and obesity hypoventilation/OSA overlap. In COPD/OSA overlap, the most studied of such "syndromes," OSA appears to have a similar prevalence in COPD as in adults without COPD. Currently, no phenotypes definitively establish risk of OSA overlap in COPD patients. Diminished hypercapnic ventilatory response awake, compared with OSA without COPD overlap, has been demonstrated in COPD/OSA [67], and the overlap appears to be a more consistent disorder of alveolar hypoventilation than COPD alone [68]. COPD/OSA overlap has been found to be associated with poorer COPD outcomes including increased mortality, and increased risk of COPD hospitalization, in patients with concomitant COPD and untreated OSA compared with patients with COPD alone or COPD/OSA overlap treated with continuous positive airway pressure (CPAP) for the OSA component [69]. Such overlap has been associated with worsened nocturnal hypoxemia than either disorder alone, as well as a high prevalence of pulmonary hypertension [70]. The most current Global Initiative for Chronic Obstructive Lung Disease statement [71] includes the following: "In patients with both COPD and OSA there are clear benefits from CPAP in both survival and risk of hospital admission." nNIV modes other than CPAP have not been explicitly studied regarding acute or long-term outcomes in the setting of such overlap, although in the COPD/OSA overlap setting, diminished hypercapnic ventilatory response awake compared with OSA without COPD overlap has been found [67], and COPD/OSA overlap appears, at least in limited data, to be a chronic awake hypoventilatory disorder, particularly in comparison to COPD without OSA and OSA without COPD [68]. The reader is specifically referred to the above-referenced recent reviews regarding COPD/OSA overlap for further reading and consideration [70, 72].

Obesity hypoventilation "syndrome" (OHS) can also be considered an "overlap" syndrome with OSA, amenable to nNIV, since OSA has been demonstrated to be present in a majority of OHS patients [73] and, with such overlap, there appears to be a worse prognosis for OHS than OSA alone. NIV applied as continuous (CPAP) and fixed bi-level positive airway pressure (BPAP) in such patients has been shown

to decrease nocturnal $PaCO_2$, daytime $PaCO_2$, and daytime sleepiness. CPAP alone, in fact, may improve the awake hypoventilation of the OHS [73]. In one randomized crossover trial, volume-adjusted pressure support showed efficacy in improving nocturnal hypoventilation, in fact resulting in significantly more decrease in nocturnal transcutaneous CO_2 than either CPAP or fixed BPAP [74]. Other randomized controlled data have shown efficacy of both volume-adjusted and fixed bi-level pressure support in improving awake $PaCO_2$ and respiratory-related quality of life in very obese OHS patients [75]. While no randomized controlled trials have assessed long-term survival in OHS patients treated with nNIV, a series of 130 patients receiving "nocturnal" (not clearly documented as during sleep) BPAP for OHS, with the addition of supplemental oxygen for persistent nocturnal hypoxemia, had 1-, 2-, 3-, and 5-year survival rates of 98, 93, 88, and 77%, respectively [76]; such survival rates are higher than the 18-month survival rate reported for mostly untreated cohorts of patients with OHS. Additionally, it has been shown that patients with OHS may be treated with NIV (not necessarily used in sleep or nocturnally) during an episode of acute hypercapnic respiratory failure with similar efficacy to, and with better unadjusted survival outcomes than, patients with COPD [54]. OHS is discussed in detail in Chap. 4.

3. Cystic Fibrosis

An evolving database provides rationale for consideration of nNIV to improve outcomes in patients with cystic fibrosis [77, 78], including randomized controlled data in patients with awake hypercapnia demonstrating improvement in disease-related symptoms as well as nocturnal hypercapnia [79], and uncontrolled data suggesting a role for nocturnal NIV as well as awake NIV as a bridge to lung transplant [47].

4. "Central Sleep Apnea"

The central sleep apnea entities represent consistent potential for nNIV application. Such entities include: (1) central sleep apnea which may occur in the congenital and acquired syndromes involving the central breathing controller, usually termed "central hypoventilation syndrome" [80]; (2) central apnea and hypopnea (i.e., hypopneas which are not associated with high upper airway resistance) disorders in sleep associated with opioid use, CNS trauma, and/or increased intracranial pressure; (3) primary neurologic disorders noted earlier, including congenital or acquired cervical spine disorders such as Arnold–Chiari malformation [58], and the NMDs. Included among the central sleep apneas, too, is so-called "complex sleep apnea" defined as repetitive central apnea which becomes prominent during CPAP application/titration for OSA [81]. A critical caveat is that NIV is NOT a reliable method for delivering, securing, and assuring critical 24-h ventilation in breathing control disorders with central sleep apnea, particularly when associated with awake hypoventilation and/or severe hypoxemia, and should NOT be considered appropriate sole therapy when such a diagnosis is made or suspected. This is so even when a "back-up" rate of ventilatory assist is set. This topic is reviewed in detail in Chap. 7 of this volume.

nNIV as CPAP

It is emphasized here, and later in this volume (Chap. 9), that CPAP can provide improved airway patency, ventilatory mechanics, and gas exchange in many patients with a sleep-related breathing disorder and therefore is a form of "nocturnal" NIV which should be considered a potential major therapeutic option, particularly in the hypoventilation syndromes which commonly involve an "overlap" of OSA, COPD, and OHS as discussed above as well as in overlaps of OSA and other pulmonary disorders not typically associated with awake hypoventilation, including pulmonary hypertension [82] and interstitial lung disease. OSA is associated with repetitive acute increases in pulmonary artery (PA) pressures and with measurable changes in the structure and function of the right ventricle. Pulmonary hypertension has been demonstrated in 20–40 % of OSA patients in the absence of other known cardiopulmonary disorders. CPAP has been shown to decrease PA pressures in patients with OSA [83]. Further, the presence of pulmonary hypertension may have prognostic importance in patients with OSA: For example, in an observational study of 83 patients with OSA, defined as an apnea + hypopnea index (AHI), of > 5/h, who underwent PA catheterization for unspecified reasons, it was found that 1-, 4-, and 8-year survival rates were lower among patients with pulmonary hypertension than among those without pulmonary hypertension [84].

Similarly, of 50 stable outpatients with interstitial pulmonary fibrosis (IPF) per American Thoracic Society consensus criteria (mean age 64.9 years; mean BMI 32.3) 68 % were found to have an AHI of > 15/h. Note, however, that in these data—as with most studies invoking PSG assessment of respiratory events "hypopneas", which were the majority of scored respiratory events comprising the AHI—were not assessed as "obstructive"; for example, associated with inspiratory airflow flattening and/or thoracoabdominal paradox. Outcome effects were not investigated in this study [85]. In a more recent study of 31 patients with OSA and newly diagnosed IPF [86], 16 were adjudicated to have "moderate to severe" OSA by AHI (although, again, the hypopneas were not assessed as "obstructive"). In the OSA + IPF patients, the degree of sleep-related SpO_2 decrease versus awake, as well as nadir SpO_2, correlated with major clinical and physiologic parameters including length of survival, pulmonary function tests (particularly DL_{CO} and SpO_2 decrease with a 6-min walk test), dyspnea, and right ventricular pressures.

The optimal strategy for applying positive airway pressure in sleep for pulmonary disorders with and without associated awake hypoventilation which overlap with OSA remains to be better delineated. Primarily, two strategies are typically used and seemingly rational to address both the OSA and the commonly observed remaining sleep-related hypoxemia after the upper airway obstructive component has been adequately addressed, as may occur in REM sleep when breathing effort is characteristically erratic and hypopneic although not obstructed: (1) titration of CPAP to address the OSA, with additional supplemental oxygen as necessary at that level of CPAP for ongoing sleep-related hypoxemia in the absence of obstructive events, and (2) aiming for a level of ventilatory support with an expanding pressure

higher than the expiratory pressure (EPAP), which is otherwise sufficient to achieve upper airway patency. This latter is "bi-level" positive airway pressure (BPAP), and, as with CPAP, can be applied with supplemental O_2 when, as is often the case, the BPAP regimen improves but does not resolve the sleep-related hypoxemia. It is, however, also a reasonably common experience of the practiced SDB expert that titrating higher levels of CPAP itself may stabilize increased work of breathing in sleep, improve oxygenation, and improve sleep consolidation in hypoventilation syndromes including COPD, NMD, and OHS, with and without OSA overlap, as well as in certain cases of severe OSA without awake hypoventilation. When successfully applied as such, CPAP represents an inherently advantageous mode of treatment compared with more explicitly ventilatory modes ("pressure" cycled, as with BPAP, or "volume" cycled) which use higher inspiratory than expiratory airway pressure levels and therefore predispose to air leak; perhaps most importantly, CPAP avoids, by definition, patient–ventilator dysynchrony (PVD), at least once any upper airway obstruction with associated uncoupling of patient effort and airflow is overcome.

Other nNIV Considerations:

- Prevalence of SDB in the primary hypoventilation disorders
- Nosology of SDB in this population
- Screening and diagnosis of such SDB in this population
- The specific role of PSG

Prevalence of SDB in the Primary Hypoventilation Disorders

Along with the foregoing discussion regarding NIV used to treat SDB (i.e., "nocturnal" NIV), and/or to "rest" the ventilatory system ("awake" as well as "nocturnal" NIV), a consideration of how and when SDB is optimally suspected and diagnosed in the chronic hypoventilation disorders seems in order. The NMDs as a whole represent the best-studied and perhaps the most potentially clinically and physiologically rational indication for the use of nNIV during the physiologic challenge of sleep and will be referred to in this brief discussion.

At the present time, the bulk of experimental data suggests that SDB, as characterized by a high frequency of some combination of obstructive or nonobstructive apnea and discrete hypopnea, frequent discrete or prolonged episodes of severe O_2 desaturation, and/or frequent or consistent pathologic sleep-related increase in measures of arterial PCO_2 [87], occurs in a *minority* of NMD patients when studied without consideration of the presence or absence of orthopnea, other dyspnea, other sleep-related symptoms, or awake hypercapnia. This seems so whether patients have been assessed at the time of diagnosis or relatively early in their course [88–91] or at the time nNIV is generally applied as current standard of practice for

a FVC < 50 % of predicted [42, 45]. For example, even in advanced ALS (e.g., FVC 46 ± 12 % predicted; revised ALS functional rating scale (ALSFRS-R) 23 ± 8) we have found in only a minority (43 %) of unselected patients (most without orthopnea) an AHI ≥ 5/h at baseline (most scored events were nonobstructive appearing hypopnea and central apnea); for the majority, who had an average AHI < 5/h, the range of AHI was only 0.6–4.9/h, the index of SpO_2 desaturation of at least 3 % points per hour of sleep was 0–4.3/h, and nadir SpO_2 ranged between 86 and 97 % [42, 45]. These parameters of SDB were without any clear correlation with age, gender, or disease severity criteria including ALSFRS-R, FVC, disease duration, and bulbar versus limb onset disease. Similarly, few outright apneas or hypopneas have been adjudicated in ALS patients with measured diaphragmatic dysfunction [89]; ALS patients with both bulbar and non-bulbar predominance having neither respiratory complaints nor subjective symptoms of sleep disturbance did not show significant SDB as a group, nor was there severe O_2 desaturation in sleep [88]. In the largest study of patients with neuromuscular weakness disorders of various etiologies undergoing screening nocturnal PSG [92], 83 % demonstrated an "apnea + hypopnea" frequency of ≥ 5 per hour of recording time, the great majority of these being "hypopneas" rather than apneas, and severe nadir SpO_2 was observed in only one patient. As with the ALS patients described above, in these data there was no statistical correlation among SDB severity parameters and disease severity parameters such as disability index, pulmonary function tests, age, sex, body mass index, and subjective sleepiness.

However, there are in fact small data sets which do demonstrate the potential for more severe SDB in patients with NMD with and without severe awake ventilatory dysfunction; for example, eight patients with NMD (mysasthenia gravis, muscular dystrophy, or other myopathy) and a vital capacity ~ 50 % predicted were found to have a mean "respiratory disturbance index" (RDI) of central apneas and "hypopneas" of 22 ± 6 and arterial oxygen saturation of hemoglobin by pulse oximetry (SpO_2) < 90 % for a mean of 160 min [20]. Six severely hypercapnic patients with kyphoscoliosis and/or NMD showed a mean REM sleep SpO_2 nadir of 69 % ± 15 breathing supplemental oxygen [28]. In NMD patients with severe awake ventilatory compromise including hypercapnia and hypoxemia, with severely reduced inspiratory and expiratory muscle pressure measures, a mean SpO_2 of 83 ± 12 % in NREM sleep and 60 ± 23 % in REM sleep was found [93]. Similarly, four patients with isolated bilateral diaphragm paresis demonstrated generally severe SpO_2 nadirs, these occurring in REM sleep, in association with "central" hypopnea and decreased EMG intercostal muscle activity [64].

Nosology of SDB in this Population

It is likely that at least some of the discrepancy noted in the foregoing referenced studies accrues from the fact that the nosology and techniques of assessing and scoring SDB, which have invariably been applied to those studies, traditionally score an AHI or RDI, which apply less to the hypoventilation disorders [8, 94–96] than to

the primary sleep apneas (CSA and OSA). Lack of controlling for positioning effect also likely informs some, or much, of this discrepancy. Presumably, much of the "hypopnea" scored in the extant literature refers to discrete periods of attenuated air flow and ventilatory effort, without differentiation between "obstructive" and "central" disordered breathing and not clearly distinguishing between hypopnea and hypoventilation [96] or even central versus obstructive apnea in the setting of severely attenuated air flow and respiratory muscle strength [94, 95].

A more appropriate nosology for SDB in all of the chronic hypoventilation disorders would continue to include central and obstructive apnea but also define whether hypopneas are adjudicated as partial upper airway obstructive episodes, common in OSA but not clearly in the hypoventilation disorders such as COPD and neuromuscular weakness, or whether they are considered episodes of hypoventilation (adjudicated via rational rules for CO_2 elevation of a valid real time marker such as end tidal CO_2 and decrease in pulse oximetry (if supplemental O_2 is not being used), or, truly, "hypopnea" in the sense of nonobstructive decrease in respiratory effort, airflow, and/or volume and not necessarily hypoventilation by CO_2. As noted by Bourke and Gibson [96], "the distinction between hypoventilation and central hypopnoeas is arbitrary; the latter usually refer to discrete short periods when ventilation is reduced compared to a preceding reference period." "Hypopnea" adjudicated as attenuated ventilatory muscle movement, with or without hypoventilation per CO_2, could then be additionally scored via criteria which incorporate specific and available visual or plethysmographically quantified parameters, such as optoelectronic plethysmography, to assess such parameters as thoracoabdominal paradox (either of the neuromuscular weakness or upper airway obstructive type, and/or REM sleep-related); use of accessory ventilatory muscles; dysynchronous chest wall and abdomen movement; and abnormal compartment (rib cage, diaphragm, abdominal) percent contribution to the tidal volume [97].

Screening and Diagnosis of SDB in this Population

Such considerations as noted above inform not only our ability to research and adjudicate the effects of sleep on breathing in the chronic hypoventilation disorders but also our ability to thereby provide patient-specific physiologically and clinically optimal NIV application and follow-up, whether "nocturnal" or otherwise, in these disorders. Therefore, there appears to be a pressing need for research which addresses the fundamental concern of incorporating a more physiologic SDB nosology with awake symptoms, and with physiologic and clinical severity parameters, for the patient with awake hypoventilation who would most benefit from PSG. Such an incorporative strategy optimally can be utilized to determine whether there is clear indication for nNIV, and as well go on to optimally titrate the nNIV to directly address that need during sleep (or, in fact, awake and in sleep). Such research must include larger data sets with demonstrated power to determine associations among the awake and sleep parameters. Such research should also be informed by better methodologies for determining awake severity parameters, both by quantifiable

screening paradigms which have methodically incorporated symptoms of sleep quality and position-associated dyspnea such as questionnaires which have been used to predict SDB in patients with diaphragmatic weakness [98], and with more quantifiable and objective assessment of symptom and physiologic disease/disorder severity, from the basics of determining whether in fact awake hypoventilation does or does not exist (as per arterial blood gas testing), through a continuum including methodologies which can yield quantification of thoracoabdominal paradox and dysynchrony awake and awake and sleep-related symptom delineation and quantification [98].

The sense that there is a need for attention to symptoms when considering nNIV is bolstered by data which indicate that orthopnea in the presence of substantial impairment of daytime respiratory muscle function may be an optimal predictor of SDB including nocturnal oxygen desaturation in ALS [99] as well as data in muscular dystrophy patients [44] demonstrating lack of improvement of progression of ventilatory insufficiency parameters (including $PaCO_2$, FVC, and need for mechanical ventilation) in patients using at least 6 h of nNIV versus controls when used in the absence of symptoms of SDB or demonstrated awake hypercapnia. Such data, in association with the cited data above indicating a paucity of clear sleep-related breathing disorder in NMD patients studied in the absence of orthopnea, other dyspnea, or sleep-related symptoms, or known awake hypercapnia, should be more consistently incorporated into the critical business of considering and prescribing NIV, “nocturnal,” awake, and perhaps in combination, for patients with manifest hypoventilatory disorders or clinically adjudicated significant diatheses for such.

The Specific Role of PSG

As Bye and colleagues stated in 1990 [93], the clinician should consider that “a sleep study is necessary to assess the extent of respiratory failure in an individual patient.” Similarly, as per such data as those of Meecham-Jones and colleagues [22], it is the practice of titrating and adjusting nNIV to objectively optimize improvement of sleep-related hypoventilation and sleep continuity parameters, and/or awake ventilatory parameters [36, 39] which shows potential for efficacy of awake hypoventilation and quality of life improvement, while a growing body of data already discussed above, including those of McEvoy and colleagues [26] conversely indicate that *lack* of such documented physiologic efficacy with the utilized nNIV is associated with lack of clinical effectiveness. From the foregoing principles in this overview then, PSG, the comprehensive monitoring and recording of a simultaneous set of physiologic channels during sleep including electroencephalography (EEG), electromyography (EMG), electrocardiography (ECG), and respiratory data (typically air flow, respiratory muscle efforts and volumes, pulse oximetry, capnography) and real-time audiovisual recording, can be seen as a dominant consideration in the art and science of nNIV use in the patient with an awake hypoventilation disorder or diathesis.

The role of PSG in the awake hypoventilation disorders can also be seen as imperative in light of the *predictive* data discussed earlier in the overview; that is, neither awake patient demographics nor parameters of disease-specific or ventilatory-specific severity consistently correlate with the presence of SDB (primarily documented as apnea, hypopnea, increased end-tidal PCO_2, or hypoxemia) in the awake hypoventilation syndromes. Clinical considerations must inform the decision regarding utilizing PSG as per current data and experience, as research, including clinical trials, progresses. It is expected that PSG as a diagnostic and therapeutic tool will be considered as more and more useful in potentially all patients with awake hypoventilation and/or diathesis, or with outright symptoms such as dyspnea associated either with awake time or sleep time, and/or sleep disruption, in whom NIV, "nocturnal," awake, or both, is being considered.

The potential for utility of PSG in the context of nNIV may therefore be summarized as follows:

1. To determine whether SDB and attendant sleep disruption is present (as assessed either by current standard criteria or as per proposed expanded criteria as stated in the foregoing of this overview)
2. To determine, in association with the above, whether such SDB would be physiologically amenable to nNIV, to improve both ventilatory parameters and sleep parameters
3. To then titrate nNIV, with or without supplemental oxygen, as per such objectively adjudicated physiologic ventilatory and sleep consolidation criteria
4. To provide objective and physiologic follow-up, as with other "pulmonary function" parameters, with objectively indicated and titrated adjustment of the nNIV as the clinical course progresses

In regard to (3) above, it is emphasized that the ability to observe physiologic efficacy of the timing, level, and mode of nNIV applied has not only intuitive but also documented rationale [100–102]. Stringently researched standards for such monitoring and objective adjustment of nNIV in clinical practice remain necessary.

In concert with the use of PSG as discussed above to objectively assess presence, type, and severity of SDB, and responsiveness to nNIV, evolving tracking systems offer the clinician an objective physiologic assessment of the patient's use of the nNIV, recording and displaying such parameters as daily amount and timing of hours of use of the NIV at the pressures set, and amount of large air leak. These systems, as an integral part of successful application of nNIV outside of the hospital setting, are discussed in Chap. 8 of this volume.

Specifics of nNIV Application: A Brief Consideration

1. Clinical and Physiologic

As discussed earlier in this overview, unlike "mechanical ventilation" delivered to the endotracheally intubated or tracheostomized patient, the major utility of

"nocturnal" (sleep-related) NIV accrues from its ability to maintain optimal sleep simultaneously with optimal ventilation, in practice a very difficult undertaking. The optimal ventilatory parameters in the unanesthetized patient must at all times be balanced by the problems of air leak, nasal and facial discomfort, aerophagia, and upper airway resistance as well as shortcomings regarding achieving a consistent balance between trigger sensitivity and response in patients with impaired ventilatory drive and/or strength and auto-triggering, each of which may result in PVD and ineffective ventilation even when close monitoring of response is made. Similarly, one cannot assume that the nNIV can be increased, and synchronized with the patient's ventilatory neural and muscular output, at will, as can ventilation in the intubated and anesthetized patient: Air leak and discomfort disallowing not just acute sleep and physiologic response but also long-term adherence, with decreased adherence correlated to a significant extent with adverse effects of nNIV, some of which may be themselves associated with physiologically suboptimal pressure prescription or interface choice in patients with chronic hypoventilation including machine noise, complaints of too high pressure or lack of enough pressure; conjunctivitis; facial (most problematic, nasal bridge) skin lesions; gastric and bowel distention, via aerophagia, and related emesis; bronchial aspiration; airway drying; mucus plugging; pneumothorax; nosocomial pneumonia; and acute and chronic sinusitis [54, 103]. These effects appear to be important not only regarding physiologic response but also patient adherence with nNIV as noted above [104].

2. Ventilator Set-up: Specifics of Modes and Interfaces

Once the clinician has decided upon utilizing nNIV, there are specific therapeutic decisions that need to be made, including which specific ventilatory mode for delivering nNIV should be used, including the primary decision as to whether negative or positive-pressure ventilation is indicated. The use of negative pressure ventilation has its own specifics including patient comfort and effective ventilation strategies awake and asleep, which are not specifically covered in this overview.

The choice of mode and settings of ventilatory support chosen to allow for optimal nocturnal (or in fact awake) ventilation is tied to the ability to achieve optimal synchrony among the three major components of such ventilatory support: the chest wall, the diaphragm/abdomen, and the ventilator itself [105]. This by definition must avoid PVD, which has been shown to consistently be present when nNIV is utilized in the hypoventilatory disorders [42, 106–109], even when PSG is used to monitor and adjust the pressures and other settings with such bi-level fixed pressure nNIV [45]. The failure to achieve optimal patient–ventilator synchrony, by optimally matching the ventilatory settings to the patient's ventilatory needs [110] carries the risk of under- or over-distention of the ventilatory system, as well as risks of the patient undergoing both discomfort and the need to "fight" the ventilator, as occurs for example when the machine inspiratory time is higher than optimal for the patient. Such failure of optimal synchrony has also been associated in numerous data with such adverse outcomes as prolonged duration of ventilation and hospital and intensive care unit stays and associated decreased survival [111, 112].

Outcomes with PVD using nNIV itself have not been systematically studied but to the extent that nNIV in many data sets represents a substantial time in sleep without any, or optimal, ventilatory support (as in non-triggering, or double triggering); such a situation likely does not represent optimal "rest" of the impaired and/or threatened ventilatory system, or treatment of outright sleep-impaired ventilation, aspired to physiologically, and clinically.

The mode of sleep-related NIV is therefore optimally and rationally determined not by convention, nor necessarily the patient's preference or response during awake ventilation, but rather as a matter of sleep-related efficacy regarding patient–ventilator synchrony, air leak, airway patency, and sensitivities of the system response. Awake and sleep NIV modes and interfaces may optimally differ, even in the same patient: For example, a patient may best synchronize to volume assured pressure support (VAPS) in sleep, with a full-face mask to address the mouth falling open inadvertently during the sleep period, while awake supplemental ventilation addressing post-exercise or paroxysmal dyspnea may be better used with a nasal pillows system which allows better ability to read (e.g., allows access to eyeglasses) and participate in conversation during ventilator expiratory cycling, which is not possible with a full-face mask. There are, therefore, numerous combinations of interfaces, ventilator modes, ventilator settings, and clinical scenarios (e.g., sleep versus awake plus sleep; acute, acute on chronic, and chronic) possible with NIV.

The most common currently available modes of positive-pressure NIV, all of which can be delivered by a variety of compact and indeed portable machines, are fixed BPAP (whereby one level of inspiratory pressure and one level of expiratory pressure is set, and then stays constant, regardless of patient effort or physiologic need changes during sleep); VAPS; servo-ventilation; and CPAP. While the specifics of setting and adjusting each is beyond the scope of this overview, it is emphasized here that each does carry its own indications and nuances of settings. Even with fixed BPAP, the clinician must set more than inspiratory (IPAP) and end expiratory (EPAP) levels: One also needs to select (optimally, titrate) minimal and maximal inspiratory time limits; trigger and cycle sensitivities; spontaneous or spontaneous timed mode, and back-up rate if the latter; maximum and minimum time in IPAP as percentage of the respiratory cycle, and need for and amount and site of application of oxygen supplementation, as well as the strategy for applying the oxygen, that is, as a gas mixture added directly to the machine in hospitalized patients, delivered to a port in the interface, delivered into an adaptor in the tubing (preferably as close to the patient's face as possible), or delivered by nasal cannulae beneath the mask when necessary and tolerated.

The clinician must monitor for patient–ventilator synchrony, as noted above, and for optimal ventilatory effects and outcomes in any setting, whether acute or chronic, when selecting between a fixed form of pressure support and a form varying breath by breath per the patient's set volume needs as with VAPS. The latter system, as a "targeted tidal volume" system, is likely to assume a future greater place among clinical settings discussed above, including, for example, the NMDs, obesity hypoventilation, and hypoventilatory COPD [55, 74, 75, 113].

Additionally, in acute respiratory failure, current data suggest better tolerance of pressure support NIV, though not necessarily when used in a "nocturnal" setting [52].

A further critical point regarding nNIV is this: Setting a back-up rate with nNIV, as for central apneas, does not assure effective delivery of a tidal breath to the patient's ventilatory system even when the machine senses and outputs at the set rate.

With any of the different forms of ventilator modes selected, the selection of interface is perhaps the most critical: air leak, ineffective direction of the pressure support to the airway, and discomfort associated with a suboptimal choice of interface will negate the effectiveness of the most elaborately contrived ventilator support strategies.

While the use of a full-face mask may be a typical "default" strategy of practicing clinicians, it should be considered that, in fact, nasal application of NIV is usually a more direct airway application than dissipating such pressure superficially to the nasal and mouth orifices, which often ventilates the cheeks rather than the airway. Consider that more effective ventilatory assist has been demonstrated in even unconscious patients using a nasal interface in comparison with a full-face mask [114]. A full-face mask is also likely to be less well fitted to a patient's anatomy, and more likely to be associated with air leak, than a nasal interface (nasal mask or nasal pillows). The risks of aerophagia, gastric distention, vomiting, and massive aspiration must also be carefully considered when applying a tight fitting full-face mask to a patient receiving NIV.

Summary (and Future Directions)

For the clinician considering "nocturnal" noninvasive positive-pressure ventilatory support for a patient with a chronic ventilation disorder or diathesis, the following applies:

- Use of such "noninvasive" ventilation (NIV) should only be considered in a patient who is *not* faced with acutely progressive ventilatory failure; or a central alveolar hypoventilation disorder requiring assurance of 24 h complete ventilatory support; or with inability to protect his/her airway such that proper airway patency and secretion management cannot be assured during NIV. Such situations will likely require tracheostomy-assisted ventilation.
- Many patients considered for nocturnal noninvasive positive-pressure ventilation (nNIV) will not have a specific sleep-related breathing disorder of the sleep apnea or periodic breathing type, nor in fact defined alveolar hypoventilation or severe hypoxemia related to sleep alone. Thus, many such patients will not have a sleep-related breathing disorder that is directly amenable to titration of, and treatment with, a specific noninvasive positive-pressure regimen.

- Therefore, patients who do have an nNIV responsive disorder, either via nNIV applied directly for a defined sleep breathing disorder, for support of a taxed ventilatory and respiratory control system during sleep, or both, have been and continue to be poorly defined due to shortcomings in any physiologically or clinically rational consensus regarding the monitoring, detection, and interpretation of potentially nNIV-responsive SDB.
- It is likely, however, that a sleep-related breathing disorder in this population would be more frequently diagnosed with a nosology more specific to sleep-related hypoventilation and increased work of breathing rather than sleep apnea. Such diagnosis would likely improve ability to apply nNIV more objectively, rationally, and effectively, either as a way of addressing a specific disorder of breathing sleep or, if not, conversely addressing the indication to "rest" the ventilatory system.
- The use of NIV targeted to a specific sleep-related breathing disorder, and the use of NIV applied to "rest" the ventilatory system, should be considered two different uses that do not necessarily demand an identical strategy of timing (sleep, awake, both); ventilator modes; or ventilator settings; in applying the ventilatory support.
- There is, therefore, a need to develop a valid and specific set of physiologic and clinical parameters to assess SDB applicable to the patient with awake and asleep hypoventilation diatheses or disorders, and an associated need to develop a valid and specific methodology for prescribing physiologically and clinically optimal nNIV, including the targeting and "titrating" of the ventilatory support to physiologic perturbation awake and in sleep, and for assessing ongoing physiologic and clinical response and outcomes.
- Regarding the above, the decision and ability to effectively apply nocturnal NIV should not override the awake ventilatory needs of patients; for example, the need to address ventilatory needs with documentation of lower awake $PaCO_2$ in hypercapnic respiratory failure, and to address dyspnea whether there is acute, acute on chronic, or relatively stable ventilatory insufficiency. In such awake use, the choice of mode and interface, and the adjustment of settings according to awake clinical and physiologic parameters, may differ from the optimal nocturnal prescription.
- While the considerations and imperatives of PSG use when considering NIV in patients remain critical for all the reasons noted in the foregoing, one other critical clinical consideration should not be ignored regarding NIV use in patients with hypoventilation disorder and/or diathesis: Physiologically and clinically successful NIV application, awake or in sleep, can be initiated at the bedside, with the clinician attending the patient exploring interfaces, fit, comfort, and best mode of ventilatory support able to synchronously displace the thorax and abdomen, allow for patient–ventilator synchrony, minimize audible and recorded air leak, lower awake $PaCO_2$, and assure adcquate oxygenation.

The following chapters are an earnest and expert attempt to advance a better understanding of the science and best practice of the use of nNIV in the service of

optimally improving the health of patients critically burdened with chronic, and typically clinically severe, ventilatory disorders, who characteristically are most challenged in their breathing when they sleep.

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Chapter 2
Negative Pressure Noninvasive Ventilation (NPNIV): History, Rationale, and Application

Norma MT Braun

Dedication

This chapter is dedicated to Jack Haven Emerson (1906–1997), who designed the most effective, widely used noninvasive negative pressure ventilator, the iron lung, in the first half of the twentieth century, and to Dr. Dudley F. Rochester, my mentor, who did so much of the research to begin our understanding of the basis of their physiologic effectiveness, and to my patients who have taught me more than they can know.

Introduction

Man has recognized the vital role of breathing since antiquity, beginning with archeological findings depicting inhalation therapy using herbs, oils, and other substances since 6000 BC [1]. Man has taken the automaticity of breathing for granted, expecting its adequacy for all activities whether awake or asleep. Dickinson W. Richards, MD, Nobel Laureate, said in 1962: "Breathing is that essential physiologic function that is straddled between the conscious & the unconscious and subject to both" [2]. The understanding of the components of this critical physiologic function that starts at birth, and must be continuous and widely adaptable to support all levels of physical, metabolic, and functional needs, has evolved slowly over the millennia by many brilliant scientists from a combination of keen observation, imagination,

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daring experimentation, trial and error, and necessity, while overcoming dogma, religious inhibitions and politics. It is this gradual chronologic process, still evolving, which guides what we do for patients today.

Breathing is an automatic, unconscious act until it is not sufficient—when symptoms of breathlessness and distress develop, or when life itself is threatened. All normal breathing is by negative pressure, accomplished by the development of negative intrathoracic, or below atmospheric pressure, when the inspiratory muscles contract, predominantly through diaphragmatic descent, distending the rib cage, thus allowing the pressure gradient from the higher atmospheric pressure to cause air to flow through open airways into the elastic lungs and chest wall. Simply relaxing these muscles allows for recoil of the lungs and chest wall to effect exhalation until higher workloads require the recruitment of additional muscles. It took hundreds of years to learn to recognize and understand this.

The slow and gradually accelerating evolution of knowledge regarding the vital connection of breathing to life and how its loss needed to be addressed was recognized as early as 3150 BC. To appreciate this process, it will be necessary to address its evolution from managing primarily respiratory emergencies with both "invasive" and "noninvasive" positive pressure ventilation (NIPPV) to the development and successful use of negative pressure noninvasive ventilation (NPNIV), enhanced by the polio epidemics, by ingenious designs, by better communications, by the availability of reliable power, by the necessary financial support, and from improved systems of care whose highlights will be chronologically described below.

The History of Ventilatory Failure and the Beginnings of Assisted Ventilation

An unknown philosopher stated "The lungs are the center of the universe and the seat of the soul [3]". The earliest reference for attempts to restore breathing was about 3150 BC when Egyptian physicians tried to save drowned victims by placing a reed in the throat and blowing into the lungs [4]. The Chinese in 2000 BC described *lien ch'i*, as a transfer of inspired air into the "soul" (life): mouth positive pressure. In the Old Testament book of Genesis 2:7, written between 1450 and 1410 B.C. by Moses, God is described "as breathing life into his dust created man by breathing into his nostrils" & thus "man became a living thing" and "when his breath was taken, he died & returned to dust." Further, it was written in 2 Kings 4: 34–35 that the Prophet Elisha "…went up…placed his mouth upon his mouth…and again…the child sneezed seven times…opened his eyes [5]."

There were long hiatuses in recorded history with sporadic descriptions on the essence of breathing and/or its restoration. In 570 BC a Greek physician, Anaximenes, emphasized that the essence of all life was *"pneuma"* or breath [6]. Hippocrates (460−375 BC) wrote the first directions for intubation in "Treatise on Air" by placing a "cannula into the trachea along the jaw bone so that air can be drawn into the lungs [7]." However, it was Claudius Galen, a physician, in 128 AD,

who followed on this by experimentation by breathing into a hollow reed placed in the throats of many different animals, and noted that their chests expanded. Human experimentation was strictly, legally forbidden. In 160 AD, as the physician to the gladiators in the arena, Galen was the first to conclude that the head controlled breathing when he observed that those gladiators who had their heads cut off at the neck ceased breathing immediately and those injured below the neck continued to breathe [8]. His scientific studies through careful dissection in animals became the basis, the "Bible," for the practice of medicine. He assumed that the anatomy of pigs, apes, dogs, and oxen were the same as in humans. His doctrines were considered so sacrosanct and inviolate by the clergy that their contradiction was punishable by death. This greatly inhibited studies in humans and severely limited the growth of knowledge about breathing in man.

It took more than another thousand years, in 1543, for Andreas Vesalius, a Dutch physician, to dare to do studies in humans. He was a meticulous physician who secretly performed detailed human dissections, despite the church's prohibitions. This massive work led to his appointment as Professor of Anatomy in Padua at age 23. He was the first to successfully resuscitate a drowning victim by "placing a tube in his throat & bringing him back to life with a return of a pulse." Previous experimenters found in opening the chest that this caused the lungs to collapse, and was always associated with cessation of heart beats and death. He observed when he opened the chest of animals that "when the lung …collapsed, the beat of the heart and arteries appear wavy, creepy, twisting; but when the lung is inflated at intervals, the motion of the heart and arteries …" resumed, the first description of ventricular fibrillation restored to a regular rhythm with the use of intermittent positive pressure breathing (IPPB). He did this by placing a tube through an "opening" in the trachea of a pig through which he could blow which caused the lung to "rise" and "restore the animal." This concept of positive pressure breathing lasts to the 21st century, intermittently abandoned, then resurrected. Vesalius stole the body of a criminal, boiled it, and thus acquired the first complete human skeleton. When he was not yet 29-years old, his seven volume book, *de Humani Corporis Fabrica*, printed in 1555, beautifully illustrated by a pupil of Titan, detailed correct human anatomy for the first time, contradicting Galen's work. This was considered heretical, creating professional and theological storms. The story is told that Vesalius performed an autopsy on a Spanish nobleman and observed that his "heart started to beat again" after he inflated his lungs through a tube placed into the trachea. This, along with his contradicting work, earned him the designation of heretic. Since the Pope had decreed that a heretic was guilty of a form of "spiritual treason" when a system of fines and exile was replaced by execution since 1200, a declared heretic was in mortal danger.It was only because of the wealth of his father and his connections to Charles V, Emperor of Spain and the Netherlands, that he was condemned to a "pilgrimage to the Holy Land" rather than execution. It was on this pilgrimage that his brilliant and audacious career ended in his premature death in a ship wreck off Greece on the Ionian island of Zante. Since the clergy were often the only educated, literate people throughout the middle-ages, their dictums were law. Anyone could be accused of being a traitor who was then summoned before a tribunal,

"per inquisitionem," where there was little recourse for self-defense, and sentencing decided. This period, The Inquisition, lasted 800 years, from 1000 to 1800, when countless people were executed, including Joan of Arc, who was executed after torture for heresy in 1431 [9]. This prolonged period dominated by fanatical ignorance with the mortal threat it imposed benefited the clergy and the monarchy both politically and financially and dramatically impeded medical progress [9].

The first recorded attempt of "mechanical" ventilation was in 1550, attributed to Paracelsus, when he used a fire bellows as a device connected to a tube inserted in the patient's mouth to blow air into the lungs to assist breathing, an "IPPB [10]."

Although first mentioned in the bible in Genesis 35:17, midwives have been practicing neonatal resuscitation of apneic infants by mouth-to-mouth breathing since the 15th century although no systematic data were reported as to consequences or the rate of success [11, 12].

Without an efficient means for information dissemination or a common language, it took more than another 100 years for Robert Hooke, an English "Leonardo" in 1667, to apply Paracelsus's IPPB idea experimentally by attaching a pump he made for his mentor, Robert Boyle, to a cut in the trachea of dogs with open thoraces to "blow air in regularly and intermittently to keep them alive," noting the difference in color between venous and arterial blood [10]. Excepting for Vesalius's work, prior to this, opening the chest always resulted in collapse of the lungs, cardiac standstill, and death.

It was John Mayow, an English physician-scientist in 1673, who first conceived and built an external negative pressure ventilator, which consisted of a unit with a bellows and a bladder to pull and expel air, suggesting that this mimicked the action of the inspiratory muscles [13]. While he was also the first to show the necessity of oxygen for life, preceding Priestley, he did not name it. His work remained obscure until 1832.

In Scotland in 1732, W.A. Tossach, a surgeon, reported the miraculous rescue of a suffocated coal-pit miner from the pit when he performed mouth-to-mouth breathing: "I… blowed my breath as hard as I could raising his chest fully" when the heart restarted, after noting that he had to pinch the nostrils to prevent the air from escaping. One hour later the miner began to move and yawn and was said to have walked home after 4 h. His duration of death "was between half an hour and three quarters." Details of the miner's age and subsequent health were not given [14].

It took another 12 years for John Fothergill, in 1744, to successfully revive a drowning victim choosing mouth-to-mouth resuscitation, because he feared lung overdistension with use of the bellows. He also believed that warm rather than cold air would be "more beneficial" that led to its promotion as effective noninvasive positive pressure resuscitation. He founded the British Humane Society in 1750 to promote this method to save lives. A common belief at that time was that a drowned person was already dead, that the lungs were already collapsed and thus not capable of responding to resuscitation. John Fothergill showed that this was not true. Another fear that worked against resuscitation efforts was that a victim brought to a home may obligate the owner for the burial expenses [15].

Twenty-three years later, in 1767, due to the continued frequency of drowning victims in the Netherland waterways, the Society for the Rescue of Drowned Persons, or The Humane Society, was formed to rescue such persons. The first protocols were expounded which included keeping the victims warm, using mouth-to-mouth breathing and the addition of hand compression of the chest or chest and abdomen to "assist expiration" for resuscitation. This inadvertently added cardiac compression to the rescue effort although no records were published as to the rate of its success [16].

Lack of such records and the slowness of information dissemination contributed to developing a litany of other local practices. Many useless ideas were espoused for reviving victims of drowning, as it was thought that strong and stimulating practices could revive a subject. These included being rolled over barrels, thrown over a trotting horse face down, being subjected to loud noises, or having bright lights shone in the eyes, or burned with hot irons. The Humane Society recommended blowing tobacco smoke into the "great bowel" as an "accessory means" to aid resuscitation. When insufficient persons or lack of any implement to blow tobacco smoke were available, induction of vomiting with emetics, pouring warmed wine down the throat, or inducing sneezing with "spirits of quick lime" on a rag placed under the nose were also recommended and practiced with no beneficial outcome. Venesection was promoted as "particularly necessary" if any life returned. Since such accidents occurred ubiquitously, similar Humane Societies were formed in England and other European countries using some combinations of effective and useless techniques [17]. The choice of mouth to mouth or bellows varied by their local popularity or by individual practitioners in the absence of controlled trials.

Between 1772 and 1774, the simultaneous but independent rediscovery of oxygen for its capacity for life support in mice placed under airtight glass domes and to keep a flame lit with "pure," "vital," "dephlogisticated air" from which nitrogen (phlogiston) had been removed by Joseph Priestley (English), and Carl Wilhelm Scheele (Swedish), led to the abandonment of mouth-to-mouth efforts in favor of the use of bellows with oxygen for resuscitation. It was thought that more oxygen could be given by the bellows than by mouth-to-mouth attempts. It was the combined work of Joseph Black, isolating carbon dioxide in 1757, Henry Cavendish, isolating hydrogen in 1766 AD, and Daniel Rutherford, isolating nitrogen in 1772 that facilitated the French chemist, Antoine Laurent-Lavoisier, to name the gas Oxygen. Born an aristocrat of independent means, and intensely dedicated to studying respiratory physiology, Lavoisier with Pierre Simon Laplace, in 1780, discovered that the nature of respiration was a process of combustion where oxygen is used and carbon dioxide and water produced. This concept also led Lavoisier to work on public health for the poor because he found the air unclean where they lived. The French Revolution was in full force and for his aristocratic connections and his investment interests his career was cut short by the guillotine. He was labeled "an enemy of the people" in part because his chemistry lab was supported by the King [18]. His work fostered the use of oxygen in resuscitation [19].

During this time in England, John Hunter in 1776 tried to improve on resuscitation efforts by devising a double bellows so that one could be used to blow in "fresh air"

or oxygen and the other used to suck out the "bad air;" the first cyclic "ventilator." This consolidated the use of oxygen for resuscitation. To prevent air from entering the stomach, Hunter applied gentle tracheal pressure to compress the esophagus [20]. He forbade venesection as being useless. The addition of oxygen to mechanical bellows resuscitation was expanded by its promotion by an Englishman, Edmund Goodwyn, MD. He was given a Gold Medal for his acclaimed dissertation "The Connexion of Life and Respiration: On an Experimental Injury Into the Effects on Submersion, Strangulation and Several Kinds of Noxious Airs in Living Animals… and the More Effectual Means of Cure" published in 1805 [21]. This was the first "evidenced-based" study published. It fostered Lord Cathcart, representing Scotland in the House of Lords, to encourage ordinary laymen to use such artificial respiratory resuscitation by offering incremental monetary rewards for saving lives this way based on the extent of action each resuscitator had taken; from a half crown for reporting a drowned victim to a surgeon or to minister, to the largest sum of four guineas for a life saved. Even providing a house for the victim and rescuer was rewarded for "covering expenses" plus one guinea for the "trouble [22]."

The first published hand book for "Life-Saving Measures for Drowning Persons" was in 1796, in Danish, by John Daniel Herbholdt, MD and Carl Gottlob Rafn, botanist. They collaborated on detailed specific resuscitation methods, and described the use for victim retrieval by several types of grappling hooks and boats. What they added was evaluation and critical analysis to their findings that led to similar techniques now still used. Lack of translated copies limited its wider application until the work was translated in 1960 by the Scandinavian Society of Anesthesiologists, on their founding [22].

By 1802, E. Coleman, a Scots veterinary professor, refined a catheter by making it in silver and of larger bore, and introduced it into the trachea to which a bellows was attached and oxygen added. He was also the first to describe the use of electrical current through placing electrodes over the base and the apex of the heart as part of the resuscitation effort [23]. The tripartite successful use of manual bellows or IPPB respiration, with or without intubation, chest-abdominal compression and electrical heart stimulation, innovative then, was overlooked for over a hundred years.

While the fireside bellows of Paracelsus and Hooke had been the "mechanical" tool used, no systematic data were collected as to its success or failure rate, or of any complications, until Leroy d'Etoille, of France, in 1827. He was the first to report a complication when he described its causing "emphysema and tension pneumothorax" and warned against its "improper use [24]." Even though Robert Hooke had suggested that this method of forcing air into the chest might cause "emphysema" in 1667, he provided no data. The lack of volume control using a bellows and the lack of ability to regulate the device for the size and weight of the victims led to Leroy's challenge to its use. A report of poor survival by Sir Benjamin C. Brodie of the Royal Humane Society in England in 1867 ended this form of positive pressure resuscitation and the societies formed to promote it [25]. Ignorance that proper use could be associated with a better outcome, and discouragement by the high mortality from infections, especially when the trachea was entered, led to the abandonment of this form of IPPB for more than 100 years.

The need for safe, effective resuscitation, however, continued for medical emergencies such as for still born infants, for victims of drowning and for asphixiations from chloroform, fire or other occupational exposures. Manual devices of individual creation were used without systematic study or analysis.

Negative Pressure "Noninvasive" Ventilation (NPNIV)

With the work of John Mayow from the 1670s "lost," between the 1830s through 1925 many scientists/physicians began to think again about "more normal, physiologic" negative pressure methods to support respiration. They set to designing devices that would develop sub-atmospheric or "negative" pressure around the body that would draw air into the lungs for persons with inability to breathe, not just victims of drowning. Early models generally failed, with often prolongation of dying for those so treated by the devices. The failure rate contributed to additional designs even when limited by the absence of available, reliable continuous power to run them.

Four main types of negative pressure devices were designed: the tank ventilator, the "iron lung," the cuirass with a variety of chest shells, and the differential pressure chamber of Sauerbruch.

The tank, the iron lung, and cuirasses will be considered together due to their overlap in development, design, and similarities of action for breathing support, although they are different in their effectiveness for different patient disorders and ages.

The initial devices were cumbersome, were largely manually operated and, except for a few reports, mostly failed. Their perceived persistent need, however, supported the enthusiasm for new designs by many physicians and scientists who collaborated with engineers.

The first unit was made of a rigid wood box housing the whole patient except for the head, around which was an airtight neck collar or "dam" by which intermittent negative pressure, alone or with positive pressure, generated manually or via a mechanically operated pump, using steam, water or electric power, which developed the pressure changes to induce air flow into the chest.

In 1832, Dr. John Dalziel, a Scottish physician from Drumlanrig wrote an easy "On Sleep, and an Apparatus for Promoting Artificial Respiration," the first account of sleep (nocturnal) and artificial respiration [26]. He created the first automatic respirator by designing a box enclosing the seated body with a seal around the head and neck and manually connected to a pair of bellows inside the box, worked from the outside by a piston rod with a one way valve, to develop sub-atmospheric pressure around the thorax so that positive atmospheric pressure caused air to flow into the lungs. The windows at the box's side allowed observation of chest movements. It was not until 1840 that Dr. Robert Lewins of Leith, England, used this model to "produce breathing" in a drowned seaman [26]. He modified it by replacing the bellows with a large syringe. The fact that breathing was restored was measured by the extinguishing of a lit candle under the victim's nostril during exhalation.

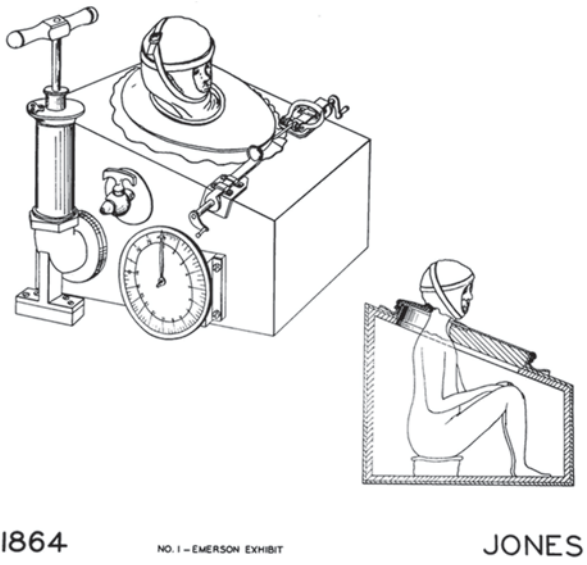


Fig. 2.1 Alfred E. Jones of Lexington, Kentucky patented first American tank respirator. (Used with permission from J. H. Emerson Co.)

Alfred E. Jones from Lexington, Kentucky, USA, following a similar design, patented the first American tank respirator in 1864 also using a large syringe to develop negative pressure for a seated subject. He treated asthma and bronchitis with his device and claimed "cures" for a host of diseases including "paralysis, neuralgia, asthma, bronchitis, rheumatism, dyspepsia, seminal weakness, deafness and … others" when "properly and judiciously" used [27] (Fig. 2.1).

In 1876 Ignez von Hauke from Austria experimented with both continuous positive pressure applied to the mouth via a mask and, initially, continuous negative pressure ventilation for up to 15 min intervals for the treatment of pneumonia, atelectasis, and emphysema. He discovered that intermittent negative pressure ventilation in phase with the patient's inspiration could be used for respiratory failure. He then made an iron cuirass covering the chest with an air-filled rubber edge to "seal." Agitated patients made this device unworkable, which led to the design for the first tank-type respirator, covering the whole body, "*Pneumatische Apparate* [28]." The whole subject was enclosed supine in this tank, including the scalp covered with an elastic cap which was sealed to the tank edge with elastic plaster, leaving the face free. It was hand operated for 2–3 h per "treatment." He used it for many conditions including neonatal asphyxia, atelectasis, pneumonia, tracheitis, croup, and diphtheria. L. Waldenburg, his colleague, reported that it kept a small girl alive for 3 months suffering from "great debilitation and double pneumonia" when she improved, and gained weight. It also "straightened" her rachitic chest wall [29].

In the same year, 1876, Eugene Joseph Woillez from France, designed a workable manually operated negative pressure tank respirator he called a "Spiroscope". Repeating the work of John Mayow, he stated that "the primary reason for the entry of air into the lungs is not the pressure of the air but the expansion of the thoracic

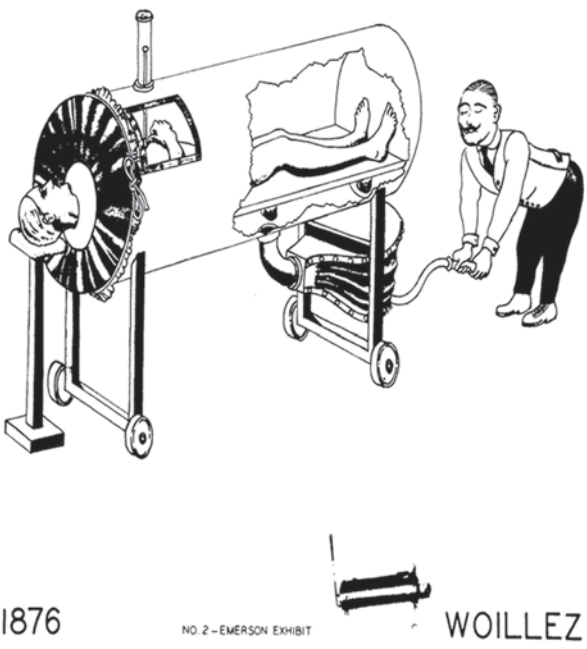


Fig. 2.2 Spirophore of Woillez: a negative pressure tank ventilator which was manually operated with the unique feature of observing chest movements with a rod resting on the patient's chest. (Used with permission from J. H. Emerson Co.)

cavity by the respiratory muscles." He then made an improved model encasing the whole body called the "Spirophore" with an adjustable rubber collar to seal around the neck with the head protruding, resting on a shelf, and a sliding bed, which became the prototype for all the negative pressure tank units that followed. A manually operated bellows generated the pressure changes from the opposite end. It had a unique feature, a rod resting perpendicular to the supine patient's chest which signaled the motion of the chest cage with each breath cycle, thus allowing for its detection [30] (Fig. 2.2). A unit lent to a Dr. Voisin for three drowned victims failed to revive the already dead victims. Woillez refused to patent his unit. His goal was to place these units all along the river Seine for drowning victims but lack of financial support doomed the project, possibly due to the failed attempts.

In 1887 Charles Breuillard, MD of Paris designed an impractical "bath cabinet" for a seated patient which required the patient to operate a valve to shift between vacuum for inhalation and release to atmospheric pressure for exhalation, requiring a conscious subject who could not fall asleep [31]. But it was the first unit to be continuously powered by steam from a boiler heated by a "spirit lamp" rather than manually (Fig. 2.3).

Alexander Graham Bell, the inventor of the telephone, and not a physician, after the death of his 1-day-old son in 1881 designed a metal vacuum jacket in 1882 which developed negative pressures with a separate hand pump to artificially "expand' the lungs to save lives. It was a unit made of two rigid halves with soft linings held to the chest by a strap, with negative pressure provided by large bellows. He successfully experimented with healthy volunteers. Even after he presented the

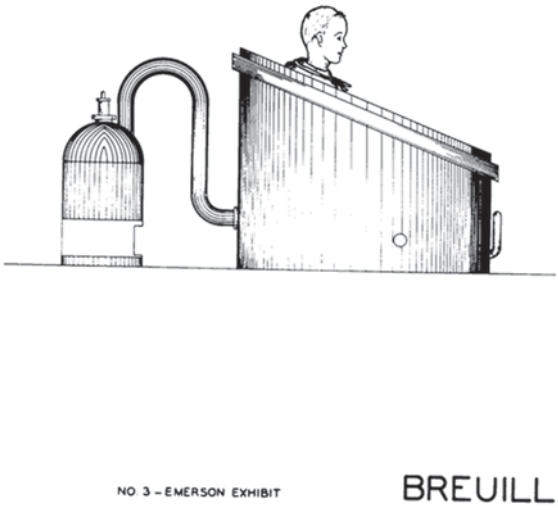


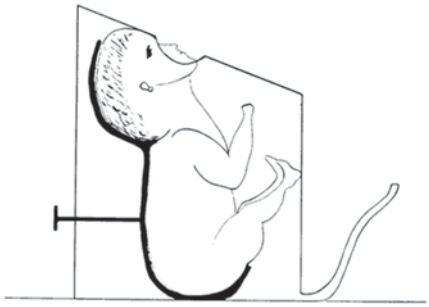
Fig. 2.3 Bath cabinet of Breuillard where the patient had to operate the valve to switch from negative to atmospheric pressure to support breathing. (Used with permission from J. H. Emerson Co.)

results to a meeting of the Advancement of Science and loaned it to someone at the University College in London, however, it generated little interest and went unused, perhaps because Bell was not a physician [32].

In 1889, Dr. Egon Braun of Vienna devised an infant "resuscitator" consisting of a box in which was placed a small supporting plaster mold conforming to an infant's body, with a rubber diaphragm seal around the head, leaving the nose and mouth exposed to air. Through a tube at the base of the box the operator would blow into the pipe to force chest compression, causing the air to exhaust out of the infant, allowing for chest recoil to generate a suction, or negative pressure, to inflate the chest (Fig. 2.4). This was repeated 20–30 times a minute by volunteers and reported to be "completely successful in 50 cases" reported by OW Doe [33].

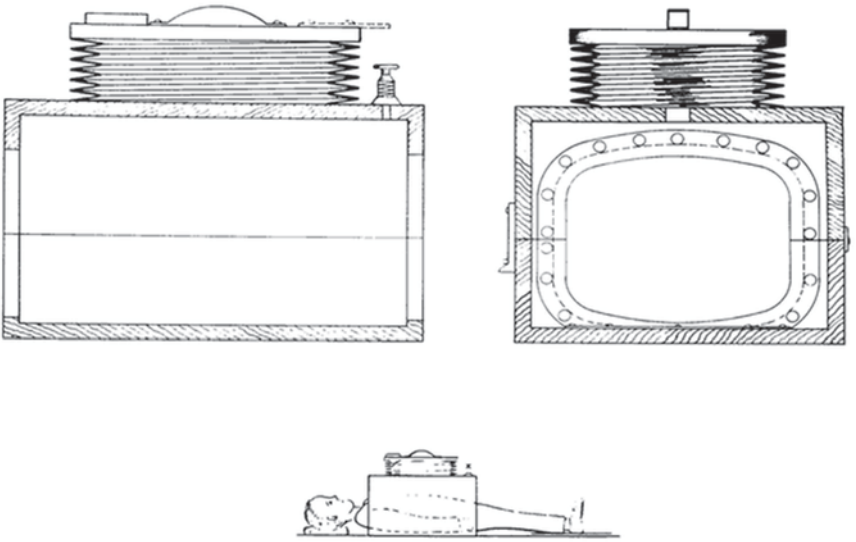
In 1901, a Hungarian physician, Rudolph Eisenmenger, patented the first portable negative/positive pressure "cuirass" ventilator used for cardiopulmonary arrest from drowning or intoxication, consisting of a two part box enclosing the chest and abdomen, allowing the throat and limbs free. A foot operated bellows was later replaced by motors in 1904 (the "Biomotor") and was reported as "extraordinarily successful" when he reported the resuscitation of a man who had hung himself [34] (Fig. 2.5).

Aside from these issues of negative pressure ventilators to allow for resuscitation, there had been no system that allowed a surgeon to operate on the lung without its collapse until 1904, when Ernst Ferdinand Sauerbruch of Germany designed and built an airtight continuous negative pressure operating room, a giant "pleural space," where the subject's head protruded through a hole, exposed to atmospheric pressure, allowing for inflow of air to the lungs, and where the surgeon, also in the room, could work on a patient with an open chest. It was completely abandoned due



1889 NO. 4 – EMERSON EXHIBIT BRAUN

Fig. 2.4 Infant resuscitator of Braun operated by blowing into the box to compress the chest and allow passive recoil for inspiration. (Used with permission from J. H. Emerson Co.)



1901 NO. 5 – EMERSON EXHIBIT EISENMENGER

Fig. 2.5 First portable negative/positive pressure when the intial foot operated bellows was replaced by motors and renamed the "Biomotor." He made a body enclosed unit as well, but this became the forerunner of the cuirass

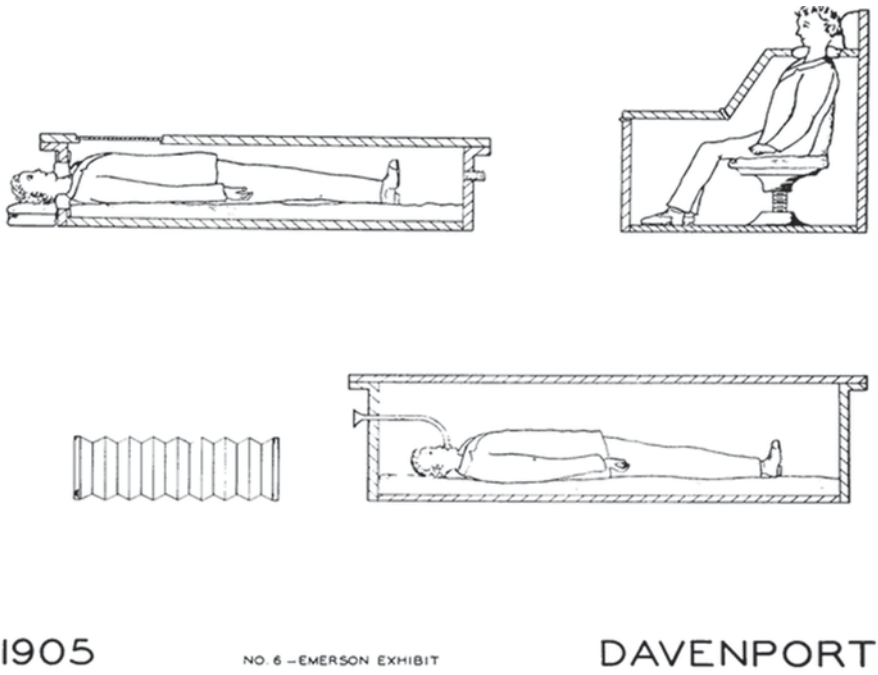


Fig. 2.6 Three models of iron lungs by William Davenport of London. All were manually operated, limiting their utility. (Used with permission from J. H. Emerson Co.)

to the heat in the room for the operators, the lack of space to work, and the inability to talk with the anesthetist. But it encouraged the brothers Willy and Julius Meyer to construct a formidable double operating room in 1909 in New York. It consisted of an outer negative pressure chamber where the patient and the surgeon worked and a positive inner pressure chamber where the anesthetist sat. While considered brilliant at the time, it too failed to be practical and never gained widespread use [35].

In 1905 Dr. William Davenport of London designed several iron lungs: one for a seated subject, one for supine use, and a portable unit modifying the one of Woillez's design. The patients frequently experienced an extended dying process with their use despite the addition of oxygen. Operating the bellows or piston pump to generate negative pressure by hand limited its application [36] (Fig. 2.6).

In 1908, Dr. Peter Lord of Worchester, Massachusetts, patented the design of a respirator room with cyclic pressure changes allowing nurses to work inside it with the patient. Huge pistons in the ceiling provided the negative pressures and the fresh air (Fig. 2.7).

In 1911, Charles Morgan Hammond of Memphis, Tennessee, patented his cabinet respirator or artificial lungs, similar in design to Woillez, having worked on it since 1905. It passed its first clinical trial in 1912, saving more human lives by 1914. He improved on his models for the next 20 years, but for lack of commercial support, its production was limited to Tennessee. When he failed to renew his patent, it expired and his sentinel "first" was abandoned [36] (Fig. 2.8).

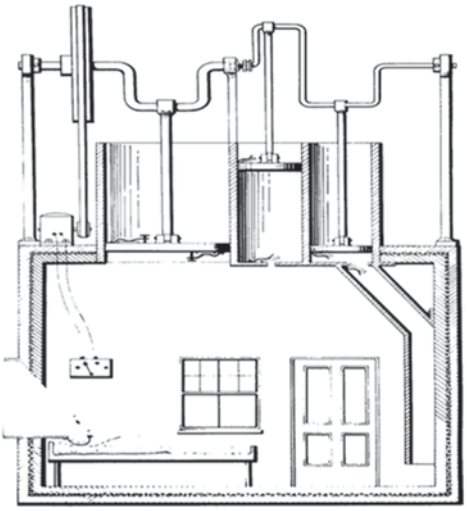


Fig. 2.7 Peter Lord of Worcester, Massachusetts, patented this negative pressure room allowing nurses to work in the room with the patient. (Used with permission from J. H. Emerson Co.)

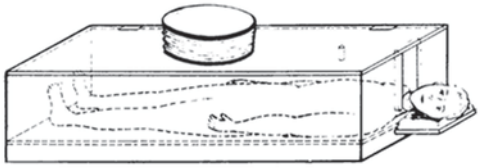


Fig. 2.8 Dr. Charles Morgan Hammond of Memphis, Tennessee designed this unit in 1905, but not patented till 1911. They were similar in design to Woillez, saving its first life in 1912. While saving lives, it was not commercially made and thus not available outside of Tennessee. (Used with permission from J. H. Emerson Co.)

In 1916 a cumbersome, useless unit patented by Melvin L. Severy of Boston was made. Here the patient had to stand in a box, pressing his nose and mouth through triangular openings between two eye slits. It was powered by a bicycle like apparatus of pulleys and electromagnets to create the negative pressures to assist breathing [36] (Fig. 2.9). Severy also designed a negative pressure cuirass.

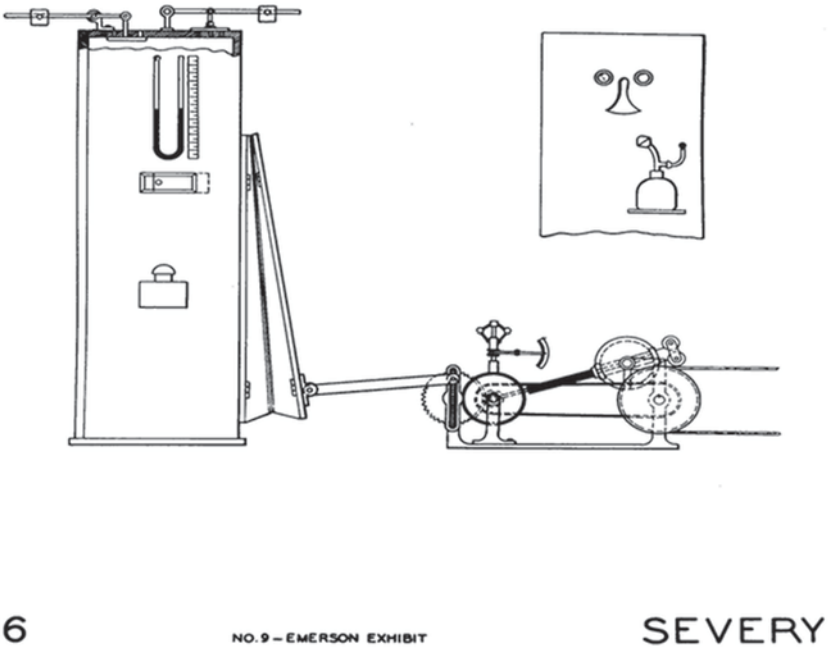


Fig. 2.9 A cumbersome design by Melvin L. Severy of Boston, Massachusetts, where the patient had to stand, pressing his face against one side with apertures for eyes and nose and powered by pulleys and electromagnets outside the *vertical box*. (Used with permission from J. H. Emerson Co.)

In 1918 two physiologists, Felix P. Chillingworth and Ralph Hopkins from Tulane University, reported a new idea, the successful use of an electrically powered body plethysmograph to ventilate tracheotomized dogs by alternating pressures around the body, when studying the effects of lung distension on circulation. With a tracheotomy tube the lack of a neck seal did not matter. They did not realize the potential for using such a negative pressure system for humans but it showed the potential for supporting breathing by alternating pressures around the body and served to inspire Philip Drinker et al. [37].

Poliomyelitis epidemics, while prevalent from the 1870s, resurged in 1916, and were spreading worldwide. Children were the most frequently affected, leading to its designation as the dreaded "Infantile Paralysis." The high mortality rate when breathing was affected was soon recognized and spurred the development of efforts to reverse the near 100 % mortality from respiratory failure. Many negative pressure ventilator innovations followed, spurred by this need, but poor communication and/or an absence of training and resources limited their application.

W. Steuart in South Africa, in 1918, made an airtight, rubber-lined rigid wooden box, with a mattress, that was applied over the chest and abdomen. It was the first workable cuirass, through which a variable speed motor drove a bellows rhythmically to produce negative pressures. Tidal breath and minute volume were adjustable

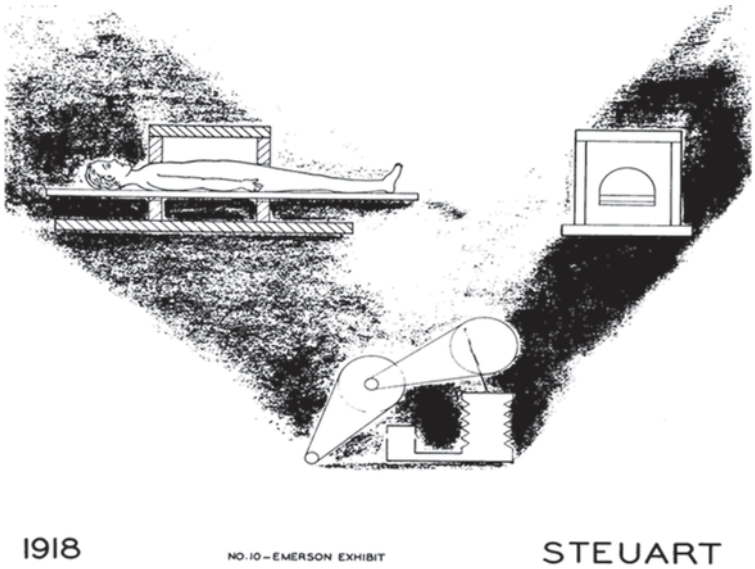


Fig. 2.10 An airtight wooden box made by South African, W. Steuart, the first workable cuirass where a variable speed with a rhythmic motor produced the pressure changes where tidal breath and minute ventilation could be set. (Used with permission from J. H. Emerson Co.)

along with valves that could adjust the amount of negative pressure. A glass panel allowed observation and the top of the box could be removed quickly in case of need for patient access. Steuart presented this work to the South African Medical Society. He was unable to conduct a clinical trial because the last patient died before he completed the work. However, the principal of longer term artificial respiratory support where breathing could be individually adjusted had now been introduced for the first time [38] (Fig. 2.10).

In 1900 Dr. Tursten Thunberg of Lund, Sweden, developed a truly novel concept: ventilating without chest movement. He designed a "Barospirator," producing the final sarcophagus-like version in 1920. It was a tank large enough to encase the whole patient. His idea was to limit chest motion to a minimum. His was the first mechanical ventilator applied successfully for "long-term" use of several months [39] (Fig. 2.11). Its first success was to save a patient from paralyzing poliomyelitis [40]. A. L. Barach, in order to make the chest cage completely immobile to "rest" the lungs to allow advanced tuberculosis cavities to "close," modified the Barospirator by making an upper section, encasing the head, and a lower body section, separated by a fine mesh nickel plated screen, producing cyclic, equal pressures both inside and outside the chest so that air would flow with no chest motion. He separated the head in his Barospirator because of a delay in pressure transfer due to airflow resistance from the upper airways, which allowed continued, albeit reduced, chest movements, and thus not total rest. He reported applying this therapy for 12 h per day and felt that it could take the place of induced pneumothorax, without or with the instilling of space occupying materials in the pleural cavity to collapse the

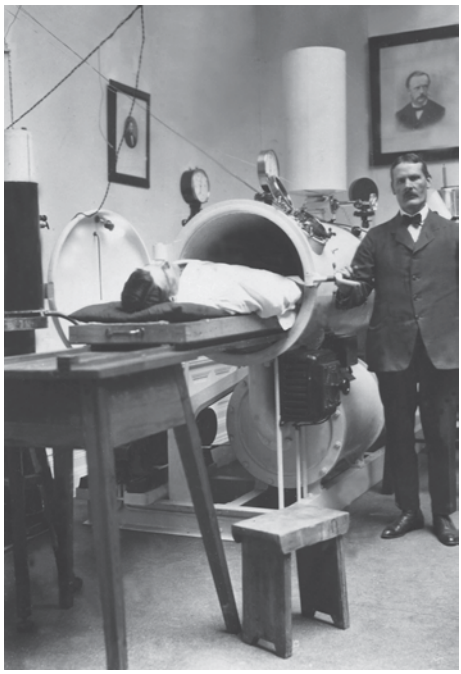


Fig. 2.11 Dr. Tursten Thunberg of Sweden with his "Barospirator," developed to ventilate with almost no chest movements, put to use in 1920. It was adapted by Alvin L. Barach, MD, to immobilize the chest for the treatment of cavitary tuberculosis while breathing was supported with continuous negative and positive pressures. (Used with permission from the South Swedish Society for the History of Medicine)

cavitated lungs, all before the availability of chemo therapy for tuberculosis [41]. The effectiveness of Streptomycin and Para-aminosalicylic acid in 1945-46 ended the need for this.

In 1926, Wilhelm Schwake of Germany patented a totally impractical pneumatic chamber in which the patient had to stand and use his own hands to move a large bellows, comprising the whole side of the box, to generate negative pressure to "draw out the gaseous by-products" [36] (Fig. 2.12).

In New York that same year, the Consolidated Gas Company faced the need for resuscitation and respiratory support for an "alarming number" of electric shock, carbon monoxide gas, and smoke inhalation asphyxiated workers. They engaged Dr. Cecil K. Drinker, Professor of Physiology at the Harvard School of Public Health, to help these victims. Dr. Drinker called on his brother engineer Philip A. Drinker, who worked with pediatrician Dr. Charles F. McKhann, III, and physiologist Dr. Louis Agassiz Shaw. Like Chillingworth and Hopkins, they had been experimenting with placing intact curare-paralyzed cats in iron boxes, with only the head protruding through a rubber, now airtight, collar. To move their thoraces, negative pressures were generated by a hand-operated syringe and later by a hand-operated cylinder piston pump causing inspiration when the air was sucked out. Pressure measurements in the plethysmograph, correlated with volumes of air moved in the cats. By 1927 they showed that, by alternating suction and release, the cats could be kept alive for several hours [42]. Such success, and the demands from the polio epidemic, led to their constructing a unit large enough to accommodate a human.

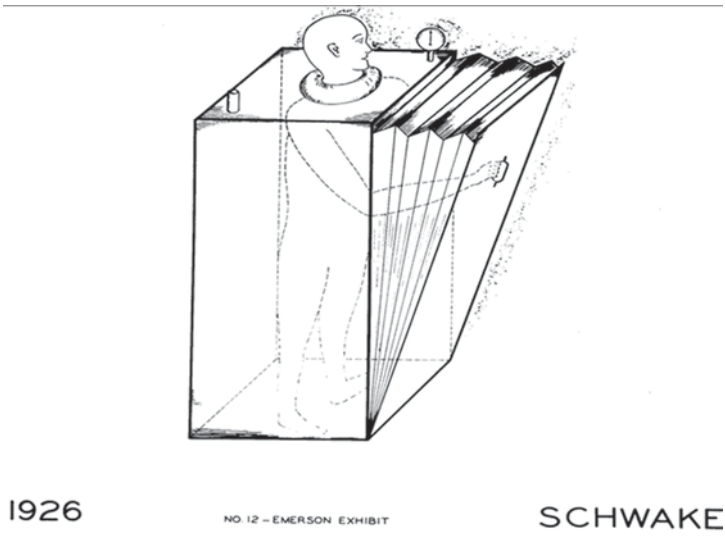


Fig. 2.12 Wilhelm Schwake patented this pneumatic chamber which required the patient to operate a large bellows to generate negative pressure. The patient can see the pressures generated by the gauge placed near the face. (Used with permission from J. H. Emerson Co.)

They salvaged materials to make the first unit for about $ 500.00 ($ 6579 in 2013 US dollars). It was a metal cylinder with one end for the head to protrude with the neck encircled by an airtight collar. The other end had a piston pump through which pressure changes were generated [43]. Reliable electricity became available first on the two coasts in the USA about 1926; [44, 45] this allowed the unit to continuously produce alternating positive and negative pressures by a series of valves, thus moving the thorax. They used the units on themselves and on a diener recruited from the laboratory. Harvey Cushing was the "audience" for these experiments. Drinker himself was hyperventilated by this device and even though he did not resume breathing for 4 min he felt no anxiety as he "simply waited until he felt the need to take a breath." Their first patient was a patient of Dr. McKhann, an 8-year-old girl with polio who was first acclimated to the noise of the unit by placing it in her room over night. By morning she was cyanotic and comatose. She was placed in the chamber and regained consciousness in several minutes and was said to have asked for ice cream a short time later [46]. Even though she died of pneumonia several days later, this dramatic success for the first reported human use of the iron lung, a device that supported breathing by externally applied alternating pressures, and the terrible polio epidemics, led to their widespread use. The funding for 14 more units was provided by the New York Consolidated Gas Co; one of these units was donated to Bellevue Hospital in New York City in 1929 when its use saved an unconscious apneic student nurse from an accidental drug overdose, a now expanded clinical indication for such ventilatory support. It was then applied to a Harvard student who had contracted poliomyelitis in Cambridge. This allowed him to gradually regain his breathing ability, to finish school, and go on to a full career. This was the first

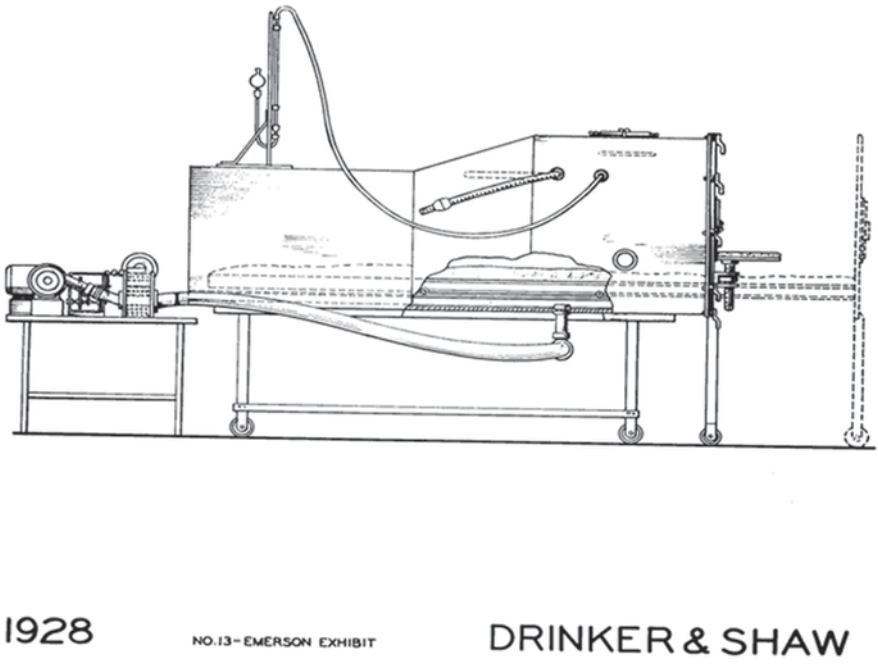


Fig. 2.13 The Drinker-Shaw model of the first successfully used iron lung powered by electricity designed by engineer Philip Drinker and physiologist William Shaw. (Used with permission from J. H. Emerson Co.)

documented instance of private corporate financial support for research that led to direct and wide spread clinical application, i.e., "translational" medicine, becoming the model for such enterprises since. The incredible success of the Drinker-Shaw iron lung tank ventilator, in conjunction with the availability of reliable electric power across the whole country, and the escalating number of polio victims (from 20,000 to 60,000 cases per annum [47], affecting mostly children), set in motion the demand for mass production of the now-named Drinker Respirator. Warren E. Collins Company of Braintree, Massachusetts, was commissioned to make the units but their cost of $2000.00 each ($ 21,444 in 2013 US dollars) equaling the cost of two automobiles in 1929, limited their distribution (Fig. 2.13).

In 1930, James L. Wilson, desperate to treat children with paralysis from polio, worked with Drinker to have the tank redesigned so many children could be treated in a "Respiratory Center," allowing concentrated nursing care, although not knowing if recovery would ensue. Most children recovered and no longer required such ventilatory support, but the ones who did not recover lived in their tank ventilators, sometimes for more than 50 years. This was the beginning of designated respiratory care units for larger numbers of patients, the pre-intensive care units of today. As the key organizer, Wilson recruited The March of Dimes to establish 13 such centers across the USA [48] (Fig. 2.14).

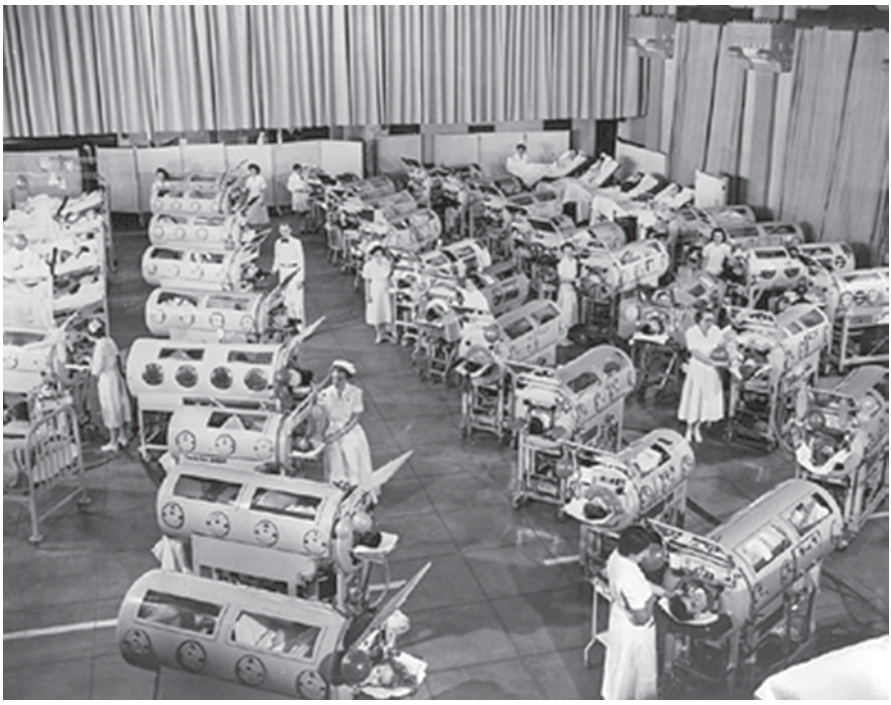


Fig. 2.14 Respiratory Center (aka: TANK FARMS"), Rancho Los Amigos, San Diego, 1953. These were dedicated units for polio patients where centralizing care into one room made it more efficient to care for the large numbers of patients. These were largely supplied with Emerson units. James L. Wilson, MD, recruited the newly formed March of Dimes to support the establishment of some 19 centers across the country. (Used with permission from Post-Polio Health International)

The polio epidemic reached its "worst in the 20th century" in 1931. The Drinker unit was bulky and complex, and its cumbersome design making it difficult to use, coupled with the unaffordable cost, inspired John Haven Emerson, an engineer in Cambridge, Massachusetts and the grandson of poet Ralph Waldo Emerson, to simplify, modify, and improve the unit at half the cost in 1931. In addition to a sleeker design, his additional innovation was adding an airtight, transparent dome for the head for the application of IPPB so the body of the unit could be opened for unhurried nursing care while the patient was continuously supported noninvasively [50]. This unit had several glass side ports and larger rectangular metal doors on both sides through which care could be administered, blood gases and bloods drawn, and clinical observations made. He made a thick leather diaphragm to move the air and powered it with a standard vacuum cleaner pump to which a cyclic feature was added. Two vacuum pumps could be connected in series to amplify the pressures if needed. It could also be manually operated should there be a power failure, not uncommon at that time. The adult unit was 33"wide × 92"long × 56" high, and despite the weights for varying sizes from 640 to 800 lbs (290–337 kg), it was a great success (Fig. 2.15a, 2.15b an opened unit; 2–15 C a unit with a transparent

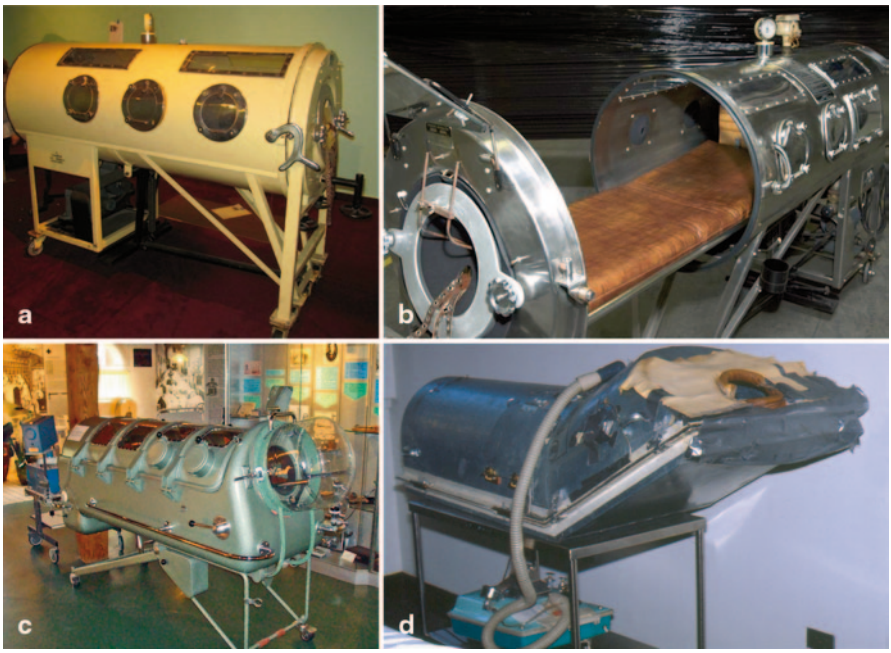


Fig. 2.15 **a** The Emerson iron lung made for half the price of the Drinker Shaw model in 1931 at the height of the polio epidemics. It weighed some 224 lbs. (102 kg). Children's models were also made by Emerson. The gauge reflecting the pressure changes is on top of the uint. **b** The Emerson iron lung open showing the neck hole with the foam cushion and a slide out cushioned bed with a pressure gauge on *top*, with the windows and the several side ports to allow nursing care and monitoring. There was a mirror *above* the patient's head so visitors to the bedside could be seen by the patient. **c** Iron lung housed in the Gütersloh Museum, Germany: Illustrating a transparent dome for positive pressure breathing when the unit is opened (Emerson) or for administering oxygen and/or CO_2 to "stimulate breathing" (Krogh). Used with permission from Post-Polio Health International. **d** Emerson customized iron lung used by a Judge for over 40 years who had had polio. A modified Hoover Vacuum pump sitting underneath was the power source. Its reapplication in the surgical recovery unit after retroperitoneal cancer surgery allowed vigorous diuresis and extubation with discharge home

dome for the head; 2-15D Custom made model for a judge). Emerson deliberately decided not to patent his design because he wanted to make the units affordable and available as soon as needed throughout the country [51]. Their use was rapidly expanded where the new "respiratory centers" could accommodate many patients into single large rooms for multiple patients (aka "Tank Farms") and became the first dedicated respiratory care units (Fig. 2.14). A lawsuit by Drinker for infringement of patent rights failed after John Emerson published a pamphlet with a series of pictures depicting *The Evolution of "Iron Lungs*" with previously designed negative pressure tank ventilators long before the Drinker model [49]. This pamphlet is the source for some of the figures in this chapter. Some of the patients, who either were unable to regain independent breathing function or only regained partial function while awake, were continuously or nocturnally supported for more than 60 years

in their iron lungs [52, 53]. One such woman, who contracted polio in 1955 at age 5 just before the polio vaccine, is still using negative pressure ventilation 58 years later. She wrote a Haiku poem: "The story of Jonah—narrow my bed in the belly of this iron lung yet wide enough for the dreams any child would chase [54]." The Emerson Tank Respirator needed only "greasing of the motor and a new fan belt once a year" to maintain reliable function for many years [55].

Another cheaper innovation was designed in Denmark in 1931 by August Krogh, a physiologist, who, as with Cecil Drinker, was concerned that the tight neck collar would limit blood flow to the head. After seeing the Drinker model work in New York, and with bulk and costs prohibitive for transporting the iron lung to Denmark, he "simplified" and improved on it by using water to power it from city pipes. A piston cylinder, acting on a large spirometer bell, created reciprocating movements from alternating the water between the upper and lower compartments of the piston to effect breathing cycles. The temperature inside the tank could be regulated by a water jacket. Another innovation was that the head could be placed in a 15° head down position and could be encased in a hood through which oxygen or a mixture of 95% oxygen and 5% carbon dioxide would be administered to "stimulate" respiration (Fig. 2.15c). Mortality fell to 30% using this ventilator. He also made an infant-sized version and a rocking stretcher, a forerunner of the Rocking Bed [56]. John Emerson advanced the Rocking Bed design and manufactured and distributed an electrically operated one used for long-term (for as long as 45 years) intermittent noninvasive ventilatory support for polio and other patients with persistent diaphragmatic paralysis [57] (Fig. 2.24). He also designed a Motion Bed to prevent skin decubitus ulcers and lung atelectasis, and to enhance circulation, in bed-ridden patients. We reported the use of the Emerson Rocking Bed for patients who developed diaphragmatic paralysis after open heart surgery, allowing for extubation or tracheostomy decannulation and recovery at home [58].

Chance favors the prepared mind, and with the extensive worldwide polio epidemics there was an increasing demand for negative pressure ventilators. In England in 1938, resources were contributed by William Morris (aka Lord Nuffield), an engineer-philanthropist, and owner of the Morris auto factory. After reading a newspaper headline that "Iron Lung Arrives Too Late" to save the life of a young woman, he conferred with Sir Robert Macintosh, head of the Department of Anesthesia at Oxford, who had earlier impressed him with a film of the Both Respirator's capacity to perform artificial respiration. This unit was invented in 1937 by the brothers Edward and Donald Both in Adelaide, Australia. It was made from plywood, making it lighter, easier to transport, and cheaper than earlier versions. Edward had gone to England to sell an electrocardiograph he designed. Learning about the polio epidemic while there, he offered his design of the *Both Portable Cabinet Respirator*, which was quickly accepted, manufactured locally, and put into use (Fig. 2.16). After Edward built a unit for Robert Macintosh, a short film was made. This was the film that inspired the philanthropic act of Lord Nuffield when he offered to manufacture 5000 Both Respirator units at a personal cost of £ 500,000 (equal to $ 2.5 million in 1938 and $ 32.7 million in 2013 US dollars) so that one unit could be given to every hospital in the UK, giving him "the pleasure"

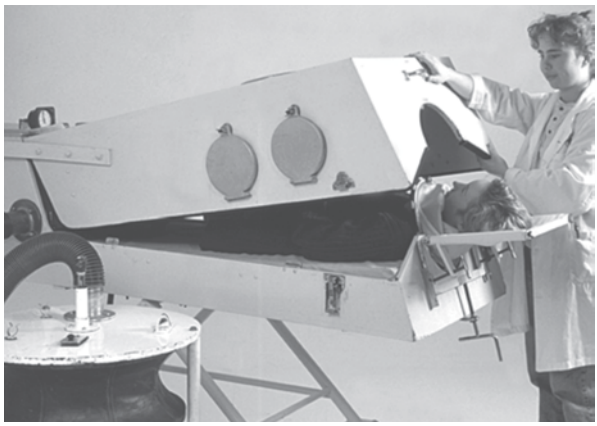


Fig. 2.16 The Both portable cabinet "Alligator" respirator at the National Museum in Australia. It was made of wood, designed by brothers Edward and Donald Both of Australia in 1937. Its use was expanded by the philanthropy of William Morris, owner of the Morris auto factory, by his gift of £ 500,000 to provide one to every hospital in the UK in 1938. (Used with permission from Post-Polio Health International)

of saving lives. Nuffield entrusted Macintosh to accomplish their distribution, and for teaching their use through daily demonstrations at the Radcliffe Clinic. By 1939, only 1 year later, more than 1700 Both Respirators had been allocated and its use taught throughout the UK. This heralded the extensive application for successful prolonged intervention for breathing inadequacies saving countless lives with NPNIV. Since Macintosh was an anesthesiologist, he conceived of using the Both Respirator to manage postoperative patients as well. He was the first, in 1940, and then with Mushin and Faux, in 1944, to demonstrate the successful prevention of postoperative atelectasis by use of the Both Respirator. This gave birth to the advent of "critical care" medicine to provide respiratory support, and eventually to critical care units [59, 60]. Space needs and nursing care demands, however, remained impediments to the widespread use of such still bulky equipment.

In 1952, an English doctor-engineer, George Thomas Smith-Clarke, made the Cape Warwick iron lung with a head down option, redesigning it from the Both model, which was then widely used in England for polio patients [61] (Fig. 2.17).

In 1961, W. Howlett Keheller, MD, modified the design of the iron lung so it could be rotated 180°, allowing for automatic turning, to treat or prevent atelectasis, successfully treating three patients with neuromuscular respiratory weakness (2 post-polio, 1 Guillain-Barre) who developed life threatening airway secretion retention associated with atelectasis [62].

In 1975, Sunny Weingarten, a polio survivor from age 7 ½, designed a lighter (100 lbs; 45.5 kg), more portable tank, a "Porta-Lung." It was made from fiberglass, in four sizes, the extra small for children at 30" length and up to 71" for adults. The unit had flexibility for clinical use in that it had several brands of vacuum pumps accommodating adjustment of pressures ranging from +20 to −60 cm H_2O, respiratory rates from 4 to 60/min, and variable inspiratory/expiratory ratios (Fig. 2.18). He traveled over 50,000 miles in his van using it in all the then 48 states. He died at age 70 in 2012 having been on ventilator support for life, initially full time, then nocturnal only, and finally back to full time, switching to positive pressure as he aged before his death [63]. The Porta-Lung was patented and FDA approved, and

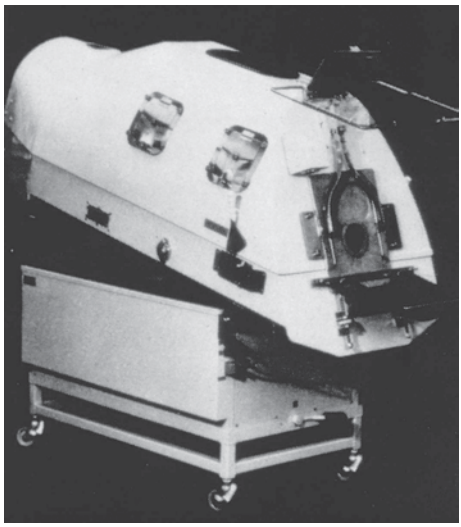


Fig. 2.17 The Cape Warwick iron lung made in England in 1952. Designed to allow the head tilt down position for pulmonary toilette. Some are still in use. (Used with permission from Post-Polio Health International)

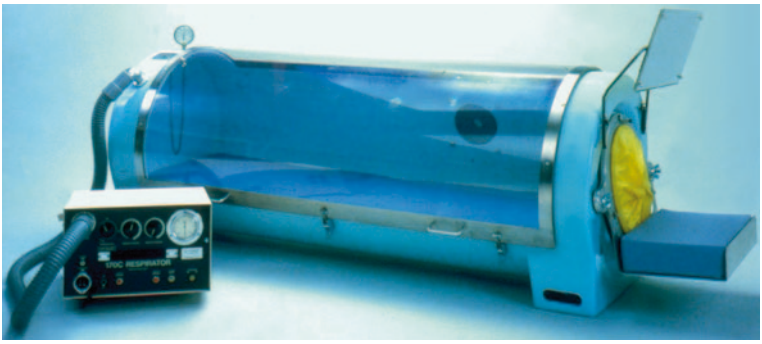


Fig. 2.18 In 1975, Sunny Weingarten designed a fiberglass model, the Porta-Lung, making it lighter (100 lbs./45.5 kg) to allow easy transportation with a larger range of pressures (+20 to−60 cm H_2O) and rates from 4 to 60/min and variable I:E ratios. A life care pump is used here

is still being used by patients due to their comfort and reliability [64]. The problem with this unit currently is replacing worn out negative pressure pumps, since the five that were available are no longer manufactured [65].

Others, especially Italian doctors, remain active in using negative pressure noninvasive ventilation (NPNIV), and some have made their own version of a tank. Drs. Sauret and his associates [66], and Corrado and Gorini summarized in 2002 the literature on the use of both NPNIV and noninvasive positive pressure ventilation (NPPV) for both acute and chronic respiratory failure, which consisted in mostly uncontrolled reports. The need for endotracheal intubation or tracheotomy was the primary end point assessed, and was not different between patients who used NPNIV or NPPV. Mortality was also no different [67–70].

Complications from iron lung use slowly became apparent with their wider use. It stemmed from their bulk and weight, taking up so much space in a hospital room that floors had to be reinforced to support many tanks (Fig. 2.14). The patients felt isolated, resulting in claustrophobia, disorientation, and loneliness for many as well as inhibiting good nursing care. One such patient of mine, a post-polio wheelchair-dependent judge in New York City, started having recurring nightmares of being "trapped" in the iron lung when he developed right heart failure from chronic hypoventilation 40 years later [71]. Using the Pneumosuit (Nu-Mo suit), instead, reversed the hypoventilation, and restored his capacity to work. Vital signs in the iron lung were cumbersome to measure, providing personal hygiene was difficult, and frequent turning to prevent decubitus ulcers was necessary. Even though the Emerson transparent dome reduced these problems for some of the time, air leak prevention from the tightness of the collar created neck skin abrasions and headaches. Patients experienced distress on hearing their own pulses from the tight collars. When less tight, the air leak made them feel cold, especially if they had total body paralysis as well. Some had difficulty initially learning how to synchronize their swallowing while in the iron lung. Aspiration due to the imposed supine posture would occur, at times resulting in death from pneumonia despite the support. Inadequate airways clearance, absent cough capacity, and lack of effective antibiotics contributed to such lethal pneumonias [72]. While some patients successfully used these units in their homes for many years, such units could not be housed there for many patients, particularly at the time that home care was not yet a developed discipline. The polio epidemics and his own polio inspired Franklin Delano Roosevelt (FDR) with friends to found The March of Dimes to provide the financial support for many patients in hospitals, in rehabilitation units, in the homes, and for scientific research for the polio vaccines. In fact it was FDR, focused on regaining the use of his legs after polio, who helped to establish the first rehabilitation unit in Warm Springs, Georgia, dedicated to the care and recovery of polio patients in 1924 [73].

These problems furthered the design of negative pressure devices that only covered the chest or the chest and abdomen called cuirasses, or chest shells, due to their resemblance to medieval protective chest armor made of leather or metal which covered the neck to the waist. While Steuart's model was designed in 1918 it was not widely known or used. The design of the earlier cuirass models also allowed for only the anterior expansion of the chest wall due to its ending at the waist which limited diaphragmatic descent by compressing the anterior abdominal wall during inspiration. Lateral expansion was severely limited when the unit was flush with the lateral chest walls. The apices were usually excluded by the shell's upper configuration and necessary seal. Other shell designs that ended at the umbilicus or just above the pubis allowed for more diaphragmatic descent. If the metabolic requirements were low, the neck to waist model could be adequate. The advantages were their portability, lower cost, and the freeing of the extremities and pelvis with greater mobility and less claustrophobia. Some patients were able to be adequately ventilated in a near sitting position with such units, allowing for more daytime use. Some combined it with positive pressure using a mouth piece

or lip-seal [74]. In fact, one of my chronic obstructive pulmonary disease (COPD) patients who had intractable dyspnea and chronic hypercapnic respiratory failure used NPNIV via a Nu-Mo suit nightly, achieving eucapnia, and went home to Brazil (Fig. 2.23). She worsened 2 years later. On her reevaluation, she had gained 35 lbs. This resulted in upper airways obstruction while using nocturnal NPNIV as Goldstein and Levy had reported [75, 76]. Increasing negative pressure from −35 to −40 cm H_2O worsened this. She refused any other form of support. Adding +5 cm H_2O nasal continuous positive airway pressure (CPAP) circumvented the upper airway obstruction, and she went home successfully using her Nu-Mo suit NPNIV and nasal CPAP.

Many cuirass models were made in several countries including the USA, UK, France, and Sweden. The first units, made by Ignez von Hauke, of Austria, who also made a body unit, in 1874, and Alexandra Graham Bell in 1882, were largely unused by the medical community. Rudolph Eisenmenger of Hungary developed his "Eisenmenger Biomotor" in 1927 made into a "simple, two-part box" and half horse power driven motor, which encased the patient's chest or abdomen (see Fig. 2.6). Suction allowed diaphragm descent for inspiration and its soft rubber lining pushed positive pressure into the abdomen during exhalation, augmenting the next breath. This unit was used for both polio patients and for patients with heart failure and acclaimed a "success [77]."

In 1930 Stille-Werner of Stockholm, Sweden, manufactured cuirasses designed by Sahlin at the Physiologic Institute at Lund. A sheet metal cuirass, available in three sizes, with a rubber-lined edge, was bolted onto an operating table into which the patient was placed, where both negative and positive pressures were generated by a power unit [78]. Bergman reported survival of 127 (15.4%) polio patients from the 827 in whom it was used, including one who was supported for 7 months [79] (Fig. 2.19).

At the same time P. Peterson in Lund created a cuirass, the "Pulsatorgurtel," for resuscitation at baths (swimming pools). Its complexity, however, doomed its use [80].

The polio epidemic in Victoria, Australia, in 1937 saw the rise of use of tank respirators from 2 to 200. The observed need inspired Aubrey Burstal, Professor of Engineering at the University of Melbourne, to make a smaller "jacket" version with a thorax shaped aluminum shell with a sponge rubber vest for children. Rubber sleeves and collar rendered it airtight (Fig. 2.20). The pump from the Drinker/Emerson tank was used as the power source, and due to the small volumes of the jackets, proved to be able to power several jackets at a time by one attaching flexible hoses from the jackets through holes drilled in the tank. They were much cheaper, and allowed for easy sterilization of the units and the nursing of patients, especially those with splints, in standard hospital beds. The disadvantages were getting an airtight seal and the time, ~7 min, it took to apply it to the patients, made longer, ~10–12 min, if the patients had splints on, making it somewhat hazardous for those who could not tolerate the absence of breathing support for that amount of time [81].

Dr. Andrew Topping from the London County Council (LCC) was given a Burstal jacket which he redesigned. Rather than being placed over the head of a patient, it

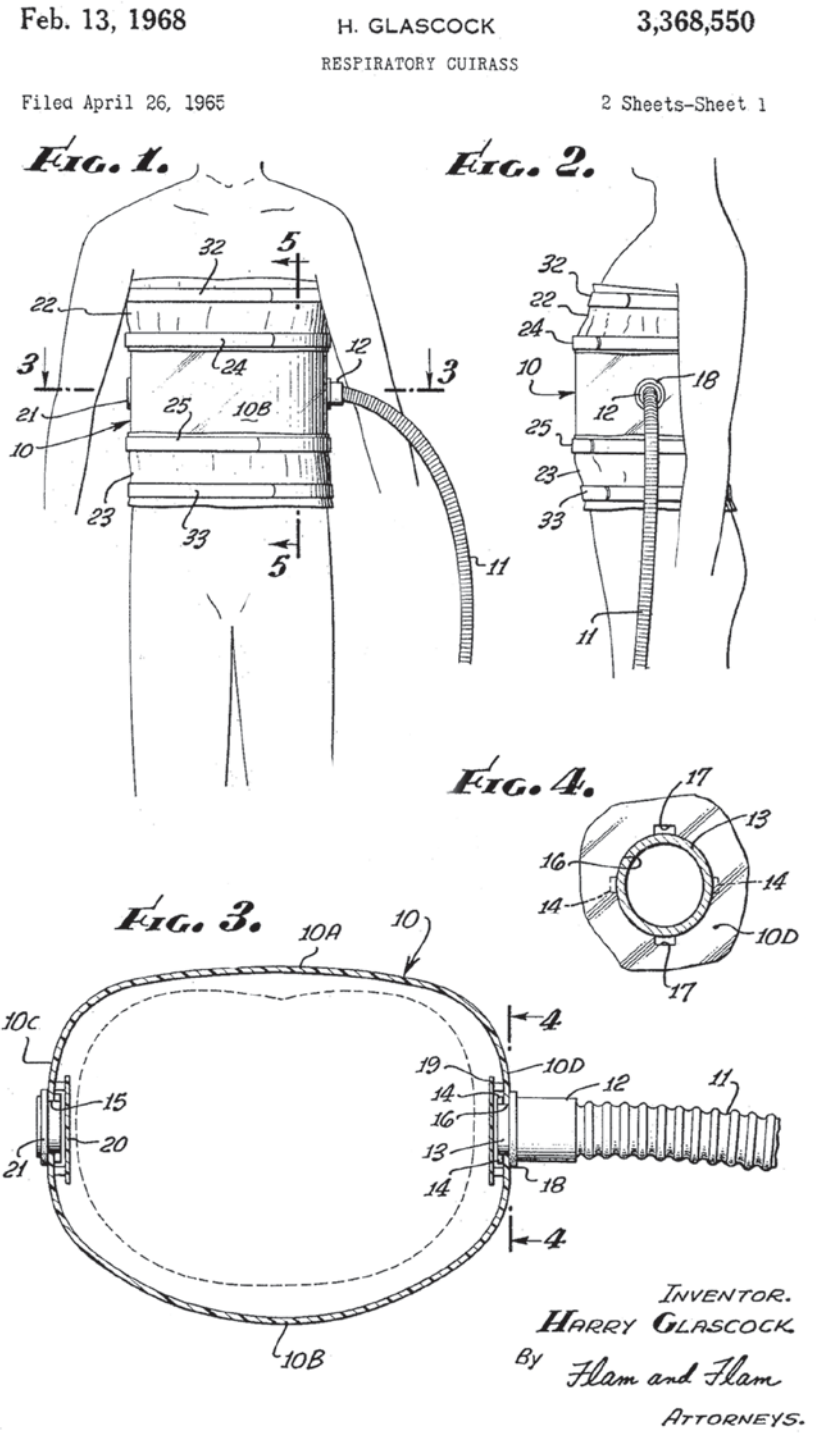


Fig. 2.19 Sahlin aluminum chest cuirass which was lighter in weight, closer to the chest wall, not allowing much lateral chest wall motion nor accommodate chest wall deformities

Fig. 2.20 The Burstall jacket: An aluminum shell for children powered by an Emerson tank through which several children could be connected to one tank. It took 7–12 min to place the child in the unit, lengthened by the presence of limb splints which could be too long for some children with severe breathing compromise. (Used with permission from Elsevier)

was made of two halves bolted together with wing nuts. Better seals around the arm holes made it more comfortable and freer for the patient. Its own power unit of 1/8 horse power drove a bellows with a set rate of 20 per min with negative pressures up to −25 cm H_2O, controlled by a variable leak valve on the cuirass. Should power fail, a hand driven mechanism could take over [82, 83].

The demand for resources in World War II put a brake on any further developments of any negative pressure ventilators. In 1947, a Council of Physical Medicine was formed which was the first to establish criteria for approval for use for all American cuirass ventilators including "efficiency, size, range, portability, standard of power unit, patient comfort…" and even "methods of advertising." Units failing testing failed approval, the first quality control [84].

From 1947 through 1950, as polio continued to infect scores of people, more cuirasses were designed and manufactured. One was Blanchard's Portable Plastic Respirator jacket from Los Angeles, driven by an electrically powered bellows, in 1947. Another, in 1949, the Chestspirator, had an innovation as the first thoracoabdominal cuirass covering the entire anterior body from the clavicles to the pelvis, allowing for larger tidal volumes [78]. From Denver, specifically from the Monaghan Company in 1949, came more sizes, now six, with pneumatic rubber seals which could be individually adjusted for each patient [85]. These were the first units I learned to use during my fellowship for patients with acute respiratory failure from overwhelming pneumonia and for patients with chronic respiratory failure due to COPD, not just from polio, with variable success.

The next modification, in 1950 from New York, was the Fairchild-Huxley Chest Respirator which was offered in both chest and thoracoabdominal models, each in three sizes. They had adjustable feet which prevented their downward movement during use. A first, an alarm system for power failure and leaks, was a unique added feature [85] (Fig. 2.21a Fairchild-Huxley model). Other models followed (Fig. 2.21b: Kifa; Fig. 2.21c: Monaghan).

Bulbar polio had been uniformly fatal until tracheotomy was performed, first in the USA, to manage such individuals. A sloping front tank was designed to accommodate the tracheotomy until the Monaghan cuirass was successfully employed to support three patients when other models failed [82]. This introduced a new type

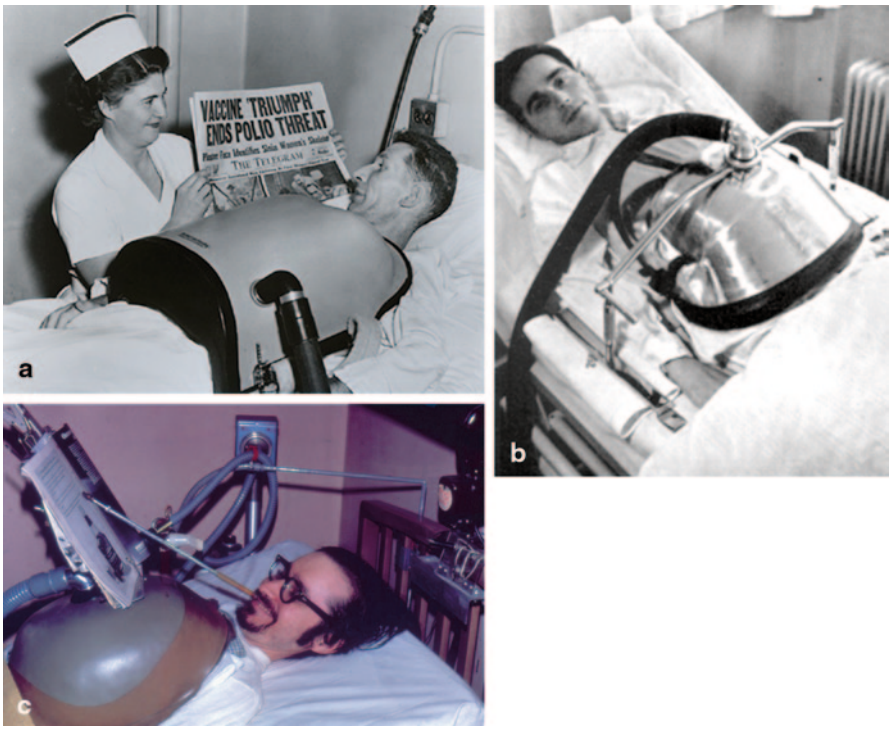


Fig. 2.21 **a** The Fairchild-Huxley cuirass from 1940 to 1950s: This one extends from the neck to the lower abdomen, effecting larger tidal breaths. The irony of the news headline for the patient is clear. Used with permission from J. H. Emerson Co. **b** The Kifa cuirass: note the low lying shell which compresses half of the upper chest cage during inspiration. Effective when metabolic loads were low as the Kifa so applied allowed only 1° of chest expansion by diaphragm descent anteriorly. Used with permission from Elsevier. **c** A patient with complete post polio complete quadriplegia using a Monahagn Chest Shell cuirass for sleep and a Pneumobelt in his wheelchair during the day for his lifetime from age 14 to age 64. He worked every day, running his own company, and survived past the 6th decade, using his mouth to write. His legislative efforts allowed patients to choose and train their own home care attendants paid for by Medicaid

of access to patients with ventilatory compromise which was to give rise to using positive pressure through a tracheotomy, enhanced by the lack of sufficient negative pressure units, the greater familiarity of anesthesiologists with positive pressure manual ventilation, and the continuing polio epidemics. The use of NPNIV with tracheotomy reduced the mortality from bulbar polio to 2−10% [86, 87].

As more and more patients began to recover from polio and no longer needed 24/7 respiratory support, Kelleher and coworkers from 1952 to 1954 demonstrated that the use of Monaghan and/or Kifa cuirasses for partial or nocturnal NPNIV support was effective after patients regained adequate awake breathing on their own [88]. There were increasing reports of successes using such nocturnal support for patients with severe skeletal deformities such as post-tuberculous thoracoplasty and kyphoscoliosis [89, 90].

An innovative inhalation therapist, F. H. Terhaar from California, designed a clear plastic shell cuirass ventilator in 1958 which fitted over the lower thorax and abdomen leaving the shoulder girdle free. The Hemo-Dyne Vital Capacitator was manufactured by Dynamic Air Engineering in 1959 in order to compare the circulatory effects of negative pressure from positive pressure ventilation, where the former was found to augment cardiac output whereas the latter decreased it. It was used to treat patients with heart failure [91]. My post polio and fibrothorax patients chronically using nocturnal NPNIV retained third space, diuretic resistant, fluid after general anesthesia for major abdominal cancer surgery when on postoperative positive pressure ventilation. They diuresed after they were replaced on their negative pressure systems, up to 7 L in 24 h [92]. A. Marks et al. using the Emerson made Poncho wrap plastic garment ("Rain Coat") applied through a rigid thoracoabdominal grid cage resting on a rigid plate, designed a novel patient-synchronized system, triggered by the patient from minute pressure changes at the nostrils or from a tracheotomy to initiate a breath. Even though the Poncho wrap could be used in children, the time and labor-intensive process of assuring an adequate seal using multiple clips along with the fitting process and for continuous supervision led to its disuse [93] (Fig. 22a, 22b and 22c).

Studies by several authors from 1951 to 1954, the first of which was Fred Plum and coworkers in 1951, compared the efficacy of cuirasses with tanks by measuring tidal volumes. Tanks were found to generate from 34 to 100% more volume than cuirasses in ten polio patients. Patients dying using cuirasses were described as having "anterior emphysema [94]." Collier and Affeldt assessed 14 polio patients using a tank, when the tidal volume was taken as 100% as base, and compared it to the thoracoabdominal cuirass and the chest shell. The patients, as their own controls, received 47% of the tidal volume that the tank generated from the chest cuirass while the thoracoabdominal cuirass generated 62% of the tidal volumes that the tank did, at the same negative pressures [95]. Upon increasing the negative pressure to obtain more volume, the pressure on the abdomen from the chest shell restricted diaphragm descent. In 1954 Bryce-Smith and Davis compared the tidal volumes delivered by the tank with the thoracic cuirass and the Rocking Bed in six healthy anesthetized volunteers given curare. To obtain equivalent tidal volumes the cuirass needed much more negative pressure [96]. This was also confirmed by Benton and Kriete in 1957 when they compared the cuirass, Rocking Bed and Pneumobelt and found that all three of these systems provided 50% less tidal volume than a tank or positive pressure through a tracheotomy [97]. Cardus et al. compared arterial blood gases using three kinds of ventilators [98]. I measured a 30 to 40% greater tidal volume from patients in the lateral decubitus position on a Rocking Bed than when they were supine, presumably due to unloading the chest and abdominal wall muscles from the hydrostatic pressure from abdominal organs and gravity, allowing both more chest expansion and diaphragmatic descent [71].

A major change in the application NPNIV and positive pressure support came about from the Danish polio epidemic of 1952. Positive pressure had been used by anesthesiologists to administer anesthesia by manually squeezing a bag for intubated patients, for temporary respiratory depression and/or when curare was

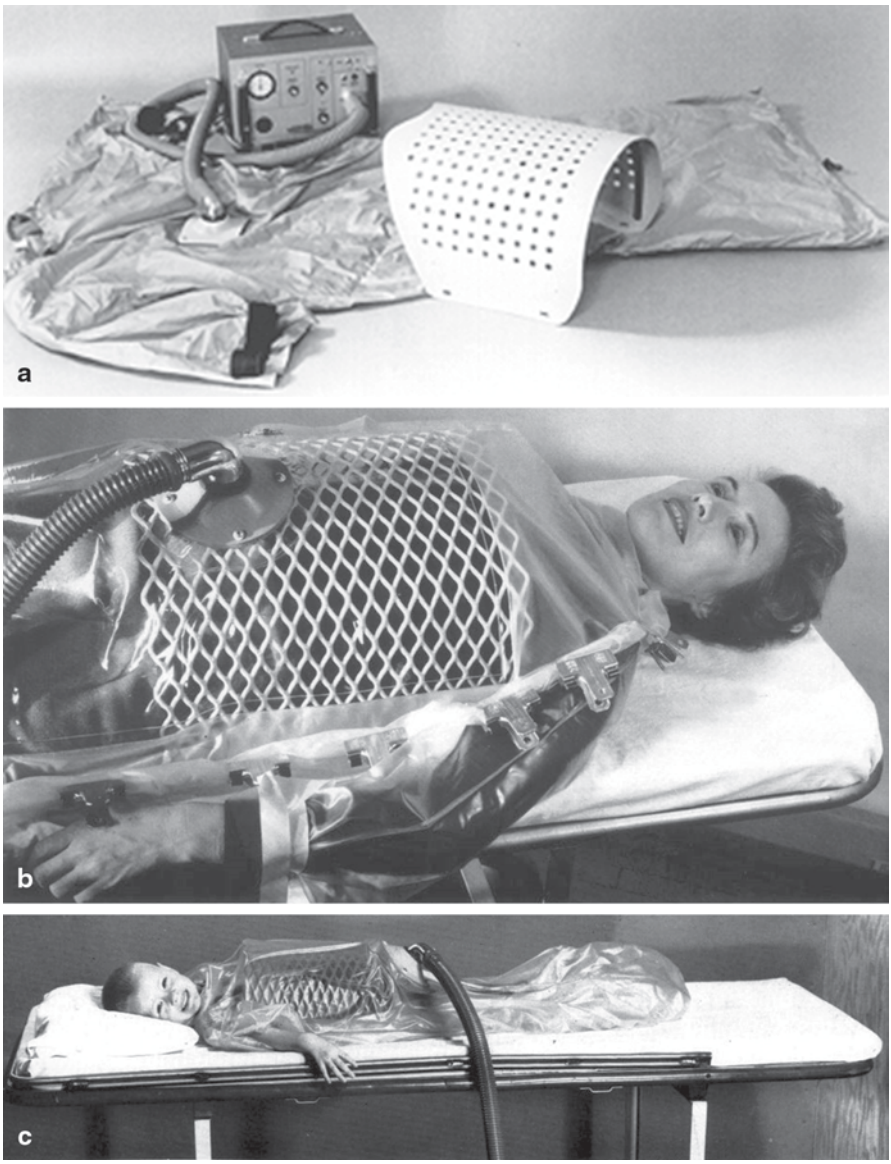


Fig. 2.22 A Emerson Body suit: Full body garment with rigid chest grid. The negative pressure pump, Maxivent, is shown. The back plate is not shown. Used with permission from J. H. Emerson Co. **b** Emerson Plastic "Rain Coat" or Poncho on a model. Note all the clips needed to "seal" the Poncho to allow a vacuum and where the upper third of the chest is compressed with inspiration. Used with permission from J. H. Emerson Co. **c** Use of the Poncho in a child when the adult Poncho encloses the whole patient. (Used with permission from J. H. Emerson Co.)

needed. That year saw 2722 admissions for acute poliomyelitis of which 866 (32%) were paralytic, of which 316 (nearly 37%) needed ventilation. For the 70 patients who needed a ventilator at the same time, there was only one tank and six cuirasses. This triggered Dr. H.C. A. Lassen with Dr. B. Ibsen to develop a high tracheotomy through which manual positive pressure could be delivered. Their previous experience in 1934 through 1944 saw a mortality of 80%, using the cuirass, drop to 40% by using positive pressure ventilation through a tracheotomy [99]. This experience and the increasing instances of less efficacious cuirass use for some patients led to expanding the use of positive pressure systems with new sets of problems.

It was just a matter of time before physicians saw the potential for use of NPNIV for support in other settings. In 1955, P. Tooker reported his use of a Kifa cuirass to ventilate patients during bronchoscopy and laryngoscopy [100]. Others soon used the Monaghan shell or the Emerson wrap for the same purpose. R. A. Green and D. J.Coleman and others reported on the difficulty of ventilating obese or emphysematous patients using cuirasses [101–104]. Of 248 patients who were cuirass ventilated for elective procedures, 16 could not be adequately ventilated either due to poor fit, obesity or chronic lung disease as reported by G. Wallace et al. in 1961 [105]. Like Helperin, [104] I used a modified poncho successfully for upper airway and GI endoscopy, both upper and lower colonoscopy, for more than 35 patients who were ventilator dependent.

In 1955, E. A. Pask from England suggested that improvement in design of the cuirass would make it more comfortable for long-term use, would deliver better ventilation, and with enough ventilation nursing could be provided in the prone position, allowing greater utility [106]. This triggered E. J. Tunnicliffe in 1958 to produce a jacket made of a blend of cotton with nylon, sealed with straps at the arms, neck, and buttocks over a plastic shell powered by an air pump which was proven to produce more than double the tidal volume of a standard cuirass (Fig. 2.23). J. M. K. Spalding and L. Opiel confirmed this with their report comparing the equivalency for the volume of air delivered with the Tunnicliffe cuirass jacket with IPPB in patients with polio and myasthenia gravis [107]. This was successful for long-term ventilation, reported after a year of customized cuirass use by Kinnear et al. with an 88% survival rate and reduced need for hospitalization in patients with thoracoplasty and neuromuscular diseases [108].

Despite the availability of customized cuirasses from J. H. Emerson, difficulties with poor fitting, pain and/or calluses at the lateral chest wall or other pressure points from chest wall deformities, and expense led H. H. Pinkerton in 1957 to develop an abdominal cuirass belt made from a large sphygmomanometer-type cuff strapped over the nipples to just below the xiphisternum, and laterally to the posterior axillary line to deliver active positive pressure for exhalation which allowed passive recoil for negative pressure inhalation and ventilatory support. It allowed supported ventilation for airway procedures, a forerunner of the Pneumobelt [109]. Others reported successful Pneumobelt use for ventilatory support for respiratory insufficiency in high quadriplegics [110, 112].

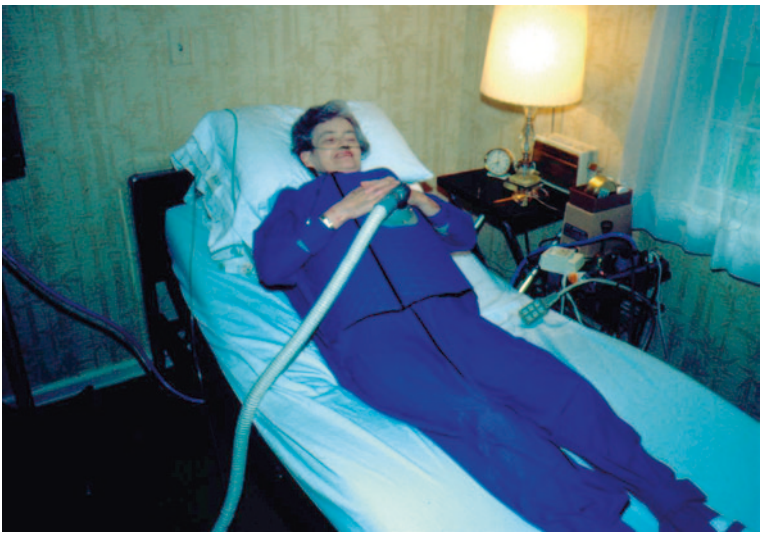


Fig. 2.23 A patient with Gold IV COPD (FEV1 0.3 L and chronic hypercapnic respiratory failure wearing a Nu-Mo suit, easier to place and effectively seal. She is using oxygen by nasal cannula at home. She was supported with negative pressures of −40 cm H_2O nightly for more than 5 years. She experienced more dyspnea relief when she used her nebulizer medications in the suit; her nebulizer is next to her bed. She was able to return to playing the church organ after the use of this system. She was never rehospitalised. *FEV1* forced expiratory volume in the first second

Specific Remarks Regarding Poliomyelitis

The polio epidemic might have been controlled sooner but for politics, limited vision, academic infighting, and personalities. Dr. Hilary Kaprowski was the first to experiment with live polio vaccine in 1948, which he cultivated in the brains of polio susceptible cotton rats. He drank a blenderized portion of the brains, first to inoculate himself and then his children. No ill effects were suffered; no one got polio. He was then asked in 1950 to inoculate 20 mentally disabled children from Letchworth Village, Rockland, New York. Seventeen of the 20 developed antibodies to polio; the other three were already antibody positive prior to inoculation; none suffered any complications nor developed polio [113]. He was asked to provide his oral vaccine to several countries in Europe with similar results. The academic medical community protested his efforts due fear of using live, attenuated virus and to a complex interplay between his outsized personality and politics with science. Thus, an unproved theoretical fear led to the delay of mass vaccination until Dr. Jonas Salk developed an injectable dead virus vaccine in 1955. The immunity lasted only a year for some and some children tragically got polio from a virulent viral contaminated batch, ending the use of the Salk vaccine. Dr. Albert Sabin, who had worked with Hilary Kaprowoski, found that the polio virus invaded through the gut epithelium which led to his development of an effective attenuated oral vaccine in 1960. Wide spread oral vaccination led to the cessation of polio epidemics in

industrialized countries [114]. However, polio remains prevalent, episodically, in third world countries where the vaccine is not available due to politics and/or ignorance and fear [115]. The most recent was an outbreak in Syria, in October, 2013, spreading to Lebanon due to the influx of Syrian refugees when vaccination was prevented by migration and lack of safety for health-care workers [116]. Taliban propaganda also halted polio vaccination in Pakistan and Somalia. In September 2013, The Bill and Melinda Gates Foundation received one of the Albert and Mary Lasker Awards for public service for their work in providing the Sabin oral polio vaccine to thousands of children in Afghanistan, Nigeria, and Pakistan, with the goal of eradicating the virus from the earth as was done with smallpox [117].

A Personal History Regarding NPNIV

As the effectiveness of the polio vaccine dramatically reduced the need for NPNIV, there were increasing reports of their application in acute-on-chronic respiratory failure from other causes between 1958 through 1961 in France, as it was considered "more physiological" than IPPB. Oxygen enriched air was added to the use of the thoracoabdominal cuirass with a "slight" positive pressure from a face mask in phase with the cuirass to improve oxygenation [118].

My introduction to negative pressure ventilation came about from a rotation on the Bellevue Hospital's Chest Service during my residency. An entire building, C & D wings, was dedicated to the care of patients with advanced tuberculosis and the increasing numbers of patients with other chest diseases. With the success of the polio vaccine, no more patients with respiratory paralysis were admitted. The iron lungs had been stored. However, recognition that many more patients with increasing respiratory compromise from other disorders such as post-tuberculous thoracoplasty, pulmonary fibrosis (PF), bronchiectasis, COPD, other neuromuscular disorders (NMD), and kyphoscoliosis (KS) appeared as antibiotic therapy became widely used and allowed recovery from devastating infections, but left persistently symptomatic dyspneic and hypercapnic patients. From the best available recall of physicians from that time, it was Dr. John McClement, the director of the Chest service, with Dr. David Simpson, who began to use the iron lungs for patients with chronic respiratory failure as there were no other effective mechanical ventilators available for longer term use [119]. Only IPPB pressure limited machines, (Bird, Bennett models) were available, and while suitable for delivering nebulized medications, were completely ineffective in providing sufficient longer term ventilation to reverse chronic respiratory failure or relieving intractable dyspnea. It was then that I reasoned that the lungs of these patients were not changed by NPNIV; they were still badly damaged or the chest walls were still noncompliant or the muscles were still too weak. Thus, the ventilatory benefit from the iron lung may be due to their assuming the work of the respiratory muscles, reducing the work of breathing while supporting gas exchange as it relieved dyspnea and thus might "rest" the over burdened respiratory muscles, and that such rest would allow some "recovery."

Some of the COPD patients had IPPB therapy synchronized with their iron lungs, enhancing nebulizer delivery of medications, and sometimes to augment their minute ventilation when the maximum achievable negative pressures were not enough to support ventilation during an acute exacerbation of the COPD. Patients were noninvasively ventilated with the iron lung on the chest service for many months, as home care for such patients did not exist, until they generally died from pneumonia. This led to my working with Dr. Dudley F. Rochester, who had shown in dogs that the oxygen consumption of the diaphragm at increasing work levels was linearly proportional to the sum of the integrated electrical activity (EMG) of the diaphragm [120, 121]. Applying this concept to humans was studied by placing esophageal electrodes to record diaphragmatic EMGs in normal volunteers and stable, hospitalized patients with diverse causes of chronic hypercapnic respiratory failure. We found in the normal volunteers that diaphragmatic EMG activity could be reduced but not abolished by iron lung ventilation even when the negative pressures caused alveolar hyperventilation to end tidal CO_2 levels of 20 to 30 mmHg. However, it was not until a resistive load, by blocking one nostril, or an elastic load, by binding the chest and abdomen at functional residual capacity were added, that the normal subjects' diaphragmatic EMG was nearly abolished, with no awareness nor discomfort, just as Drinker described in himself. The patients with COPD, KS, and NMD were all easily "captured" by the second to third cycle after turning on the iron lung ventilator; [122] we observed that as soon as the iron lung ventilator was turned on the patient's use of accessory muscles and nasal flaring ceased, and the patient no longer felt air hunger. The relief of dyspnea coincided with the loss of the EMG activity when ventilation was fully supported. This occurred even when changing the pressures to allow the $PaCO_2$ level to rise, stay the same, or fall, indicating that the mechanism was not due to acutely altering the CO_2 level. Oxygen saturations were kept constant with the same or lower level of oxygen supplementation. EMG activity was regularly increased by the use of a mouth piece and by IPPB therapy. Thus, the dyspnea relief stemmed from the assumption of work by the NPNIV and not due to a change of the CO_2. When patients were allowed to choose the pressure level for breathing satisfaction, which I call "Respiratory Satiety," they all chose higher ventilation levels that would lower their $PaCO_2$, for example, to levels below 34 mmHg in the neuromuscular patients. This fostered the use of negative pressure ventilation for sleep for these patients in their homes, anticipating that such support might allow for improved ventilatory efficiency and function and less dyspnea during the day, better sleep at night, and a better quality of life. Many gained weight with improved appetites. Body composition analysis showed it was mostly muscle and some fat but not water. This led to preliminary studies which showed that "nocturnal" noninvasive ventilation at the patient's chosen level of support reduced the work of breathing enough to enhance appetite and food intake, possibly also due to better nutrient absorption with the reduction in right-sided pressures on mesenteric blood flow and/or better appetite as gas exchange improved and sleep was now possible [71]. The better sleep stimulated me to help establish a Sleep Laboratory in 1976 so that this efficacy could be better studied. Since then the neurobiology of sleep has become a whole new discipline affecting many spheres of

the lives of normal people and those with cardiopulmonary, neurological, obesity-related, and neuropsychiatric disorders. More than 100 of my patients have used NPNIV at home successfully for from 2 to 40 plus years. One such 6 foot 5 inch man would roll his iron lung into the hospital for use when he developed a new medical problem as the nearest hospital did not have such a unit and he refused to be intubated [71]. This stimulated me to design a more patient friendly, easier to apply unit, a garment, Pneumosuit or Nu-Mo suit, made from breathable, machine washable Gortex fabric, (used for garments for Astronauts) into an adult pajama-like suit with a full length sealing zipper, used with the Emerson grid cage on a back plate, adding a cushion for greater comfort on the back plate, and vacuum pump. The grid chosen was one that covered the thorax from the clavicles to at least mid-abdomen or to just above the symphysis pubis. A larger grid could accommodate patients with severe chest wall deformities with additional padding at pressure points for comfort. With the availability of Velcro it was much easier to make individually adjustable airtight seals at the neck, wrists and ankles (Fig. 2.23). An optional Velcro opening in the lower back would allow toileting without the removing the suit. The gentle compression "massage" of the arms and legs by the negative intrasuit pressure enhanced venous return and increased the oxygen saturation or PaO_2 without an increase in nasal oxygen supplementation, reflecting a better distribution of blood flow to the better expanded lungs, and thus improving ventilation–perfusion matching. This suit was made by a parishioner in the church of a minster whose wife had end-stage hypercapnic COPD with right heart failure, and who had successfully used the Emerson Poncho in the hospital. The cumbersome, time consuming multi-clip closure system from the plastic Emerson Poncho "Rain Coat" was replaced by the Nu-Mo suit. Available in several sizes including for children, it was distributed by the New York Emerson Company and Life Care company representatives who supplied it to anyone who requested it. The negative pressures needed to adequately ventilate were in the range of −20 to −45 cm H_2O, while often higher than the pressures needed for younger polio and/or other neuromuscular patients without chest cage deformity, it was needed for those with very stiff chest walls, increasing with age [123].

Elective diagnostic procedures have now been safely/successfully performed using NPNIV in the Nu-Mo suit or cuirass jacket for endoscopies including laryngoscopy, bronchoscopy, and esophagogastroscopy. For colonoscopy and cystoscopy, the suit was cinched just above the symphysis pubis with a Velcro belt allowing for diagnostic evaluation and intervention for such compromised patients [124].

After presenting data at an Aspen lung conference [125], several different groups at different institutions tried using NPNIV in trials for patients with COPD with variable results. In two randomized prospective trials; both in ambulatory patients with COPD, one from McGill University [126] and one from Boston [127] to determine if respiratory muscle rest could be achieved with improved function using NPNIV, there was no difference between the sham and actually treated patients. These patients were not all as dyspneic and the pressures used were not individualized for satiety of dyspnea. Based on these findings as well as poor adherence to therapy, the trial was terminated and NPNIV was not recommended. However, Feranadez

et al. confirmed our report with a shorter duration of 8 h of NINPV 2 days in a row [128]. The studies showing no effect differed from ours, even though nonrandomized, as few of their patients had revolving door hospitalizations without recurring infections as the cause for their COPD exacerbations or were as hypercapnic (>54 mmHg CO2) as all of our 18 patients. Fourteen of these used the Nu-Mo suit NPNIV, where settings were individualized till "Respiratory Satiety" was achieved in-hospital before discharge to home. The other four were treated with NPPV with oral or nasal masks due to developing upper airway obstruction with NPNIV. After 5 months of nocturnal home ventilator support all had improved pulmonary function, respiratory maximum static pressures, and awake gas exchange [129]. Despite now being classified as having Gold Stage IV COPD, all were domiciled and none were readmitted to the hospital for more than 3 years.

The Italian physicians, Antonio Corrado and others continue to apply NPNIV for acute, acute-on-chronic and chronic respiratory failure, using an iron lung of their own design. Their goal has been to provide ventilatory support without endotracheal intubation. They were successful in 77% of 258 consecutive patients with acute respiratory failure, of which 40% were supported with NPNIV. The complication rates from NPNIV stemmed from upper airway obstruction during use, the most frequent (16%), claustrophobia (11.4%), back pain (5%), GI bleeding (2%), and gastric insufflation (1.3%) in one patient who contracted pneumonia (0.6%) [130]. Raymondos et al. compared the hemodynamic consequences in 46 intubated patients with Acute Respiratory Distress Syndrome (ARDS) from diverse causes using continuous negative NPNIV versus continuous positive pressure noninvasive ventilation in the same patients. They found lower transpulmonary and intra-abdominal pressures, and improved hemodynamics, with NPNIV [131]. There was 50% mortality, all in those whose ARDS stemming from aspiration. In 2012, Engelberts et al. reported in mice that when waveforms and lung volume history are matched, positive and negative pressure ventilation, both ex vivo and in vivo, are biologically indistinguishable [132].

The most recent innovation in NPNIV is the biphasic cuirass ventilator (BPCV) of Hayek, an Israeli physician who designed a chest shell unit with an electronic digital circuit with both negative and positive pressure options over a wide range of rates and pressures, which can both be individually set for "best support" dictated by individual circumstances. He proposed that the BPCV be used for wounded soldiers, during anesthesia for diagnostic and otolaryngogical procedures, in neurosurgical trauma patients, for acute respiratory failure in COPD patients, in children, for support during weaning from positive pressure ventilation of intubated patients, in patients with neuromuscular disorders, and patients with central alveolar hypoventilation syndromes. It has an external high frequency oscillator option for the mobilization of secretions which has been reported to be effective [71, 133–141]. A 27-year-old male artist patient of mine has rare lymphatic tumors, disfiguring and causing pain in multiple bones, including most of the right rib cage, from which many surgical extirpations (one per year from age 7 weeks) and rod placement for severe scoliosis of his spine have been done, resulting in an extremely rigid, deformed thorax with no functional right lung. This left him ventilator dependent

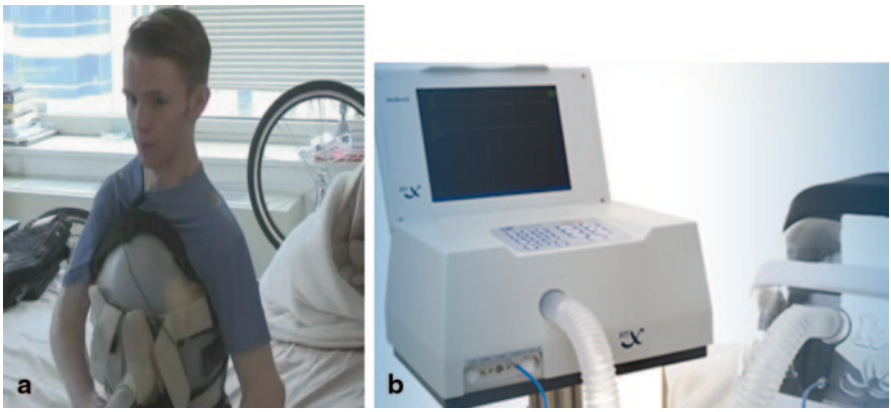


Fig. 2.24 A Hayek biphasic cuirass ventilator (*BPCV*) and customized chest shell being used by a 27-year-old patient with a severely deformed and noncompliant rib cage and one functioning lung with bronchiectasis and chronic hypercapnic respiratory failure. Successful use allowed tracheotomy removal and a return to school and work. B Hayek biphasic ventilator pump unit at bedside. The unit is not yet portable. It has a high frequency oscillating feature, allowing use for secretions mobilization

through a tracheotomy. His frequent debilitating pneumonias with hemoptysis and bouts of recurring tracheitis with the development of bronchiectasis in the functioning left lower lobe prompted him to try the Hayek biphasic cuirass for sleep, and for rest after physical therapy sessions. He needed negative pressures of −40 to −45 cm H_2O. He now has been successfully decannulated and has gone back to school while he pursues his livelihood in art [142] (Fig. 2.24a and 2.24b).

As critical care units expanded across the country when intubation became a more rapid, effective means for ventilating acutely failing patients, use, experience with, and availability of NPNIV units diminished. There has been resurgence of interest in NPNIV, especially in Italy, as the complications of positive pressure ventilation from intubation and tracheotomy have continued to rise as sicker and older patients with more comorbidities are resuscitated [143]. However, all the companies making or supplying negative pressure systems have been sold, and no longer supply such equipments in the USA. Not being able to obtain replacements for worn out shells, or Porta-Lungs, or Nu-Mo suits or their pumps, patients still supported with NPNIV are having to have them custom made by orthothic specialists willing to do so, often not covered by insurance. Since these patients are functioning, secure, and surviving for over 60 years with NPNIV, they are loath to use positive pressure devices.

Other novel noninvasive support systems exist, as discussed above, such as the Rocking Bed, introduced in 1932 [142–144], a gravity motion bed, where gravity is used to move the paralyzed diaphragm passively to effect air flow (Fig. 2.25), and the Pneumobelt, where positive pressure is cyclically applied through an inflatable wide belt or with a balloon inserted into a corset for compressing the abdomen for “active” exhalation and “passive” recoil inhalation [145] (Fig. 2.26). Both were

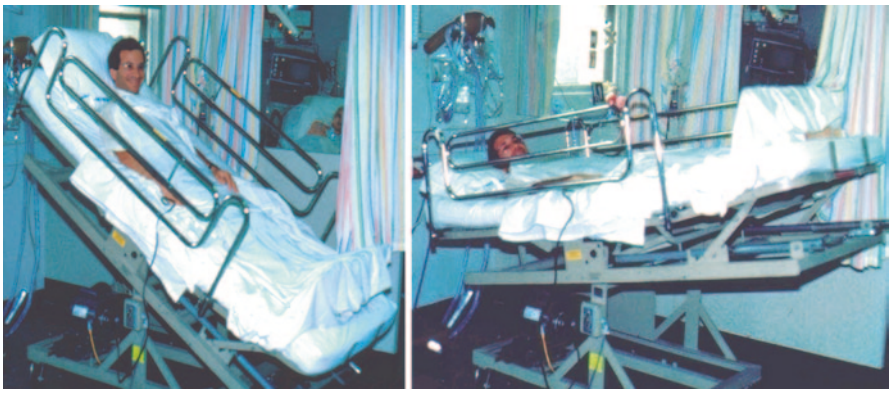


Fig. 2.25 The Emerson Rocking Bed: Feet down −45°: diaphragms descend and chest wall moves outward from gravity for passive inspiration. Head down − 15°: for exhalation when the abdominal contents are moved up against the passive diaphragms into the chest and the chest wall recoils. The degrees of motion could be individually adjusted. This bed was used for post-polio patients for greater than 45 years, and for patients with post-open heart surgery diaphragm paralysis until recovery ensued

Fig. 2.26 Patient with Duchenne's muscular dystrophy in his customized wheelchair using a Pneumobelt during the day and negative pressure suit night. The pump uses the same battery that powers his chair which is placed on a shelf on his wheelchair behind him, making him mobile

successfully used for many years during the polio epidemic era as noted. In 1989, Abd and Braun et al. reported of 1225 patients having open heart coronary by-pass and/or valve surgery over an 18-month period from one institution, the use of the Rocking Bed in 13 unweanable patients, due to phrenic nerve injury during open

heart surgery, allowed them to be extubated after 1–2 days, and discharged home where they used the beds until recovery ensued from 4 to 27 months after [58]. The Rocking Bed is no longer available, and patients who prefer to continue use of the Pneumobelt have been driven to making customized units on their own [146].

With the advent of better noninvasive, smaller, portable positive pressure units and greater choice of more acceptable, comfortable interfaces for NPPV, the evolution of knowledge about sleep respiratory disorders, and the complications of lung injury and infections from endotracheal/tracheotomy supported ventilation, noninvasive positive pressure modalities are being increasingly used to support infants through all ages for all causes of respiratory insufficiency and failure. Patients with central apneas and severe facial deformities can still be supported with NPNIV. Engineering system developments with digital technology and wider recognition and diagnoses of many disorders of ventilation, both acute and chronic, with the view to lessen complications from invasive ventilator support, are continuing to evolve. Flexibility of options with knowledge, dedication, experience, and patient preferences can make NPNIV a still useful modality for patients, as in Italy.

Summary Many brilliant scientists, physicians, and engineers have made keen, ingenious observations, contributed knowledge, evolved physiological principles through experimentation in animals and man, developed innovative ideas, and have offered an astounding and intriguing number of designs, from positive pressure, to negative pressure, to combined modalities and then back to positive pressure support, while finding new applications of ventilator support for inadequate or absent ventilation from a host of causes since pre-Biblical times. Many were impractical or useless and failed, but their failures fostered new efforts and designs, demanded by events, notably, drowning or asphyxiations, from pre-Biblical times, increasing in the seventeenth through the nineteenth centuries, and the polio epidemic in the twentieth century. Financial support, first from industry, then from private and government sources, permitted research to foster understanding and to developing and manufacturing workable systems for widespread application. The wealth of knowledge and experience gained led to the saving of many lives. These efforts through the ages takes us to the current day, bringing together the data to serve as a basis for improving the care of the ever increasing numbers of patients who might still benefit from using negative pressure noninvasive ventilation for a variety of respiratory disorders awake, in sleep, or both, and for potentially extended periods of time, up to a lifetime for some.

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Chapter 3
Nocturnal Noninvasive Ventilation in Heart Failure

Sogol Javaheri and Shahrokh Javaheri

Introduction

Heart failure (HF) is a highly prevalent condition affecting approximately 2% of the general population. The estimated prevalence of HF is 10% in individuals over age 65, making it the most common Medicare diagnosis-related group. Hospital discharges for HF have not significantly changed from year 2000 to 2010, with first-listed discharges of 1.008 million and 1.023 million, respectively. In 2009, there were about 700,000 emergency department visits and in 2010, 1.801 million physician office visits with a primary diagnosis of HF. The estimated total cost of HF was 32 billion in 2013, and will increase almost 120% to US$ 70 billion in 2030 [1]. Not surprisingly, a considerable sum of the costs is due to rehospitalizations.

Sleep apnea (SA) is a common comorbidity contributing to the progression of HF and is associated with increased morbidity, mortality, and hospital readmissions. Multiple studies have demonstrated a 50% prevalence of moderate to severe SA (apnea–hypopnea index: AHI ≥ 15/h of sleep) in stable ambulatory patients with HF both with reduced ejection fraction (HFrEF) [2–7] and preserved ejection fraction (HFpEF) [8]. Furthermore, the literature supports that effective treatment of SA (both obstructive and central) in HF improves cardiac function, morbidity, readmission rates, and mortality [9–15]. Thus, it is important to screen for and treat SA in this population.

The two major phenotypes of SA are obstructive SA (OSA) and central SA (CSA). The best treatment option for both phenotypes is titration with positive airway pressure (PAP) devices. OSA generally responds to continuous PAP (CPAP)

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devices, whereas approximately 50% of CSA is not suppressed by CPAP [9, 16]. Adaptive servo-ventilation (ASV), the most advanced of all PAP devices [17, 18], is effective in treating CSA and is the focus of this article.

Historically, ASV devices were designed to treat periodic breathing in CSA associated with HF. This breathing pattern, known as Hunter–Cheyne–Stokes breathing (HCSB), is characterized by prolonged crescendo-decrescendo changes in tidal volume and airflow with an apnea or hypopnea in the midst. The prolonged breathing cycle is due to the long circulation time caused by pulmonary congestion, left atrial and ventricular engorgement, and decreased stroke volume, all pathological features of congestive HF. If this unique pattern of breathing is observed polysomnographically in other disorders such as a stroke, asymptomatic left ventricular systolic or diastolic dysfunction should be suspected as a potential underlying mechanism of such periodic breathing in these patients. Under such circumstances, ASV should prove helpful.

There are currently two ASV devices (BiPAP auto-SV Advanced System One and VPAP Adapt) available in the USA. Though these two devices have different algorithms, they share three important features making them effective in the treatment of CSA as well as CSA coexistent with OSA, a combination that is not uncommon. The first feature is the variable amounts of inspiratory pressure support (the difference between the inspiratory and expiratory pressures) during different phases of periodic breathing (Fig. 3.1). This feature is in contrast to CPAP, which provides

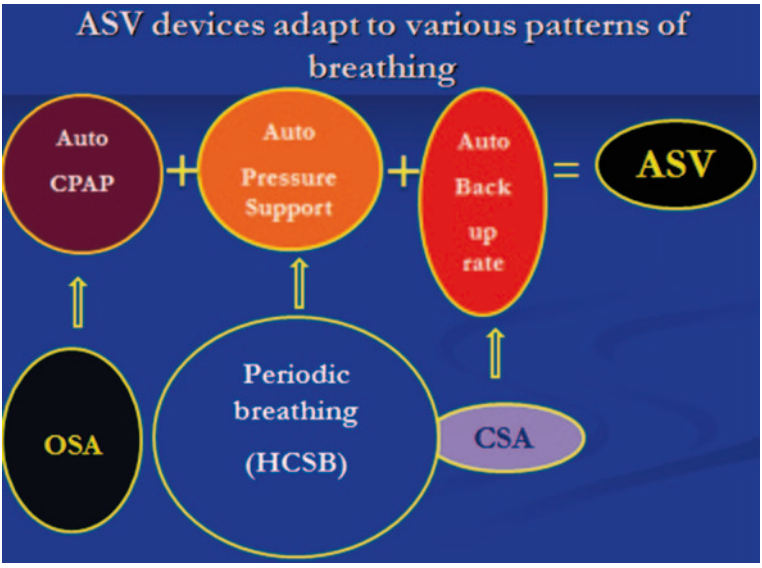

Fig. 3.1 Various components of an adaptive servo-ventilation *(ASV)* device with automatic *(auto)* continuous positive airway pressure *(CPAP),* auto-inspiratory pressure support (IPS), and auto-backup rate. The algorithm driving these three components makes ASV devices effective in treatment of hybrid sleep-related breathing disorders consisting of obstructive *(OSA)* and central *(CSA)* sleep apneas and hypopneas. *HCSB* Hunter–Cheyne–Stokes breathing. (Modified from [49])

a fixed continuous pressure, and bilevel PAP, which provides a fixed amount of constant inspiratory pressure support. In ASV devices, the inspiratory pressure support is variable and anti-cyclic, meaning that the degree of pressure support is inversely proportional to the patient's intrinsic breathing pattern. For example, during the hyperpneic phase of periodic breathing, the inspiratory support is minimal and could even be zero in the most recent generations of these devices (see below). The second feature is that both devices deliver a mandatory breath, aborting the course of any impending apnea based on their unique algorithms. The third feature in common is that the expiratory positive airway pressure in automatic mode eliminates obstructive sleep-related breathing disorders.

Here, we briefly review two features of ASV devices: First, the importance of the variable inspiratory pressure support as it relates to improving the underlying periodic breathing. ASV devices continuously monitor the patient's ventilation throughout the sleep period in a moving window of several minutes' duration. By having information regarding values of the current minute ventilation, ASV devices assist the patient's breathing if it falls anywhere below 90–95% of the recent average ventilation. When the patient's ventilation decreases below this level, e.g., due to an apnea or hypopnea, the device support is engaged, which should maintain ventilation and prevent development of further events. When the patient is hyperventilating, the inspiratory support decreases and could be zero. In this context, the device ventilation is anti-cyclic to the periodicity of the patient's breathing. It augments ventilation during the hypoventilatory phase of periodic breathing to avoid consequent hypercapnia and hypoxemia (both of which cause chemostimulation of the peripheral arterial and central chemoreceptors resulting in hyperventilation). It also sufficiently reduces inspiratory pressure support during the hyperventilatory phase of periodic breathing to avoid undue hypocapnia (which is chemoinhibitory). Correction or minimization of periodic-breathing-induced cyclic pulmonary blood gas chemistry is fundamental to ASV being effective in the treatment of HCSB in HF.

The second feature of ASV devices to emphasize is the function of the automatic positive end expiratory pressure in eliminating obstructive sleep-disordered breathing (SDB). This feature is important since in HF, OSA may frequently coexist with CSA. This coexistence was first appreciated in early studies [2, 3], which was the reason sleep breathing disorders in HF were classified as predominantly central or obstructive in nature.

Furthermore, in HF, the phenotype of SA is a moving target and may change acutely depending on sleep stage, position, and fluid status/shift, and chronically with changes in weight, medications, and status of HF. For example, with acute decompensation of HF, fluid accumulation and increased right atrial pressure cause upper airway edema and venous congestion, which could result in further upper airway obstruction. This is another reason why ASV devices with automatic end expiratory pressure algorithms are extremely effective in the treatment of a "hybrid" type of SDB present in the stormy natural history of HF.

Use of PAP Devices for Sleep-Disordered Breathing in HF

1. OSA

In patients with OSA with or without known HF, the treatment of choice is CPAP [3]. Multiple studies in the general population have shown the efficacy of this device in eliminating OSA. The same principle applies to patients with HF and OSA. In a cohort of Medicare beneficiaries with HF and SA, treatment with CPAP resulted in improved survival, decreased number of hospitalizations, and reduced Medicare costs [14]. Similarly, an observational study from Japan [15] also showed that HF patients with OSA who accept and are adherent to treatment with CPAP have improved survival compared to those patients who either refuse or remain nonadherent to CPAP.

Although CPAP is quite effective in eliminating obstructive events, in some individuals with or without HF, CSA may emerge when CPAP is used. This has been referred to as "complex SA." In the largest study of patients with OSA [19] and without known HF, the prevalence of persistent complex SA was initially 6% but decreased to 2% after several weeks of treatment with CPAP. In regard to HF and complex SA, we first saw development of worsening CSA in an occasional HF and OSA patient during CPAP titration [20]. In a recent large study of patients with HFrEF [32], the prevalence of complex SA was estimated at 15%. It was not clear if these patients would have suffered from persistent complex SA because repeat titration study was not performed after continued use of CPAP. Rather, CPAP therapy was discontinued and ASV was recommended. Of note, in this study [20], complex SA was defined as on AHI $\geq$ 15 per hour during CPAP titration with obstructive disordered breathing events < 10% of these. These are not the usual criteria used to define complex SA [19]. In addition, various diagnostic and therapeutic modalities were utilized including polygraphy, full-night polysomnogram, CPAP, and auto-titrating CPAP.

In the aforementioned observational study [20], 27 patients with complex SA underwent ASV titration with a mean follow up of 14 months. The central apnea index (CAI) decreased from 17/h on CPAP to less than 1/h on ASV with an associated increase in minimum saturation from about 82 to 87%. With ASV, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), and VO_2 max significantly improved, whereas the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) decreased significantly.

2. CSA

Initially, ASV devices were designed to treat the periodic breathing associated with HF as studies have demonstrated that CPAP fails to suppress CSA in a considerable number of patients. For example, in one overnight study, 53% of subjects with CSA and HFrEF were nonresponders [16], and 43% of patients failed to respond to CPAP after 3 months in another study [9]. Furthermore, continued use of CPAP in such patients is actually detrimental, resulting in increased mortality [9]. Patients in whom CPAP failed to suppress CSA had poorer survival when compared to those in whom CPAP was effective [9]. Given the risk of excess mortality, we do not recommend [21]

continued use of CPAP in any patients whose CSA is CPAP-nonresponsive (i.e., CPAP fails to lower to an AHI below 15/h) on the first night of titration. Why CPAP does not suppress CSA in a large number of HF patients remains to be elucidated. However, it appears that HF patients with severe CSA are characteristically nonresponders. Further, nonresponders have a lower awake arterial partial pressure of carbon dioxide (PCO_2) than responders. A reduced awake PCO_2 is a reflection of increased wedge pressure, an augmented ventilatory response, and a high loop gain. In this regard, it has been shown that a high loop gain predisposes to periodic breathing [22, 23].

There are multiple ASV studies in HF patients evaluating treatment of CSA [10, 11, 13, 24–44] and CSA coexisting with OSA [45, 46]. Most of these studies are observational with only two randomized clinical trials (RCT), one in HFrEF [25] and the other in HFpEF [13].

We first review studies in HFrEF. Pepperell et al. [25] utilized sham ASV in the control group [25], the only sham-controlled double-blind RCT. In the sham-controlled study, 30 patients with HFrEF were randomized to either therapeutic ASV ($n=15$) or subtherapeutic sham ASV ($n=15$). ASV decreased AHI from 25 to 5 events per hour, with a concomitant decrease in urinary metnorepinephine. LVEF did not increase significantly, though the study was only 1 month in duration. In a multiple arms study [24], 14 subjects with CSA and HFrEF were randomized to one night each of ASV, CPAP, bilevel, and oxygen therapy. The ASV device significantly decreased AHI more than the other arms.

There are currently two meta-analyses of ASV devices [47, 48], with only one [47] exclusively in HF. In this study [47], we performed a systematic review of ASV studies for treatment of SDB in adult patients with HF. We identified studies of ≥1 week duration that compared ASV to a control condition (i.e., subtherapeutic ASV, continuous or bilevel pressure ventilation, oxygen therapy, or no treatment). Fourteen studies were identified ($N=5538$). Comparing ASV to control conditions, the weighted mean difference in AHI, LVEF, and 6-min walk distance favored ASV.

There are multiple observational long-term studies that assess mortality in patients with HFrEF and CSA using ASV. Jilek et al. demonstrated that HF patients with SDB, primarily CSA, had significantly improved survival compared to those who declined or were nonadherent with PAP treatment [11]. PAP included CPAP and/or ASV Owada et al. [12] evaluated 80 HFrEF patients with chronic kidney disease and demonstrated that ASV improved prognosis of HF, cardiorenal function, and event-free survival including decreased hospital readmissions [12]. Takama and Kurabayashi showed improved 1-year prognosis including decreased mortality in HFrEF patients adherent to ASV compared to nonadherent patients [10].

As noted earlier, there are two RCTs of ASV devices. The one in HFrEF was discussed above. The other trial involves a small number of patients with HFpEF. In this study, Yoshihisa et al. [13] randomized 36 patients with LVEF > 50 % and severe SA (AHI = 37/h, CAI = 12/h of sleep) to either an active group with ASV or standard care. There were 18 patients in each arm. The ASV group demonstrated improved cardiac diastolic function, arterial stiffness, and reduced symptoms compared to the non-ASV group. In **Kaplan–Meier** (KM) analysis, cardiac events (cardiac death and worsening HF) were significantly less in ASV-treated patients. In Cox analysis,

only the use of ASV was an independent predictor of improved cardiac events with a heart rate (HR) = 0.58, confidence interval (CI) = 0.18, 0.8, and $p = 0.016$.

In summary, the new generations of ASV devices are equipped with sophisticated algorithms providing automatic anti-cyclic variable inspiratory pressure support, automatic positive end expiratory pressure, and an automatic backup rate. They possess the potential to effectively treat hybrid sleep-related breathing disorders consisting of both central and obstructive events and to be responsive and adapt to the changing and dynamic phenotype of the sleep-related breathing disorders observed in congestive HF. We expect that systematic long-term studies with ASV devices will prove efficacy in treatment of CSA and CSA coexistent with OSA. We also hypothesize that adherence to ASV devices is superior to that to CPAP. To that regard, in the Canadian multicenter study, at 12 months, the adherence to CPAP was only 3.5 h. If ASV devices are more effective and have improved adherence compared to CPAP, then ASV therapy should translate to improved survival of patients with HF. Currently two RCTs are in progress. For now, we recommend the use of ASV devices for treatment of CSA in patients with HF if CSA is not suppressed by CPAP during the first night of titration (please see Addendum below). In HF patients with OSA who develop complex SA with CPAP titration, we recommend a reevaluation within 4 weeks with CPAP, and if CSA persists, we recommend ASV therapy.

For further information on algorithms and application of these devices, the interested reader is referred to [49] and [50].

Addendum

SERVE-HF is a multinational, multicenter, randomized parallel trial assessing the effects of ASV [51] (PaceWaveTM, AutoSet CSTM; the old generation ResMed ASV) with medical management compared to a medical management control. The sample consisted of 1325 patients with symptomatic chronic HF, LVEF ≤45 %, and predominant CSA. After submission of the current review article, in May 2015, ResMed declared that the SERVE_HF trial demonstrated a 2.5 % absolute increased risk of cardiovascular mortality (a secondary endpoint) per year in the ASV group compared to controls. Furthermore, there were no statistically significant differences between the ASV and control arms for any of the following primary endpoints: (1) all-cause death, (2) unplanned hospitalization (or unplanned prolongation of a planned hospitalization) for worsening HF, (3) cardiac transplantation, (4) resuscitation of sudden cardiac arrest, or (5) appropriate life-saving shock for ventricular fibrillation or fast ventricular tachycardia in implantable cardioverter defibrillator patients.

The patients in this sample had chronic HF with LVEF ≤45 %, NYHA class III or IV, or NYHA class II with ≥1 hospitalization for HF in the previous 24 months as well as predominant central SDB defined as an AHI ≥15 events/h with ≥50 % cen-

tral events and a central AHI ≥10 events/h, derived from polygraphy or polysomnography. ASV was started in the hospital with full-face mask on standard settings, meaning a fixed end expiratory pressure (typically 5–6 cm of water), a minimum obligatory inspiratory pressure support of 3 cm water and a maximum inspiratory pressure support of at least 5 cm water above the minimum inspiratory pressure support. The study was powered to show a 20% reduction in the primary endpoint with the expectation of a 35% event rate in the control group. We must emphasize that lack of efficacy of ASV in improving cardiovascular outcomes occurred despite ASV effectively attenuating SA.

Given the findings of this trial, the makers of ASV devices have declared that ASV is contraindicated for patients with chronic heart failure with reduced ejection fraction. We therefore recommend that patients already on an ASV device be counseled on the results of the aforementioned study and discontinue use independent of any benefit they feel from use of the device. If the patient defers medical advice and continues use then this should be carefully documented. We must emphasize that this contraindication only applies to heart failure with reduced ejection fraction. Specifically, the recommendations to come off ASV do not apply to patients with heart failure with preserved ejection fraction, those on opioids, or complex sleep apnea without heart failure. However, it is important to perhaps perform evaluations of left ventricular function at least in those with heart failure with previously preserved ejection fraction.

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Chapter 4
Nocturnal Noninvasive Ventilation in Obesity Hypoventilation Syndrome

Amanda Jane Piper and Carly Ann Hollier

Background

Introduction

The obesity epidemic is currently one of the most significant health issues facing individuals, local communities, and nations, both economically and psychosocially [1]. Rates of obesity have increased alarmingly in recent decades [2] in both developed and emerging economies, such that the prevalence of obesity has almost doubled since 1980 [3]. Obesity is a chronic health condition associated with low-grade inflammation [4], and carries with it an increased risk of cardiovascular disease, hypertension, metabolic disorders, obstructive sleep apnea (OSA), and death [5]. The prevalence of people with morbid obesity (body mass index (BMI) >40 kg m^{-2}) is increasing at rates two to three times faster than the prevalence of moderate obesity [6]. This is of some concern since the risk of comorbidities, death, and health care costs rise linearly with increasing BMI [5, 7, 8].

Obesity impacts the respiratory system in a number of ways, the most serious being the development of chronic hypercapnic respiratory failure. This condition, known as the obesity hypoventilation syndrome (OHS), is defined as the combination of obesity (BMI$\geq$30 kg m^{-2}) and daytime hypercapnia (arterial carbon dioxide partial pressure ($PaCO_2$)$\geq$45 mmHg) in the absence of other potential causes that could better explain the hypercapnia [9]. People with OHS typically present with severe obesity (BMI$\geq$40 kg m^{-2}), hypersomnolence, and/or dyspnea, and often report a history of nocturnal choking, witnessed apneas, and morning headaches [10, 11]. Daytime hypoxemia, polycythemia, and signs of cor pulmonale are frequent [11–13]. Nocturnal polysomnography (PSG) invariably reveals the

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presence of severe sleep-disordered breathing (SDB), characterized by nocturnal hypoxemia and hypercapnia, most commonly in the presence of moderate to severe OSA [11]. OHS is a common cause of respiratory failure and is now a leading indication for the use nocturnal noninvasive ventilation [14–16].

Prevalence and Consequences of OHS

The prevalence of OHS in the general population is unknown, but has been estimated to be 0.15–0.3 % of the US population [17]. However, prevalence rates vary depending on the characteristics of the population sampled. Among people with OSA attending ambulatory sleep clinics, data consistently show that 10–20 % will have OHS [18], irrespective of geographical location or racial background [10, 11, 13, 19–23]. In those awaiting bariatric surgery, a prevalence of 8 % has been reported [24]. As obesity increases, the likelihood of developing hypercapnia also increases. Around 20 % of OSA patients with a BMI > 40 kg m^{-2} are found to be hypercapnic [20, 21], rising to 50 % of hospitalized patients with a BMI > 50 kg m^{-2} [25].

Patients with OHS are heavy users of health care resources [26], presenting with significant morbidities several years prior to a definitive diagnosis of SDB being made [26, 27]. Compared with eucapnic obese individuals, people with OHS have greater levels of systemic inflammation, endothelial dysfunction, higher insulin resistance and use more antihypertensive drugs, suggesting a higher cardiovascular and metabolic risk in this group [28]. This is borne out clinically: untreated patients with OHS are significantly more likely to seek medical attention for systemic hypertension, cardiovascular disease, and metabolic disorders [27]. In addition, they are significantly more likely than those with simple obesity to be diagnosed with congestive heart failure, angina or cor pulmonale [26] and to have higher rates of pulmonary hypertension [11]. Hospitalization rates are also higher in individuals with OHS than obese controls, and once admitted to hospital they are more likely to require invasive ventilation in intensive care units (ICUs), and have longer lengths of hospital stay [25]. Daytime hypoxemia and high inflammatory blood markers are associated with a poorer prognosis in patients with OHS [12, 29], consistent with the significant cardiovascular risk this disorder poses.

There are also significant social and economic costs associated with the development of OHS. Data from the Danish National Patient Registry found patients with OHS were less likely to be employed, and if they were in paid work, have lower incomes compared to control subjects matched for sex, age, and socioeconomic status [30]. Moreover, partners of those with OHS also experience a worse health status and social outcome [31].

Despite frequent contacts with the health care system, including hospital admissions and ICU [27, 32, 33], the severity of the respiratory aspects of this condition are frequently overlooked [25, 34] or misdiagnosed [34], delaying or preventing more definitive and appropriate therapy being offered [35]. In a study

of 61 patients with extreme obesity and hypercapnic respiratory failure presenting to an ICU, only three had previously been given a confirmed diagnosis of OHS, while 75 % of the group had been misdiagnosed as having chronic obstructive pulmonary disease (COPD) or asthma [34]. If left untreated, however, OHS is associated with a high rate of morbidity, social impairment, and increased mortality compared not only to the general population but also to those with eucapnic obesity [25, 26, 30].

Pathophysiology

At first glance it may seem obvious why daytime hypercapnic respiratory failure occurs in morbid obesity. High loads placed on the respiratory system by obesity reduce lung volumes and chest wall compliance, promote atelectasis and increase the work of breathing, making it difficult for the individual to maintain normal levels of ventilation. As tidal volume decreases, carbon dioxide levels can rise and daytime respiratory failure could ensue. However, the mechanisms involved are not that simple, and even among the super obese (BMI > 50 kg m^{-2}), only around 50 % will develop hypoventilation [25]. Although the pathophysiology of this disorder is not fully understood at present, it is clear that maintaining ventilation in the presence of significant obesity relies on a balance of complex interactions designed to compensate for the additional stresses placed on the respiratory system by excess weight. Hypoventilation develops when one or more of these compensatory mechanisms fail. An understanding of these factors and their interactions is of practical relevance in terms of better understanding why therapies work, and developing new and sustainable interventions to combat the problem.

Alterations in three major physiological aspects of breathing appear to underlie the development of OHS: (1) obesity and the mechanical load this places on the respiratory system, (2) altered ventilatory control, and (3) SDB.

Lung Mechanics and Load

There is no doubt that the excessive load placed on the respiratory system by extreme obesity makes a significant contribution to the development of OHS, with several studies showing that restricted lung mechanics is a significant predictor of hypercapnia in patients with OSA [20, 36, 37]. Compared to eucapnic obese individuals, subjects with OHS have reduced chest wall compliance [38], increased respiratory resistance [39], lower lung volumes [40], and higher upper airway resistance [41]. As a consequence, the work of breathing is increased significantly in subjects with OHS compared to those able to maintain eucapnia [42, 43]. Expiratory flow limitation and intrinsic positive end-expiratory pressure

(PEEPi) develop during tidal breathing in eucapnic obesity [44, 45], especially in the supine position. This can contribute further to the work of breathing by placing an additional load on the inspiratory muscles.

Although increasing BMI is associated with an increasing prevalence of OHS [20, 46], the distribution of this excess weight is an important factor in how it affects respiratory function. The impact of obesity on lung volumes is greatest when the adipose tissue is distributed centrally [47]. Individuals with OHS have a more marked pattern of central obesity, with higher waist-to-hip ratios than those with eucapnic obesity [48]. This is consistent with the finding of greater chest wall restriction in individuals with OHS compared to those with eucapnic obesity, even at similar BMIs [48]. The waist-to-hip ratio also has a stronger association with gas exchange than either weight or BMI [49]. Since expiratory reserve volume (ERV) is lower [40, 50], and waist-to-hip ratio higher in patients with OHS, the greater degree of hypoxemia present during both sleep and wakefulness compared to eucapnic individuals is not unexpected.

Endurance of the respiratory muscles as measured by maximum voluntary ventilation has generally been reported to diminish as BMI increases [51] and to be lower in OHS patients than in those with eucapnic obesity [52]. Whether this is related to reduced chest wall compliance or to breathing at low lung volumes [53] is unclear. It is also possible that structural changes in the respiratory muscles may be present. In an animal model of obesity, remodeling and thickening of the diaphragm was reported. This would act to enhance force generation and maintain ventilation in the presence of the added chest wall load [54]. In another study, obesity produced an increase in respiratory muscle oxidative capacity along with a fast-to-slow shift in skeletal muscle myosin heavy chain phenotype, changes that would promote fatigue resistance with the high work of breathing [55]. If similar changes in respiratory muscles occurred in human obesity, then reductions in inspiratory muscle endurance and strength reported in OHS [51, 56] could represent another compensatory mechanism that is overwhelmed by the excessive loads of massive obesity, contributing to the development of carbon dioxide retention.

Lung volume also has an important effect on upper airway collapsibility, affecting the size and patency of the upper airway [57, 58]. In the supine position, the diaphragm is pushed upward by the abdominal contents, reducing traction on the upper airway and rendering it more collapsible [59]. Consequently, patients with greater abdominal mass would be more susceptible to upper airway collapse particularly when supine [59]. This may, in part, contribute to the increased apnea–hypopnea index (AHI) seen in OHS compared to eucapnic OSA [37]. Even sitting upright, patients with OHS have increased upper airway resistance compare to morbidly obese individuals who remain eucapnic [41]. This likely contributes to the abnormally high work of breathing irrespective of whether these individuals are awake or asleep [42].

Ventilatory Control

Obese individuals have high ventilatory requirements related to increased basal oxygen consumption and raised carbon dioxide production [60, 61] as well as increased work of breathing [42, 43]. This means that increased levels of minute ventilation must be generated if eucapnia is to be maintained. Consequently, the neural drive in obese subjects is two to three times higher than that of normal weight subjects, and increases even more when supine [45]. In contrast, individuals with OHS lack the augmented drive needed to compensate for the increase in load [62, 63], which would increase their vulnerability to develop worsening respiratory failure in situations where the respiratory system is put under stress [64].

In addition to reduced respiratory drive, a key feature of OHS subjects is their blunted ventilatory responses to carbon dioxide and hypoxia [65–68]. An association between ventilatory responsiveness to carbon dioxide (hypercapnic ventilatory response, HCVR) and the percentage of hypoventilation during REM sleep has been reported, with lower carbon dioxide responses related to more of REM sleep time spent in hypoventilation [66]. Furthermore, this lower HCVR is associated with increased daytime sleepiness [66]. It was initially thought that this reduced chemosensitivity could have a genetic basis [69]. However, studies of first degree relatives of OHS patients and normal controls have failed to find a difference in ventilatory responses to hypoxemia or hypercapnia between the two groups [70, 71]. Obesity itself has also been proposed as a possible mechanism underlying the depression of ventilatory responses since significant weight loss can produce improvements in awake $PaCO_2$ levels [72]. However, this is not the case, as both respiratory drive and HCVR are increased in eucapnic obesity [73, 74], and decrease back towards the normal range with weight loss [73]. It is more likely that diminished chemoresponsiveness as an acquired phenomenon arising from the presence of SDB. Improvements in respiratory drive and HCVR have been shown to occur within a few weeks of commencing positive airway pressure (PAP) therapy in the absence of changes in BMI or lung function [62, 66, 74]. This suggests that reduced chemosensitivity is a consequence of the syndrome rather than its primary cause [75].

Several mechanisms may link diminished ventilatory responsiveness to carbon dioxide, obesity, and SDB. Leptin is a hormone produced by adipocytes to suppress appetite and stimulate ventilation [76]. In humans with obesity, circulating leptin levels are typically higher than normal weight controls [77], suggesting that leptin plays an important role in matching ventilation to the metabolic requirements imposed by excess weight [78]. However, leptin levels are higher again in OHS compared to eucapnic obesity [79] suggesting a state of leptin resistance or central leptin deficiency exists in this disorder [79–81]. In obese subjects, hyperleptinemia is associated with reduced respiratory drive and diminished ventilatory responses to hypercapnia [80], while circulating leptin levels are a strong predictor of hypercapnia in this population [79, 82]. Makinodan and colleagues [83] found a significant positive relationship between serum leptin

levels and HCVR in weight and age-matched control subjects and eucapnic obstructive sleep apnea syndrome (OSAS) patients. In contrast, HCVR was significantly lower in those patients with hypercapnia despite similar levels of serum leptin, BMI, and lung volumes.

In addition to its effects on respiratory drive, leptin may also compensate for the mechanical loads of obesity on the upper airway [84]. Patients with severe OSA have higher circulating leptin levels compared to patients with milder OSA [85], and reversal of this type of SDB reduces plasma leptin levels without significant changes in body weight [86, 87]. In a mouse model of obesity, Polotsky and coworkers [84] demonstrated that leptin deficiency, independent of obesity, promoted pharyngeal collapsibility and markedly reduced active pharyngeal neuromuscular responses to reductions in airway pressure. High circulating leptin levels may enhance neuromuscular control of the upper airway in the presence of obesity as part of the generalized increase in respiratory drive [84]. However, the development of leptin resistance or CNS leptin insensitivity would attenuate this compensatory mechanism, adding an additional link between upper airway obstruction, reduced respiratory drive, and the development of awake hypoventilation.

Alterations in other hormonal or inflammatory factors could also contribute to changes in respiratory control. Previous work has demonstrated a positive correlation between hypercapnic ventilatory responsiveness and insulin-like growth factor-1 (IGF-1) in patients with acromegaly [88]. In addition, the use of growth hormone in children with Prader–Willi syndrome improves HCVR and central respiratory drive [89]. Patients with OHS have lower levels of IGF-1 compared to eucapnic obese controls, with IGF-1 strongly and negatively correlated with $PaCO_2$ and bicarbonate [90]. The impact of recombinant growth hormone on ventilatory control in OHS is unknown [91].

Sleep Disordered Breathing

A spectrum of breathing disturbances during sleep is seen in OHS ranging from frank obstructive apneas and hypopneas through obstructive hypoventilation from partial upper airway obstruction, and "central" (i.e., not clearly obstructive) sustained sleep hypoventilation [65]. In general, patients will demonstrate some combination of these different sleep breathing abnormalities, with only 10–15 % presenting with central sleep hypoventilation alone [13, 92] (Fig. 4.1a and b). Full PSG is useful in characterizing what type of SDB predominates in an individual and therefore the type of PAP therapy most likely to correct gas exchange. Although nocturnal oximetry is widely used in diagnosing severe OSA, it does not accurately distinguish central from obstructive events. Furthermore, while time spent with $SpO_2 < 90\,\%$ has been shown to be a strong predictor of daytime hypercapnia [37], no specific threshold has been identified to separate out OHS individuals from those with eucapnic OSA. Despite differences in nocturnal breathing patterns, the clinical presentation is typically similar.

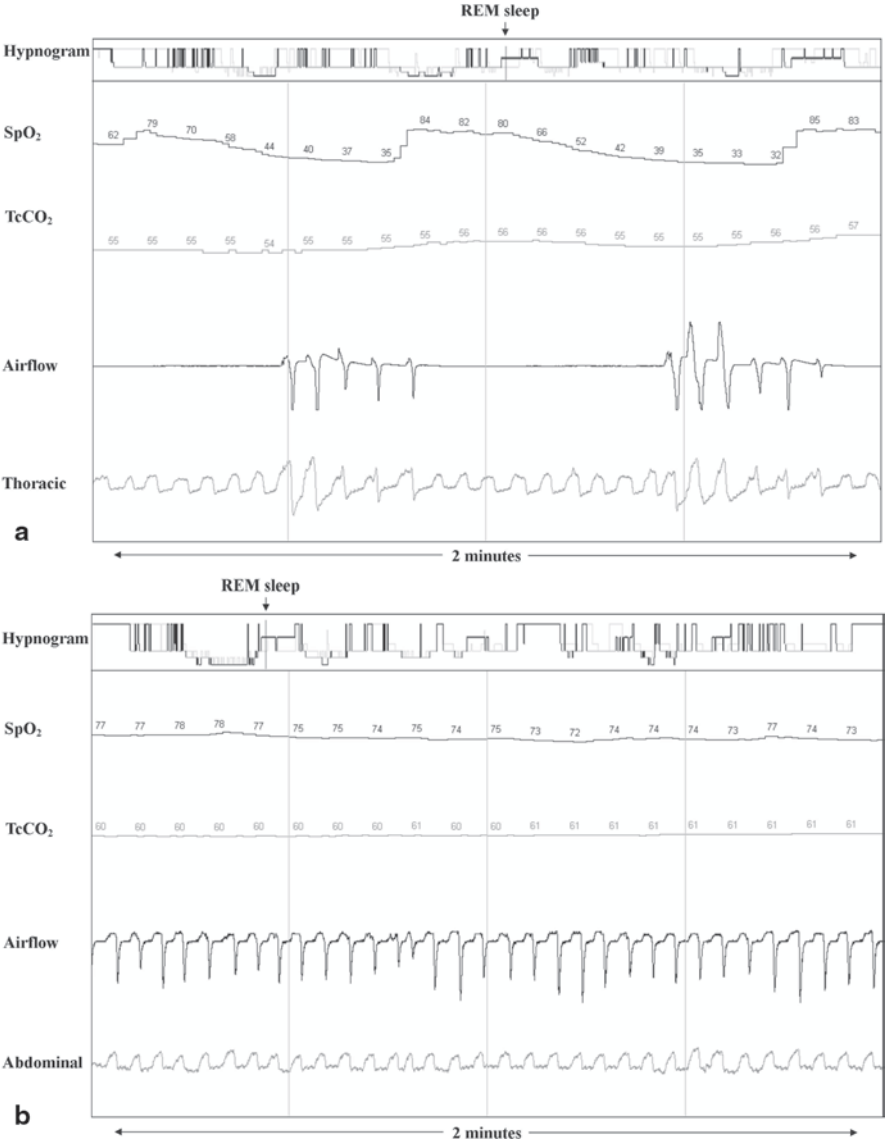

Fig. 4.1 **a** and **b**: *Top panel* illustrates a 2-min period of breathing during REM sleep in a patient with OHS characterized by repetitive obstructive events and severe nocturnal desaturation. Upper airway obstruction is a common finding in OHS. In contrast, the *bottom panel* for another patient shows REM hypoventilation with sustained hypoxemia in the absence of identifiable hypopneic events. SpO_2—oxygen saturation measured by pulse oximetry; $TcCO_2$—transcutaneous carbon dioxide

At least moderate OSA is seen in the majority of individuals with OHS [11, 66, 93]. Although AHI has been identified as a significant predictor of hypercapnia by a number of studies [19, 21, 37], it was unclear how these events during sleep

could lead to carbon dioxide retention during wakefulness, or why only a minority of patients even with severe OSA developed chronic hypoventilation. Data collected over the past few years has led to the development of a model describing a potential two-stage process which may explain this phenomenon [94]. The first stage involves the development of acute carbon dioxide retention during sleep. Accumulation of carbon dioxide occurs during apneic and hypopneic events, with the degree of carbon dioxide unloading that then occurs being dependent on the length of the interapneic period. If periods of abnormal breathing are prolonged and/or the time interval available to clear carbon dioxide is short, or respiratory efforts are reduced, then a net accumulation of carbon dioxide could occur [95–97]. In response to this, there would be a gradual compensatory increase in bicarbonate during sleep. However, during wakefulness, apnea disappears and carbon dioxide along with bicarbonate would return back to baseline levels. The next stage in the process occurs if there is insufficient time or ability of the individual to clear the bicarbonate load during wakefulness. The following sleep cycle would then commence with a slightly raised carbon dioxide level. Through modeling studies of whole body kinetics, Norman and colleagues [98] demonstrated that when the ventilatory response to carbon dioxide and renal bicarbonate excretion were normal, no change in either $PaCO_2$ or bicarbonate occurred. However, if the carbon dioxide response was abnormally low or renal bicarbonate excretion inadequate, modest rises in carbon dioxide were seen over time. Most notably, when both situations arose together, the impact on carbon dioxide increase over time was synergistic [94, 98] (Fig. 4.2). This model highlights the various elements that need to be in play at any time for the development of awake hypercapnia in patients with upper airway obstruction, and helps to explain why only a portion of obese patients with OSA may develop hypercapnia.

The model proposed by Norman and colleagues [98] is also consistent with clinical findings. In hypercapnic OSA patients, significant overnight rises in transcutaneous carbon dioxide occur which are not seen in those with eucapnia, with these nocturnal rises significantly influencing early morning carbon dioxide levels [99]. Elevated bicarbonate is known to blunt the HCVR in OHS patients [100], and lower awake HCVR is associated with a higher proportion of time spent hypoventilating during REM sleep [66]. Even mildly raised daytime serum bicarbonate levels (>27 mEq/L) have been shown to be a sensitive indicator for the presence of hypercapnia in patients with morbid obesity [21].

Changes in breathing related to upper airway obstruction and sleep hypoventilation result in a substantially greater burden of hypoxemia in people with OHS compared to eucapnic obese individuals. Studies have shown that the proportion of sleep time spent less than 90% (% total sleep time (TST) $<90\%$) is strongly associated with the development of awake hypercapnia [37]. In healthy nonobese males sustained hypoxia delays arousal from sleep in response to resistive loading [101]. This mechanism could play a role in worsening daytime respiratory failure in morbidly obese patients with sleep hypoxemia altering the synthesis of various neurotransmitters involved in central respiratory drive and chemoresponsiveness [102, 103].

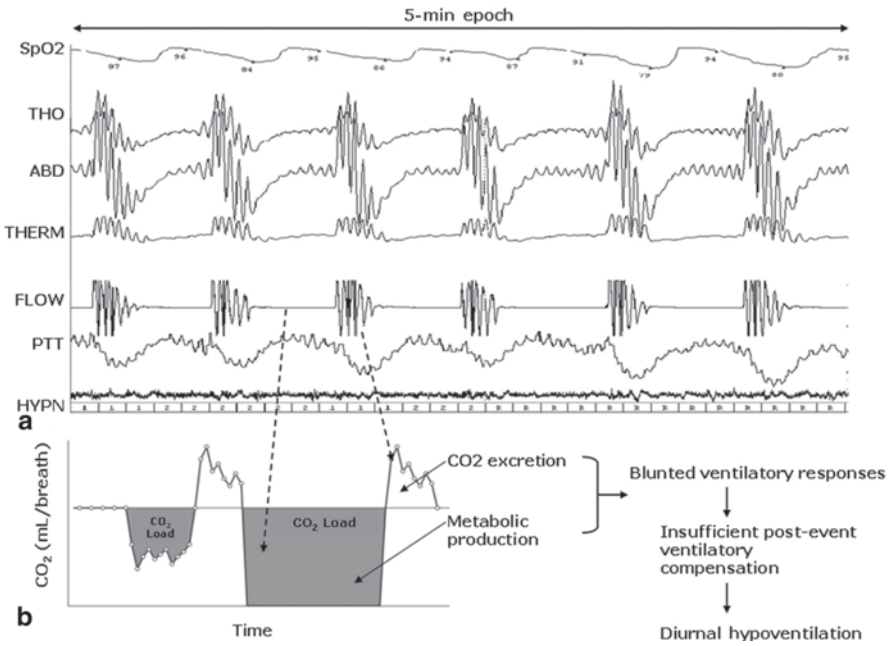

Fig. 4.2 The potential link between upper airway obstruction at night and the development of chronic daytime hypercapnic respiratory failure. During apneic and hypopneic events, carbon dioxide loading occurs which is then unloaded during the interevent period. However, the ability to eliminate carbon dioxide is influenced by the duration of the apneic relative to the interevent period [95] and the magnitude of ventilation during the postevent breathing period [97]. These factors can produce an acute rise in carbon dioxide overnight which is compensated for by bicarbonate. The transition to chronic hypercapnia requires the persistence of elevated bicarbonate levels or a reduction in respiratory drive, or both [94, 98]. (From Borel et al., Respirology 2012, with permission)

Nocturnal Positive Airway Pressure Therapy

Nocturnal PAP can be applied to the patient in a number of different ways. The simplest and most common therapy is continuous positive airway pressure (CPAP) where a single level of pressure is applied to the airways. In contrast to CPAP, noninvasive positive pressure ventilation (NPPV) is used to actively increase the patient's tidal volume, and can be delivered as either pressure preset (most commonly bilevel) or volume preset ventilation. As the name implies, fixed bilevel PAP therapy applies two fixed levels of pressure, with the transition between the inspiratory and expiratory pressures being entirely patient triggered (spontaneous mode), entirely machine driven (timed mode) or, more commonly, a combination of the two (spontaneous/timed or ST mode). In addition, a hybrid mode of bilevel PAP therapy—volume-targeted pressure support—has been developed where a target tidal volume is delivered through variation in the level of inspiratory support. This mode has been proposed to provide the benefits of a consistent level

of ventilation arising from the "volume" aspects of the flow delivered with the comfort and leak compensation advantages of pressure ventilation. A purely volume-preset mode of ventilation has also been used to treat OHS, especially in the early years of NPPV prior to the widespread availability of bilevel devices [104]. However, volume preset ventilation has largely been replaced by pressure preset ventilation [15] and is now only used occasionally [29, 92], primarily where volume-targeted pressure support therapy is unavailable.

CPAP Therapy

A number of uncontrolled trials have demonstrated the utility of CPAP in controlling SDB [105], reversing awake respiratory failure [93, 106], and improving quality of life [107] in patients with OHS. Improved ventilatory responses to hypercapnia with nocturnal CPAP have also been shown [62, 74]. To a large extent it is not surprising that a significant number of patients with OHS would respond to CPAP given the high incidence of upper airway obstruction in this population [11, 29, 66] and the relationship between severe OSA and hypercapnia [21, 37, 94]. By preventing apneas and hypopneas, acute accumulation of carbon dioxide would be prevented, helping to normalize not only oxygen saturation but also carbon dioxide. In addition, even low pressure CPAP (7 cmH_2O) has been shown to reduce inspiratory pressure swings and neural drive substantially in obese persons [45]. This is possibly due to offsetting the PEEPi that develops in the supine position in these individuals [45]. The volume-inflating effect of CPAP may also help to stabilize the upper airway via caudal traction on the trachea rendering it less collapsible [59], and improve oxygenation by increasing functional residual capacity.

Data from observational and controlled trials suggest that in up to 80 % of patients presenting with stable OHS to sleep laboratories, upper airway obstruction and nocturnal gas exchange are likely to be corrected by CPAP either during the first night of pressure titration [108] or following a period of bilevel therapy [93]. Similarly, in those patients presenting with acute respiratory failure requiring assisted ventilation initially, a significant proportion can be managed adequately with CPAP in the longer term [33, 92].

Several factors appear to distinguish those individuals responding to CPAP and those that "fail" CPAP (non-responders). In a study of "super" obese patients with OHS (BMI > 50 kg m^{-2}), 43 % of subjects failed CPAP (defined in this study as > 20 % of TST spent with $SpO_2 < 90\,\%$) during the initial night of therapy [105]. Baseline awake blood gases and spirometric measurements could not distinguish CPAP responders from non-responders. However, CPAP non-responders were significantly more obese (BMI mean (SE): 62(2) versus 57(1) kg m^{-2}, $p = 0.02$) and spent more time with $SpO_2 < 90\,\%$ while asleep during the diagnostic study night compared to those responding to CPAP [105]. In a study looking at patients with OHS initially managed with bilevel PAP therapy, Perez de Llano et al. [92] found that a higher FVC% predicted, less time spent with

$SpO_2 < 90\%$ and a higher AHI at baseline were characteristics of those able to be switched to longer term CPAP therapy. Taken together, these data suggest that in individuals with OHS in whom upper airway obstruction is the predominant mechanism underlying the development of hypercapnia, CPAP is likely to be effective long-term therapy. In contrast, where mechanical and neurohormonal factors arising from severe obesity are primarily driving the development of hypoventilation, an incomplete response to CPAP therapy is more likely [108]. At present, there are insufficient data regarding threshold values for AHI, BMI, or vital capacity (VC) which can predict an individual's clinical response to CPAP, and overnight manual titration of PAP therapy remains the standard method of determining pressure needs. This is best carried out in a sleep laboratory, monitoring not only oxygen saturation but also some surrogate of carbon dioxide such as transcutaneous carbon dioxide monitoring to identify the degree to which sleep hypoventilation is corrected.

A major limitation in the evidence regarding the long term use of CPAP is the paucity of data regarding clinical outcomes. Most studies have followed patients managed with CPAP up to 3–6 months with regard to blood gases and quality of life [93, 107]. However, little is known about how these individuals fare compared to those managed with bilevel PAP therapy with regard to longer term adherence to therapy, treatment failure, improvement in cardiometabolic risk factors, or survival. It is also unclear what degree of residual breathing abnormality and hypoxemia can be accepted during the initial CPAP titration night without affecting longer term outcomes, since a progressive improvement in response to CPAP seems to be possible in some [93, 104, 105, 109].

Bilevel PAP Therapy

Most of the literature regarding the management of OHS has focused on the use and outcomes of bilevel PAP therapy rather than CPAP. In many countries, OHS is now the main indication for home NPPV [14, 16]. Bilevel PAP therapy is generally introduced when sustained nocturnal hypoxemia persists despite correction of upper airway obstruction [65, 108], or if the patient is intolerant of CPAP [110]. However, the most effective mode of bilevel PAP therapy for OHS has yet to be determined, and there are very few studies comparing clinical outcomes with different modes of bilevel PAP in the longer term.

Until recently, no randomized trials had compared NPPV to conservative management in terms of its impact on sleep and breathing. Borel and colleagues [111] allocated 37 patients with OHS and mild chronic hypercapnia to either bilevel PAP or lifestyle counseling over a 1-month period. They demonstrated that bilevel PAP (ST mode) was significantly more effective in improving sleep and daytime blood gas parameters than counseling. Although both sleep macro- and microstructure improved significantly under bilevel PAP therapy, subjective daytime sleepiness did not improve to any greater extent than with the conservative management approach.

In a 3-month randomized study comparing CPAP to spontaneous mode fixed bilevel PAP, Piper et al. [93] found no difference between modes with respect to changes in awake $PaCO_2$, adherence to therapy, vigilance, or generic quality of life measures in 36 patients with OHS of mild to moderate severity. However, findings of this study are limited, as patients in whom sustained falls in oxygen saturation below 80% for more than 10 min during an initial CPAP trial were not enrolled. Nevertheless, those randomized to CPAP therapy still spent 39% of total sleep time with an oxygen saturation <90% at optimal pressures during their first night of CPAP therapy. However, after 3 months of treatment, CPAP was effective in normalizing nocturnal gas exchange in 30 of the 36 subjects. In a retrospective study of OHS patients with concomitant OSA, Mokhlesi et al. [108] reported no difference in the degree to which either of these two modes of PAP improved awake blood gases, suggesting that bilevel PAP therapy is not inherently superior to CPAP in patients with concomitant OSA so long as the PAP therapy used effectively controls SDB.

The majority of trials evaluating NPPV in OHS have compared ST mode bilevel PAP therapy with or without the addition of volume-targeted pressure support [112–115]. Although volume-targeted pressure support may increase ventilation and reduce carbon dioxide during sleep to a greater extent than standard fixed bilevel pressure support [112, 113, 115], clinically important differences between the two modes have yet to be shown. In a comprehensive study of 50 OHS patients (mean BMI 50±7 kg m^{-2}; $PaCO_2$ 49±6 mmHg) randomized to volume-targeted pressure support or fixed pressure bilevel ST support over a 3-month period, no difference between modes was seen in terms of arterial blood gas improvement, weight loss, daytime sleepiness, quality of life or physical activity levels [114].

For patients who present in acute hypercapnic respiratory failure, or those without significant upper airway obstruction during sleep, bilevel support is generally used [33, 109, 116, 117]. Even in these groups, a switch to CPAP therapy may be possible longer term [92], with one study finding a significant proportion of patients presenting initially with purely sleep hypoventilation went on to develop OSA when taken off NPPV once hypercapnia was corrected [109].

CPAP Titration

A common approach for determining CPAP in patients with OHS and OSA is to perform an in-laboratory overnight titration study, increasing pressure to prevent obstructive apneic and hypopneic events [65, 75, 118]. If prolonged periods of flow limitation with persisting hypoxemia occur [65], pressure is further increased until the inspiratory flow pattern on the flow trace is normalized [105, 119], and SpO_2 is maintained >90% [65, 120]. Since persisting hypoventilation is most likely to occur during REM sleep, particular attention needs to be paid to gas exchange and breathing during this sleep stage. If supplemental oxygen has been added to maintain SpO_2 >90% in the absence of apneas and hypopneas, persisting hypoventilation

may be masked. In these circumstances, transcutaneous carbon dioxide monitoring can be a useful tool in identifying the problem [121, 122] and guiding the choice of alternative interventions.

At present there is no evidence to support the safety or efficacy of using auto-titrating CPAP technology for either determining a fixed pressure to correct SDB or as a long-term therapy option in patients with OHS [123]. The algorithms used by auto-titrating CPAP devices have not been adequately evaluated in terms of the persistence of hypopneas that are not pressure responsive (i.e., hypopneas arising from reduced effort and hence decreased tidal volume rather than flow limitation and upper airway instability). In the unattended setting, oximetry is infrequently used during auto-titration studies. Consequently, ongoing hypoventilation and hypoxemia despite control of obstructive events may go unrecognized [124].

Bilevel PAP Titration

Despite the widespread use of NPPV for OHS [14, 16], there is limited evidence to guide what mode and settings most effectively manage this disorder, although general recommendations for the overnight titration of fixed bilevel PAP therapy have been published [120]. While the goals of NPPV are to prevent upper airway obstruction and reverse hypoventilation, therapy itself may induce abnormal breathing events, producing asynchrony between the patient efforts and support from the ventilator [125]. Inadequate or excessive settings may also induce various problems. Patients may not be aware of these events [126] nor may their presence be obvious during routine daytime clinical review [127]. However, asynchrony may contribute to patient discomfort, poor tolerance of therapy, or an incomplete response to treatment. Poor patient–machine synchrony occurs commonly and the importance of overnight monitoring to identify such problems and to improve the efficacy of nocturnal bilevel PAP is increasingly recognized. Consequently, PSG studies for bilevel titration is highly recommended to optimize settings and compare various modes of PAP therapy between different sleep stages and body positions [112, 120]. A systematic description of the types of respiratory events that may occur during NPPV has been developed with the aim of optimizing ventilatory support during PSG studies [128]. However, the relevance of these events with regard to adherence to therapy, quality of life, and survival has yet to be fully evaluated.

Mode

The spontaneous mode has been recommended as the default setting for bilevel PAP unless the patient is unable to trigger the machine consistently, or has a significant number of central events or a low spontaneous breathing rate [120]. Studies

reporting positive outcomes with bilevel PAP in OHS patients have used both spontaneous and ST modes [15, 93, 114]. In order to determine if one mode offers greater benefits over another, Contal and colleagues [126] performed a randomized trial evaluating three different backup respiratory rate (BURR) settings over three consecutive nights in ten patients with OHS previously established on bilevel PAP. The three settings were spontaneous mode (i.e., no BURR), a low BURR (ST mode set at two breaths below the average nocturnal respiratory rate recorded over the previous 2 weeks, approx 11 breaths/min), and a high BURR (ST mode set at the nocturnal 95th percentile of respiratory rate of the past 2 weeks, approx 21 breaths/min). Compared to both ST mode settings, the AHI and the oxygen desaturation index were significantly higher in the spontaneous mode, with the majority of events being central or mixed in nature. There was little objective difference in sleep architecture or microarousal index between the three modes apart from a longer sleep latency in the spontaneous mode. Subjectively, patients noticed little difference in sleep quality and comfort between the spontaneous and ST modes. Based on these findings, the authors questioned the wisdom of using a spontaneous mode in this population. However, the protocol used in this study may have influenced the findings. The levels of IPAP and EPAP used across all three nights were not altered from the usual home settings which had previously been determined using only oximetry and transcutaneous carbon dioxide monitoring. The high rate of obstructive events persisting during the spontaneous and low BURR nights suggests the level of EPAP was insufficient to stabilize the upper airway. Repeated arousals from sleep due to upper airway obstruction could have contributed to breathing instability and central events [129]. Mean tidal volume and its variability were also higher during the spontaneous mode compared to the other modes. Although not statistically different, the mean overnight transcutaneous carbon dioxide was 3 mmHg lower during the spontaneous mode night, and this small reduction in carbon dioxide could have favored the development of central events. It is of interest however that in a post hoc analysis, Murphy and colleagues [114] found that patients who had a lower triggering rate (i.e., more machine controlled breaths) during NPPV experienced greater improvements in nocturnal and awake gas exchange and health-related quality of life (HRQoL). These findings provide some supporting evidence that using a mode with a BURR sufficient to achieve a more controlled mode of ventilation may be more effective in this population, and should be further evaluated [130].

Pressure Settings

Comprehensive guidelines for setting IPAP and EPAP levels and adjusting pressure support during in-laboratory titrations have been published [120]. While the general recommendation is to aim for tidal volumes based on 6–8 ml/kg ideal weight, values of 8–10 ml/kg may be more effective in OHS [12, 114]. Although it has been suggested that IPAP above 20 cmH_2O may be poorly tolerated [92], other

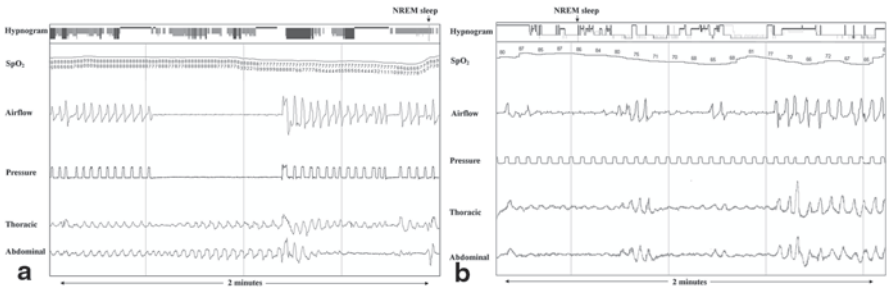

Fig. 4.3 **a** and **b**: The first panel shows the presence of upper airway obstruction during a bilevel titration during NREM sleep with the machine set in spontaneous mode. Note the paradoxical chest wall movement and the absence of airflow. The second panel demonstrates upper airway obstruction during ST mode of bilevel support. Continued efforts are present but with significant truncation of the airflow signal. These events are causing repetitive desaturation

studies have used pressures higher than this without affecting adherence [12, 114]. The EPAP level required to maintain upper airway patency can vary considerably between individuals, with some studies using a fixed pressure of 4–5 cmH_2O for all patients [12, 117, 131] while others have used up to 14–16 cmH_2O [29, 65, 114]. Appropriate nocturnal monitoring to adjust settings adequately, particularly EPAP, is important to ensure normalization of breathing pattern and gas exchange during sleep. However, significant residual upper airway obstruction or oxygen desaturation persists for many patients despite bilevel PAP therapy [114, 125, 132] (Fig. 4.3a and b). In many of the reported studies, NPPV settings have been determined by nocturnal oximetry and awake blood gases [15, 92, 131]. However, it may not be easy to judge the level of EPAP required to stabilize the upper airway in all sleep stages and body positions based on these two parameters alone. Importantly, sleep fragmentation and impaired sleep quality can occur in the absence of changes in SpO_2 or nocturnal carbon dioxide [125], but could nevertheless affect clinical outcomes or acceptance of therapy. These findings support the use of nocturnal polygraphy or PSG to titrate IPAP, EPAP, and BURR settings as well as adjusting other features of the bilevel device to optimize patient–ventilator interactions [125].

Oxygen Therapy

Baseline awake hypoxemia and the requirement for supplemental oxygen have both been found to be independent predictors of mortality in long-term retrospective studies in OHS populations [12, 29]. This has largely been attributed to the presence of pulmonary arterial hypertension (PAH), a common sequela of chronic hypoxemia [12]. Therefore, when NPPV alone is inadequate to maintain daytime and/or nocturnal SpO_2 greater than 90 %, supplemental oxygen is prescribed. Current recommendations and practices surrounding the prescription and titration

of supplemental oxygen in OHS are based on studies in patients with COPD, despite the obvious pathophysiological differences between the two disorders.

Oxygen alone does not correct hypoventilation and may worsen symptoms and clinical complaints [133]. However, it appears to be prescribed for a significant number of patients with OHS as first line therapy [33]. As seen in other groups with hypoventilation, excessively high concentrations of supplemental oxygen producing hyperoxia are potentially harmful to individuals with OHS, and can lead to significant worsening of carbon dioxide levels and respiratory acidosis in some even during wakefulness [134, 135]. Importantly, more hypoxemic patients are more likely to experience larger rises in carbon dioxide with high concentrations of supplemental oxygen [134]. Based on the potential risks surrounding high concentration oxygen in people with OHS, oxygen flow rates should be carefully titrated to maintain SpO_2 within a target range (e.g., 88–92%) [120, 135], whether during NPPV titration, for daytime use or in the acute care setting.

Supplemental oxygen is required in approximately 15–40% of patients with stable OHS during NPPV initiation [29, 93, 108] and as many as 80% of those commenced on domiciliary NPPV during an admission to hospital with acute respiratory failure [92]. After the initial phase of 1–3 months, an improvement in nocturnal and daytime gas exchange can be expected [104, 108]. At this time, the need for supplemental oxygen should be reassessed and can often be withdrawn, with only a small proportion (less than 10%) of individuals with OHS requiring oxygen on a long-term basis [93, 108, 136].

Prior to adding nocturnal supplemental oxygen, NPPV settings should be optimally titrated to otherwise correct SDB and hypoventilation [120]. Residual hypoxemia despite NPPV may arise from the therapy itself related to large leaks or intolerance of high IPAP. Atelectasis or underlying parenchymal lung disease may also contribute to the problem [29]. Clinical guidelines recommend that oxygen be added into the NPPV circuit (via a T-connector at the device outlet) when awake supine SpO_2 is less than 88% while breathing room air in the supine position, or after NPPV settings have been optimally titrated but SpO_2 remains less than 90% for more than 5 min [120]. Oxygen flow rate should be commenced at 1 L/m and increased in 1 L/min increments every 5 min until a stable SpO_2 greater than 90% is achieved [120]. Although these recommendations are not specific to patients with OHS, similar oxygen titration protocols have been successfully implemented in this group [12, 29, 46, 93, 108].

Acute Respiratory Failure and OHS

A significant proportion of patients with OHS present with acute hypercapnic respiratory failure [29, 33, 92, 137, 138], and are successfully managed with NPPV. However, in contrast to patients with acute exacerbations of COPD [139], the same level of evidence for the efficacy of NPPV in OHS patients presenting with acute respiratory acidosis is lacking due to a paucity of controlled trials [116]. Nevertheless, clinical response appears to be as good as or better than that reported for COPD. In

a prospective study of 716 consecutive patients receiving NPPV for severe acute hypercapnic respiratory failure caused by either COPD or OHS, Carillo et al. [33] found NPPV to be equally effective in both groups (failure rate 11% in COPD versus 6% OHS, $p=0.11$) despite a similar degree of acidosis (pH 7.22 ± 0.08 both groups). Furthermore, rates for late NPPV failure, readmission to ICU, and hospital mortality were all lower in patients with OHS than for those with COPD. Over the follow-up period, hospital readmission rates were not significantly different, being around 50% in both groups, while unadjusted survival was better for those with OHS. However, the 12-month outcome in the OHS group was poorer than that previously reported, and may have been a consequence of the older age of this group and greater severity of their respiratory acidosis compared to previous reports [29, 92]. It is also of note that at discharge just half of the OHS patients were prescribed home PAP therapy, and while reasons for this were not given, it may have influenced readmission and survival rates compared to previous observational studies of NPPV users.

At the extreme end of the spectrum of severity in OHS are those presenting with acute severe hypercapnic respiratory failure and multisystem dysfunction requiring ICU management. This has been labeled the malignant obesity hypoventilation syndrome (MOHS), and carries with it significant management and prognostic implications [34]. In a retrospective chart review on a single ICU over an 8-month period, Marik and Desai [34] identified 61 patients (8% of all admissions) with OHS and multiorgan dysfunction. Of note, all had been admitted to the Emergency Department or as an inpatient at least once in the preceding 24 months, with an average of 6 admissions per patient (range 1–39). During each admission, $PaCO_2$ was above 45mmHg. Forty-six patients (75%) had been diagnosed and treated for COPD or asthma, and during the index hospitalization all had been admitted with a diagnosis of COPD exacerbation and/or heart failure. Twenty four of these individuals had previously been prescribed CPAP or bilevel PAP therapy for SDB, but only three had been diagnosed with OHS. Bilevel PAP therapy was used in 58 patients (three already had tracheostomies), with 23 failing and requiring intubation. Eleven patients (18%) died. The presentation and outcomes in this subgroup of patients with OHS highlights a very important issue. Individuals with OHS need to be identified early in their disease course to minimize the development of advanced multisystem dysfunction. The high proportion of patients still presenting acutely [29, 33] and the severity of their comorbidities by the time intervention occurs highlights the need for better early screening of morbidly obese individuals to reduce the burden of disease and functional disability [26, 27, 140].

Outcomes of PAP Therapy in OHS

The most immediate and obvious improvements arising from the use of PAP therapy relate to improvements in daytime gas exchange [29, 92, 93, 108, 111, 114] and amelioration of symptoms, especially daytime sleepiness [66, 92, 93, 135]. In

uncontrolled studies, hospitalization rates in the 2–3 years following the initiation of NPPV are significantly reduced [15, 26]. Although not well described, sleep architecture is improved with both CPAP and bilevel PAP therapy, with increased amounts of REM and slow wave sleep and reduced stage 1 sleep reported [66, 74, 93, 105, 111].

The use of PAP therapy is associated with improved HRQoL, although whether significant differences between modes of therapy are present is unclear. In a prospective study of Japanese patients with either OSA or mild-to-moderate OHS, both groups reported significantly impaired HRQoL (measured by the Medical Outcome Survey Short Form questionnaire (SF-36)) compared to age matched controls [107]. Following 3–6 months of CPAP, all domains apart from bodily pain showed significant improvements. In a randomized trial comparing CPAP and bilevel PAP therapy in the spontaneous mode over a 3-month period, Piper et al. [93] reported significant within group improvements in the domains of physical functioning, role physical, vitality, and social functioning of the SF-36 in the bilevel PAP group. Only vitality improved significantly in the CPAP group. However, no between treatment differences were observed. The SF-36 is a generic instrument and may not be sensitive enough to identify subtle change in quality of life. Studies comparing bilevel PAP ST therapy to volume-targeted pressure support using a disease-specific instrument (the Severe Respiratory Insufficiency (SRI) questionnaire) have reported significant improvements in HRQoL with NPPV compared to baseline, but not between treatment differences [114, 132], even when better control of nocturnal carbon dioxide with volume-targeted pressure support was achieved [132].

Reports of the impact of fixed bilevel PAP on lung function in OHS have been inconsistent. One study found increases in TLC of 7.5% after as little as 4 weeks of NPPV [111] while two other studies found significant improvements in VC and TLC [12, 50] as well as ERV [50] which appeared to plateau at 12 months [50]. In contrast, a number of controlled and observational studies have failed to find any significant change in lung volumes during follow-up periods of 3–50 months [12, 92, 114, 136]. Longer term follow-up of lung function in patients with OHS managed with CPAP has not been documented.

With both CPAP [62, 74] and bilevel PAP therapy [66, 117, 131] improvements in HCVR have been reported, with changes observable within 2 weeks in some studies [62, 66, 74]. However, normalization of HCVR may not be achieved in all patients [66, 117]. One study found substantial individual difference in both baseline HCVR as well as changes following therapy [66]. In another study no significant change in HCVR was seen following 4 weeks of effective NPPV despite a mean fall in awake $PaCO_2$ of 5 mmHg and in bicarbonate of 2 mmol/L [111]. However, these patients were at the mild end of the severity spectrum in OHS, and baseline HCVR was in the low range of normal values.

Pulmonary hypertension is more common and more severe in patients with OHS than those with OSA or overlap syndrome (the coexistence of COPD and OSA) [11]. The likelihood of developing cor pulmonale is also high [26]. In a small,

prospective observational study, bilevel PAP therapy used over a 6-month period significantly reduced pulmonary artery systolic pressure and increased 6-min walk distance in patients with OHS with right ventricular overload [141]. CPAP has been shown to reduce pulmonary artery pressure and hypoxic pulmonary vascular reactivity in patients with eucapnic OSA [142]. However, in patients with OHS mild to moderate pulmonary hypertension persists in a substantial proportion of individuals despite bilevel PAP and is inversely related to therapy use [143]. The presence of pulmonary hypertension despite PAP is associated with greater impairments in HRQoL, physical functioning and daytime sleepiness compared to OHS individuals without pulmonary hypertension [143], highlighting the importance of early recognition of the disorder and the need to promote strategies to maximize adherence to therapy.

Once treated with NPPV, survival rates of 97% at 1 year and 70–80% at 3 years can be expected [12, 29, 137, 138] which are significantly better than those reported for patients remaining untreated [25, 92]. Similar data for patients managed with CPAP alone have not been reported. In one study, a reduction in $PaCO_2$ (>23%) and in hemoglobin following the commencement of NPPV was associated with better survival [12]. Nevertheless, at present there is a lack of evidence to show that normalization of gas exchange has a significant effect on cardiovascular risk factors such as blood pressure, arterial stiffness, or endothelial function [111]. The persistence of cardiovascular comorbidities despite NPPV remains a significant mortality risk [137]. These findings reinforce the need to identify and treat OHS prior to the development of significant comorbid conditions [27] and once present, the importance of effectively managing these complications [137, 144].

Despite the clinical and survival benefits of NPPV, around 20% of patients will refuse or be non-adherent with therapy longer term [12, 29, 50, 92, 137]. In contrast to CPAP therapy for OSAS where a significant body of literature has looked at barriers to CPAP use [145–147] and the use of different approaches to improve adherence [148–150], few studies have considered these issues in patients with OHS. Being female [29, 92] and the presence of psychiatric illness [92] have been associated with a higher likelihood of refusal of therapy in patients with OHS. On the other hand, initiating treatment in the acute setting or during a period of clinical stability does not appear to influence acceptance or adherence to NPPV [29]. In those patients continuing on therapy long term, adherence is high with an average nightly use of 5–7 h reported [12, 15, 29, 50]. Somewhat similar to CPAP, it appears that around 4–4.5 h per night of NPPV is the minimum nocturnal usage required to achieve significant changes in $PaCO_2$ [108, 114].

Even when the patient remains compliant with therapy, correction of daytime hypercapnia and hypoxemia is not always achieved. Mohklesi and colleagues [108] found that almost one quarter of patients using PAP therapy an average of 7 h per day did not have a significant change in awake hypercapnia (defined as a drop in $PaCO_2$ of less than 4 mmHg). These non-responders had less severe upper airway obstruction (AHI 44 ± 45 versus 86 ± 47 per hour, $p = 0.03$) than those responding to PAP therapy. Similarly, in a group of Japanese patients with

hypercapnic OSA, those failing to respond to CPAP were significantly more obese than CPAP responders [19]. This suggests that upper airway obstruction may not be the primary mechanism responsible for the development of chronic hypercapnia in some patients with OHS [108], and management needs to address other factors such as respiratory drive and obesity to improve daytime hypercapnia. The clinical consequence of persisting hypercapnia despite control of SDB has not been investigated.

Weight Loss, Physical Activity, and OHS

Excess weight contributes to the development and progression of OHS not only through its association with SDB, but by impairing lung mechanics and respiratory drive. If significant weight loss occurs, improvements in pulmonary function [53, 151, 152], awake blood gases [49, 151] and pulmonary hypertension [153] can be expected. Although bariatric surgery produces significantly greater and more sustained weight loss [154], well-structured lifestyle modification programs for morbidly obese individuals which include diet and exercise can achieve clinically important degrees of weight loss of around 10–20 % [155]. This degree of weight loss is sufficient to produce significant improvements in cardiovascular risk factors including insulin resistance, blood pressure and waist circumference in patients with obesity [155]. Since PAP therapy alone in OHS does not appear to alter cardiometabolic risk despite improving SDB and daytime gas exchange [111, 156], engaging these individuals in more formal rehabilitation and life-style modification programs to reduce sedentary behavior, improve functional capacity and reduce weight [144, 157] are important aspects of long-term care.

A number of barriers to improving physical activity in this group exist. Musculoskeletal disorders including knee and hip problems are common [27]. This, combined with a high prevalence of breathlessness [11, 46, 92] and daytime sleepiness [46, 92, 93, 107, 108] could influence the willingness and ability of these individuals to be physically active. In a survey of patients with OHS undertaken to gauge their interest in attending a pulmonary rehabilitation program, the response rate was less than half, and of those respondents 43 % felt they “were not at all likely” to attend [158]. Therefore, in designing rehabilitation programs for this population, consideration must be given to potential motivational problems as well as practical ones that could prevent participation.

The use of NPPV therapy itself may encourage greater physical activity and preparedness to exercise. One study has shown an improvement in daytime symptoms and physical activity in patients with OHS following the commencement of NPPV, and this was associated with greater weight loss [114] (Fig. 4.4). In other patient groups with nocturnal hypoventilation, using NPPV during exercise training reduces breathlessness and improves exercise capacity [159, 160]. Although this has not been specifically studied in OHS, the effect of NPPV in the form of proportional assist ventilation has been evaluated during exercise in patients with

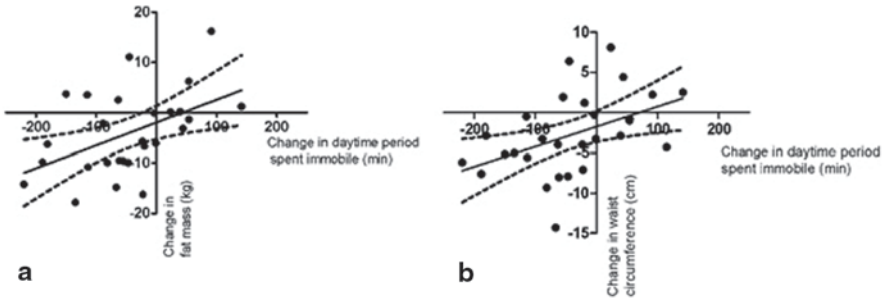

Fig. 4.4 The use of NPPV can lead to increases in physical activity (measured by time spent immobile) which are associated with **a** a change in fat mass and **b** a change in waist circumference. (From Murphy et al., Thorax 2012)

eucapnic obesity [161]. This intervention increased exercise endurance, although only 10 of the 18 patients studied responded. Interestingly, these "responders" were characterized by a reduced TLC, a feature of many patients with OHS. This suggests a potential role of NPPV during exercise training in OHS to further enhance exercise capacity. Inspiratory muscle training (IMT) may also be of benefit in improving functional capacity. When added to a low-calorie diet and physical activity program for patients with primarily morbid obesity, IMT significantly increased 6-min walk distance and reduced dyspnea compared to a group on the same program who were not given IMT [162]. The degree to which these interventions are successful in improving physical activity, reducing sedentary behavior and altering biomarkers of cardiometabolic disease in the longer term needs further exploration.

Conclusions

The simplicity of the term "obesity hypoventilation" belies the complexity of mechanisms underlying the development and progression of this disorder. If left untreated, these individuals face significant health, social, and financial burdens. The use of CPAP and bilevel PAP therapy is now a standard of care for patients with OHS, with an increasing number of non-invasive positive pressure ventilation modes available to optimize the management of SDB. Effective nocturnal PAP therapy is associated with significant improvements in awake gas exchange, symptoms, and quality of life. However, the incomplete correction of carbon dioxide with PAP therapy in a substantial minority of patients, despite adherence to therapy, reminds us that treating SDB only addresses one aspect of the problem. Furthermore, the extent to which PAP reduces cardiometabolic risk in these individuals has yet to be determined. The use of nocturnal ventilation in patients with OHS should be seen as a key, but not sole, aspect of a managing these

individuals. In order to maximize the gains achieved with PAP therapy, efforts also need to be directed towards weight loss and reducing sedentary behaviors. In the future, evaluation of long-term data regarding the most effective PAP and how this should be used in combination with weight reduction, pharmacotherapy and behavioral strategies will be vital in minimizing the substantial impact of this increasingly prevalent condition.

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Chapter 5
Nocturnal Noninvasive Ventilation in Neuromuscular Ventilatory Disorders

Brian Palen and Joshua O. Benditt

Introduction

Normal respiratory function depends on a complex interaction of the central and peripheral nervous and musculoskeletal systems that is regulated by multiple feedback mechanisms [1]. Respiratory function in sleep is prone to destabilization due to: (1) the loss of voluntary respiratory drive located in the cortex and the subsequent reliance on regulation via automatic breathing centers and (2) rapid eye movement (REM) sleep atonia that results in reliance on the diaphragm for generation of the breath volume [1]. Sleep-related breathing disorders (SRBDs) encompass a group of disorders characterized by abnormalities of respiratory pattern and/or ventilation during sleep. Specific types of SRBDs include hypoventilation, obstructive sleep apnea (OSA), and central sleep apnea (CSA) [2].

The effects of neuromuscular disorders on nocturnal respiratory function are complex and varied given the differences in disease physiology, progression, and patient comorbidities including presence, type, and severity of SRBDs. This chapter reviews the common physiologic mechanisms regulating nocturnal respiration, the impact of neuromuscular disorders on these mechanisms, modalities to assess nocturnal respiratory impairment, and the effectiveness of treatment with noninvasive positive pressure ventilation (NPPV) in the patient population with neuromuscular disorders.

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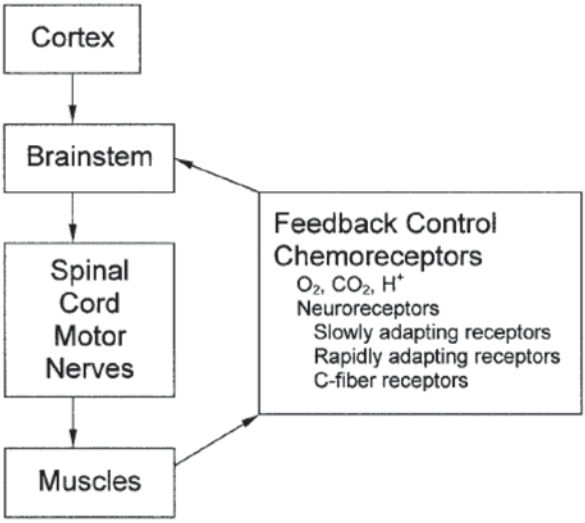

Fig. 5.1 Schematic of the neurorespiratory system. (Benditt [27])

Physiology of Respiration

Components of the normal neurorespiratory system include central nervous system control centers and feedback mechanisms working in conjugation with the spinal cord, motor nerves, and respiratory muscles. In combination, they sustain life via air movement into and out of the lungs with resultant gas exchange. The system is made up of the cortex of the brain, which controls voluntary breathing; the brainstem, which is the generator of automatic breathing; the spinal cord and motor neurons, which conduct nerve impulses; the respiratory muscles, which are the mechanical effectors of the system; and a complex network of feedback receptors and nerves that regulate the system and maintain arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) levels (Fig. 5.1).

Central Mechanisms

Voluntary-Breathing Controllers Awake respiration is primarily driven by voluntary-breathing controller mechanisms located in the parietal cerebral cortex. Stimulation of the cortex occurs with routine wake behaviors such as vocalization and physical exertion. Centers within the cortex send signals for inspiration or expiration which are then conducted through corticospinal tracts in the spinal cord to motor neurons [3].

Automatic-Breathing Controllers Automatic breathing is regulated via a complex system of respiratory generating centers located in the medulla and pons, nerve tracts located in the brainstem, as well as chemical and mechanical feedback mechanisms. During wakefulness, the automatic-breathing system is functional, but respiration is primarily driven by the voluntary-breathing mechanism from the cortex. During both Non-REM and REM sleep, the voluntary-breathing mechanism is absent and respiration is driven entirely by the automatic-breathing mechanism. Destabilization of the automatic breathing centers that can occur in some neurologic diseases has a significant clinical impact on nocturnal (i.e., sleep) respiratory function [4–6].

Peripheral Mechanisms

Lower Motor Neurons Lower motor neurons are composed of cell bodies located in the anterior horn cell of the spinal cord, and spinal nerve roots, which leave the spinal cord to stimulate the respiratory muscles. At the muscle fiber, the nerve roots interface with the muscle membrane at anatomical junctions known as motor endplates. With nerve firing, acetylcholine is released and subsequently binds to receptors on the muscle side of the motor endplate resulting in depolarization and subsequent muscle contraction [7].

Respiratory Muscles The respiratory muscles are the mechanical effectors of the respiratory system and consist of four major groups: inspiratory muscles, expiratory muscles, accessory muscles, and muscles of the upper airway. The diaphragm is the major muscle of inspiration, contributing approximately 70% of inspiratory tidal volume in non-diseased individuals [8]. Innervation of the diaphragm is via the phrenic nerve, which has nerve roots at C3–C5. Stimulation of external intercostal muscles as well as the accessory muscles (sterncleidomastoid, scalene, trapezii, latissimus dorsi, pectoralis major and minor, and platysma) further assists with inspiration via expansion of the rib cage.

Abdominal muscles including rectus abdominus, internal oblique, external oblique, and transverse abdominus are typically thought of as expiratory muscles, but may also play a minor role in inspiration [9]. Internal intercostal muscle stimulation further assists with expiration via contraction of the rib cage.

The muscles of the upper airway (abductors of the vocal cords, palatal elevators, retractors of the tongue, and dilators of the nares) are often included as respiratory muscles and function to maintain airway patency and ensure air exchange.

Feedback Control Maintenance and fine control of respiration are sustained via feedback networks comprised of chemical and neural receptors in both the central and peripheral nervous system. Neural receptors (muscle spindles, stretch/mechanical/irritant receptors) respond to physical stimulation and are present in the upper airway, respiratory muscles, and vasculature. Chemoreceptors responsive to

changes in $PaCO_2$, PaO_2, and pH are found both centrally and peripherally. Peripheral chemoreceptors include the carotid and aortic bodies which primarily sense and respond to changes in PaO_2, with lesser response to $PaCO_2$ and pH [10]. Central chemoreceptors are located in the brainstem and sense and respond to changes in $PaCO_2$ which is primarily mediated through resultant alterations in cerebrospinal fluid pH [11].

Respiration in Sleep

During sleep, numerous physiologic changes occur (even in normal individuals), which potentially jeopardize respiration. These changes include the absence of voluntary respiration activity, alterations in chemo-responsiveness, and decreased respiratory muscle function with resultant reduction in airway patency and ventilation. Ventilation commonly is most affected in REM sleep, because of the muscle atonia that occurs in that stage of sleep, which spares only ocular and diaphragmatic function. Ventilation in REM sleep is thus largely dependent on diaphragmatic functioning and may demonstrate the earliest manifestations of SRBDs.

Neuromuscular disorders can impact any or all of the aforementioned physiologic mechanisms resulting in significant nocturnal (sleep) respiratory dysfunction. As expected, diaphragmatic dysfunction is a key pathway for SRBDs in this patient population. Diaphragmatic impairment may present in conjunction with generalized muscular weakness due to disease progression, or as an isolated dysfunction attributed to phrenic nerve impairment. Respiratory function may further be impaired in patients with neuromuscular disorders via the subsequent development of restrictive physiology, chronic atelectasis, and aspiration [12].

The aforementioned impairments commonly result in one of, or a combination of SRBDs. Nocturnal hypoventilation is the most common SRBD in this patient population and occurs when ventilation is inadequate to perform needed gas exchange, with resultant ≥ 10 mmHg increase in sleep $PaCO_2$ compared to awake values [13]. Nocturnal hypoventilation should be suspected in patients with documented daytime hypercapnea and hypoxemia. Dysfunction of pharyngeal muscle tone is also commonly seen in neuromuscular patients during sleep, and allows soft tissue in the back of the throat to block the pharyngeal airway with resultant decreased airflow, decreased gas exchange, increased work of breathing, and stimulation of brief arousals to allow resumption of normal breathing. These findings place patients with neuromuscular disease at risk for OSA. Prevalence of OSA in NMD depends on the particular disease with those with bulbar involvement at higher risk. This pattern of repetitive collapse (apnea) and/or partial collapse (hypopnea) can repeat itself hundreds of times throughout the night resulting in significantly fragmented sleep patterns. CSA is characterized by the cyclical or intermittent absence of inspiratory effort in the presence of a patent airway. CSA is less common than hypoventilation and OSA in the neuromuscular patient popula-

tion, but is often seen with disease associated central neurologic impairment. The overall degree of clinical and physiologic complexity seen in SRBDs emphasizes the importance of thorough sleep evaluation including consideration of polysomnography (PSG).

Clinical Presentation

Impairment of nocturnal breathing in neuromuscular disease patients is often insidious in onset and patients commonly will not be aware of, or volunteer obvious signs/symptoms of, dysfunction. This underscores the importance of routine questioning and clinical assessment. Clinical indicators of impaired nocturnal breathing commonly include fatigue, daytime sleepiness, snoring, and witnessed apnea. Other complaints reported by patients include nocturia, night sweats, heartburn, sexual dysfunction, and morning headaches reflecting the multisystem effects of this disorder. Snoring is a sensitive indicator of OSA, but is a more specific finding when it is very loud and occurring habitually (>3 days/week). Witnessed apneas and self-report of choking/gasping episodes are also specific indicators [14]. The variable clinical presentation of neuromuscular disorders may confound the identification of examination findings and patient symptoms attributable to the underlying neuromuscular process versus SRBDs.

Routine screening of this patient population for nocturnal as well as daytime symptoms should be standard of practice. This includes interviewing and questioning bed partners and caretakers. Questionnaires for daytime somnolence such as the Epworth Sleepiness Scale (ESS) have shown to be effective screening tools for patients in the general population with OSA [15]. The correlation of such questionnaires with measures of hypoventilation commonly seen in neuromuscular patients is less clear [16]. Efforts to design a questionnaire specific to neuromuscular patients include the five question sleep-disordered breathing in neuromuscular disease questionnaire (SiNQ-5). Values greater than 5 on this questionnaire have been shown to demonstrate abnormal nocturnal respiration with sensitivity of 86 %, specificity of 89 %, positive predictive value of 69 %, and negative predictive value of 96 % [17] (Table 5.1).

Disease specific patient symptom scales such as the amyotrophic lateral sclerosis functional rating scale revised (ALSFRS-R) questionnaire are commonly recorded in data collection, but there is limited evidence for correlation with SRBDs [18].

Established risk factors for SRBDs in the general population include obesity (BMI >30), increased neck circumference (>17 in. in men and >16 in. in women), middle and older age, postmenopausal women, smoking, craniofacial abnormalities, use of central acting medications, congestive heart failure, and family history of SRBDs [14]. It is likely that these risk factors also make SRBDs more likely in the neuromuscular disease population, although data in this area are lacking.

Table 5.1 SiNQ-5 questionnaire for neuromuscular disease patients

Do you feel breathless if			
You lie down?	Yes(2)	Sometimes (1)	No (0)
You lean forward?	Yes(2)	Sometimes (1)	No (0)
You swim in water or lay in a bath?	Yes(2)	Sometimes (1)	No (0)
Have you changed your position when in bed?	Yes(2)	No (0)	
Have you noticed a change in your sleep (waking more, getting up, and poor quality sleep)?	Yes(2)	No (0)	

Table 5.2 Central nervous system diseases

Cerebral cortex	Brainstem	Basal ganglia	Spinal cord
Stroke	Multiple sclerosis	Parkison's disease	Trauma
Neoplasm	Encephalitis	Chorea	Demyelinating disease
–	Multiple system atrophy	–	Motor neuron disease
–	Primary alveolar hypoventilation	–	Pontine myelinolysis
–	Stroke	–	Poliomyelitis
–	Neoplasm	–	Stroke
–		–	Neoplasm

The variable clinical picture in neuromuscular diseases can make it difficult to identify findings predictive of SRBDs aside from the documented risk factors. Indicators of respiratory muscle weakness while awake such as orthopnea, accessory muscle use, paradoxical breathing, tachypnea, shallow breathing, and cyanosis should alert the provider to likely nocturnal respiratory disturbances and merit further investigation.

Neuromuscular Diseases

Neuromuscular diseases are perhaps most easily classified based on the anatomic area in the nervous system where they create dysfunction, with common groupings including: cerebral cortex, brainstem, basal ganglia, spinal cord, motor neuron, neuromuscular junction, and muscle. Tables 5.2 and 5.3 list various neuromuscular disease processes according to their site of action in either the central or peripheral nervous system. The broad spectrum of disease courses emphasizes the importance of careful consideration of individual patient findings with regard to their underlying disease process (Tables 5.2, 5.3)

Table 5.3 Peripheral nervous system diseases

Motor neuron	Neuromuscular junction	Muscle
A myotrophic lateral sclerosis	Myasthenia gravis	Muscular dystrophy
Guillain–Barre syndrome	Lambert–Eaton syndrome	Myotonic dystrophy
Poliomyelitis	–	Polymyositis
Spinal muscular atrophy	–	Glycogen-storage disease
Vasculitides	–	Acid maltase deficiency
–	–	Nemaline myopathy
–	–	Mitochondrial myopathy

Diseases of the Central Nervous System

Voluntary Breathing Voluntary breathing may be impaired by lesions affecting the descending corticospinal or corticobulbar tracts, and is particularly impaired in association with destructive vascular lesions of the basal pons or the medullary pyramids causing what is known as the "locked in" syndrome [19, 20]. Interruption of these voluntary pathways leads to a regular and unvarying respiratory pattern during wakefulness as well as sleep, with loss of the ability to take a deep breath, hold a breath, or produce a voluntary cough [19]. Respiration is then entirely dependent on automatic breathing, largely based on changes in $PaCO_2$. Lesions impacting voluntary breathing are most commonly secondary to ischemic stroke, but may also be secondary to pontine tumor, pontine myelinolysis, high cervical demyelination, syphilitic arteritis of the medulla, diffuse cortical vascular disease, and head injury [21, 22]. Extrapyramidal disorders such as Parkinsonism have also been associated with impaired voluntary control of breathing as well as SRBDs [23].

Automatic Breathing "Ondine's Curse" is the preservation of voluntary respiratory control in the setting of disrupted automatic breathing resulting in central apnea and subsequent failed respiration while asleep. Common associated lesions include bilateral medullary infarction, bulbar poliomyelitis, bilateral cervical tractotomy, and congenital central hypoventilation [21]. Abnormal patterns of respiratory rate and rhythm such as ataxic respiration and Cheyne–Stokes breathing are often a reflection of impairment of the automatic respiratory centers in the brainstem [19]. Ataxic respiration is characterized by an irregular respiratory cycle of variable rate and tidal volume alternating with periods of apnea. It is associated with medullary lesions such as brainstem stroke or compression from rapidly expanding lesions and may indicate impending respiratory arrest. Cheyne–Stokes breathing is classified as a type of CSA and is characterized by a cyclical crescendo–decrescendo waxing and waning of respiratory rate and tidal volume separated by periods of apnea [13, 24]. CSA and in particular Cheyne–Stokes breathing is a common finding post cerebrovascular accident [25]. A prospective study of 161 patients with first-ever transient ischemic attack (TIA) or stroke demonstrated 71 % of patient to have evidence of sleep disor-

dered breathing with 26% manifesting Cheyne–Stokes breathing. At 3-month follow-up, 62% of patients demonstrated sleep disordered breathing with 7% manifesting Cheyne–Stokes breathing. These findings were independent of stroke subtype or event location [26].

Brainstem and Spinal Cord Spinal cord lesions are most commonly secondary to traumatic injury, but may also include vascular injury, tumor, epidural abscess, transverse myelitis, and syringomyelia [27]. The level of spinal cord injury has a direct impact on the type and severity of ventilatory compromise. The diaphragm is innervated via C3–C5 spinal nerve roots and its loss of function due to C3 and higher lesions typically results in continuous ventilatory requirements. Lesions affecting C3–C5 nerve roots result in varying impact of ventilatory function and will require varying levels of ventilatory support [28]. Lesions below the C5 spinal roots result in preserved diaphragmatic function, but may still significantly impact accessory respiratory muscle function and sympathetic bronchomotor tone resulting in impaired cough and secretion clearance [28, 29].

Poliomyelitis is a disease that affects the anterior horn cell in the spinal cord as well as the motor nerves. Although acute polio is rarely seen in the USA, it is still prevalent in underdeveloped countries [30]. In developed nations, the late effects of polio constitute a collection of findings known as the post-polio syndrome (PPS). PPS is a poorly understood process characterized by muscular weakness, joint pain, and fatigue, which affects as many as half of patients with history of poliomyelitis [31]. Nearly 50% of patients with PPS report sleep complaints including daytime fatigue and somnolence, headaches, and restless leg symptoms [32]. PSG findings have confirmed increased frequency of nocturnal hypoventilation, CSA, OSA, cortical arousals, and periodic limb movements. Further, kyphoscoliosis is a common complication in PPS patients and is associated with increased frequency of restrictive respiratory dysfunction [33–35].

Diseases of the Peripheral Nervous System

Motor Nerves and Neuromuscular Junction Disorders of the motor nerves and neuromuscular junction represent a broad spectrum including acute processes such as Guillain–Barré syndrome, botulism, and drug toxicities to more chronic processes such as myasthenia gravis and amyotrophic lateral sclerosis (ALS). Myasthenia gravis is a neuromuscular junction disorder manifest by production of acetylcholine receptor antibodies with resultant generalized muscle weakness and bulbar signs (dysarthria, dysphagia, and diplopia). Respiratory muscle involvement is common in uncontrolled disease states such as myasthenia crises [36]. While there is little debate to the occurrence of SRBDs such as hypoventilation and CSA during periods of disease activity, the occurrence of SRBDs in stable myasthenia patients is much less clear and is limited by quantity of studies as well as small study populations. Early studies suggested increased PSG findings of varying prevalence of CSA,

OSA, as well as hypoventilation [37–39]. Later data demonstrated no increased prevalence of CSA and OSA, and no correlation between pulmonary function and SRBDs [40].

ALS is a neurodegenerative disease characterized by the progressive degeneration of motor neurons in the cerebral motor cortex, the corticospinal tracts which conduct impulses to the brainstem, the structures of the brainstem, and the spinal cord [41]. The resultant combination of upper and lower motor neuron dysfunction causes progressive, irreversible weakness affecting respiratory muscles required for airway patency, clearing of secretions, and ventilation. This commonly manifests as a combination of hypoventilation with central and/or OSA. The presence of bulbar dysfunction has not shown to be associated with increased rate of OSA [42–44].

Observational studies have demonstrated >50% of ALS patients to report sleep complaints with the most common symptoms being nocturia, sleep onset and maintenance insomnia, nocturnal muscle cramping, morning headaches, and daytime sleepiness [45, 46]. PSG analysis in ALS patients has demonstrated reduced sleep efficiency, increased sleep fragmentation, increased frequency of cortical arousals, increased periodic limb movements, and increased frequency of obstructive and central events as well as hypoventilation [43, 45, 47]. ALS patients with documented diaphragmatic weakness have been shown to be at particular risk for nocturnal hypoventilation and subsequent shorter survival [44, 47]. Bourke and colleagues demonstrated quality of life assessments to be more reliant on respiratory muscle function than PSG data such as the apnea hypopnea index (AHI) [48].

Despite attempts at early recognition and treatment, respiratory failure remains the most common cause of death in the ALS population, with forced vital capacity (FVC) values shown to decline as much as 2.4% every 30 days [20]. A randomized controlled study by Bourke and colleagues demonstrated that in ALS patients without severe bulbar dysfunction, NPPV improves survival and quality of life. In patients with severe bulbar impairment, NPPV was shown to improve quality of life, but failed to confer a large survival advantage [48]. In summary, the use of NPPV in ALS patients has shown to improve survival, improve quality of life, slow the rate of respiratory muscle decline, and prolong the need for tracheostomy [48–50].

Respiratory Muscles Neurologic disorders of respiratory muscle function span a broad spectrum of acute and chronic disease processes including myotonic dystrophy, muscular dystrophy, glycogen-storage diseases, and myopathy. Respiratory muscle involvement is common in this disease population with diaphragmatic weakness and SRBDs typically occurring later in the disease course. Acid maltase deficiency (Pompe disease) is an exception to this rule, with early diaphragmatic involvement and nocturnal hypoventilation often preceding limb or other muscle weakness [51].

A prototype of chronic progressive muscular disease affecting respiration is Duchenne muscular dystrophy (DMD), an X-linked disorder characterized by progressive skeletal muscle weakness leading to respiratory dysfunction and failure

late in the disease course. A prospective study of 19 DMD patients demonstrated either a $PaCO_2 \geq 45$ mmHg or a forced expiratory value in 1 s (FEV_1) < 40% of predicted value to be indicative of nocturnal hypoventilation as determined by PSG [52]. PSG studies in patients with DMD have demonstrated increased occurrence of nocturnal hypoventilation, sleep fragmentation, and OSA. Hypoventilation is significantly worsened in REM sleep, likely due to combined respiratory muscle weakness and restrictive lung physiology often exacerbated by kyphoscoliosis [53, 54]. Noninvasive positive pressure ventilation (NPPV) use in DMD patients has shown to reduce daytime $PaCO_2$ values, prolong survival, increase likelihood of tracheostomy decannulation, and decrease daytime ventilation requirements [52, 55, 56].

Assessment of Respiratory Muscle Impairment

Early recognition of respiratory muscle impairment and subsequent risk for SRBDs is a challenging task in the neuromuscular patient population. While PSG is the gold standard for identification of SRBDs, it is costly and often logistically difficult to complete in this patient population. There has been extensive research to identify home- or office-based clinical predictors to be used in place of or adjunctive to PSG. Modalities investigated have included symptom-based questionnaires, serologic laboratory analysis, nocturnal pulse oximetry (NPO), nocturnal carbon dioxide monitoring, as well as pulmonary function testing (PFT). To date, no single modality has proven effective as a solitary tool. Individual consideration of each patient's clinical picture and combined testing data should drive the decision of when and how to initiate treatment.

The utility of symptom-based patient questionnaires in predicting SRBDs was discussed earlier in this text.

Laboratory Analysis Daytime arterial blood gas (ABG) analysis for detection of hypercarbia and hypoxemia has been extensively evaluated as a screening tool for SRBDs, and in specific disease populations it has shown to be a good screening tool for nocturnal hypoventilation [52]. In general, daytime $PaCO_2$ values >45 mmHg are viewed as sensitive measures of nocturnal hypoventilation [52]. However, normal $PaCO_2$ values do not exclude the possibility of nocturnal hypoventilation. In fact, it is established that normal daytime ABG analysis may occur in patients with significant nocturnal hypoxia and hypercarbia. There is subsequently, significant concern that normal daytime ABG analysis may fail to identify patients with significant nocturnal respiratory disturbances. This is of particular consequence given data showing that early initiation of treatment improves quality of life and survival in certain disease populations [48–50].

Nocturnal Pulse Oximetry (NPO): NPO is a relatively inexpensive and practical test that has been used extensively in neuromuscular patients to screen for SRBDs. Baseline oxygen saturation levels as well as duration and frequency of desaturation

events have been utilized as rough estimates of hypoventilation and possibly OSA. While NPO has demonstrated some efficacy in the detection of nocturnal hypoventilation in specific disease populations such as ALS [57], it is possible to fail to identify patients with hypoventilation due to the absence of direct measurement of hypercarbia. Thus, while commonly used, NPO alone has shown to be a limited tool for diagnosis and monitoring of hypoventilation [58].

Nocturnal Carbon Dioxide Monitoring Use of nocturnal carbon dioxide monitoring via transcutaneous and end-tidal sensors has also been evaluated for the detection of early nocturnal hypoventilation. While not a direct measurement of $PaCO_2$, transcutaneous and end-tidal sensors have been validated in clinic-based settings [59, 60]. Recent technological advancements have increased the availability and quality of transcutaneous monitoring, and retrospective studies of home-based monitoring have demonstrated utility as a screening tool in conjunction with NPO [58, 59].

Pulmonary Function Testing (PFT): PFT including office-based spirometry and measures of respiratory effort has undergone extensive evaluation as a diagnostic indicator of nocturnal SRBDs. The literature on this topic is vast and often confusing. Patients with neuromuscular disorders frequently demonstrate restrictive physiology with diminished FVC in relation to forced expiratory volume in 1 s. The FEV1/FVC ratio is thus commonly preserved with values approaching 1 or greater. Respiratory muscle weakness is commonly seen in this patient population and is often quantified via maximum inspiratory and expiratory pressures (MIP and MEP) as well as sniff nasal inspiratory pressure (SNIP).

Disease specific guidelines, including ALS practice parameters, have previously recommended use of FVC values to identify respiratory muscle weakness, risk for nocturnal hypoventilation, and subsequent need for treatment. Despite several studies suggesting that FVC values alone are inadequate predictors for respiratory muscle weakness and survival [57, 61–63], various absolute cutoffs for FVC in multiple disease populations have been proposed ranging from 25 to 75% of predicted values. Both the consensus guidelines from the American College of Physicians (ACP) and the ALS practice parameters from the American Academy of Neurology recommend initiation of NPPV for FVC values < 50% of predicted [22, 64]. Dynamic assessment of FVC has also been investigated by utilizing differences in measurements of supine and upright FVC values. When diaphragmatic function is normal, the difference between upright and supine FVC values (ΔFVC), ranges from 0 to 7.5% [65]. ΔFVC values in patients with diaphragmatic weakness are significantly larger and may reach differences up to 50% [66, 67]. As with absolute FVC values, there is no definitive ΔFVC value shown to be an isolated predictor of SRBDs across this patient population.

Assessment of respiratory muscle weakness via evaluation of MIP and MEP has also been thoroughly evaluated. MIP values are traditionally viewed as indicative of inspiratory muscle function predominately driven by the diaphragm, while MEP values are considered reflective of accessory expiratory muscle function. In healthy

middle aged adults mean (+/− SD) values of MEP and MIP are 111 +/− 25 cmH_2O and 79 +/− 19 cmH_2O in females and 192 +/− 42 cmH_2O and 117 +/− 25 cmH_2O in males, respectively [68]. MIP has been suggested as a more sensitive and earlier indicator of respiratory muscle weakness in ALS patients, with data demonstrating deficiencies in MIP to occur 4–6.5 months earlier than deficiencies in FVC [69].

Obtaining accurate, reproducible MIP and MEP values in neuromuscular patients is often limited by their ability to create and hold a tight lip seal. "SNIP" provides a noninvasive alternative and consists of measuring nasal pressure in an occluded nostril during a maximal sniff performed through the contralateral nostril, and has been validated in normal adults and children as well as those with neuromuscular disease [70, 71]. As with other PFT measures, there is broad range of published cut-off values for which MIP, MEP, and SNIP are felt to be indicative of need for NPPV, with no universal guideline to date [72–74].

Polysomnography PSG provides real-time objective data to assess the type(s) and severity of SRBD. PSG allows assessment of airflow, respiratory effort, oxygen saturation, presence or absence of hypercarbia, quantification of sleep stages, frequency of cortical arousals, and limb movements. Although the absolute need for PSG to identify SRBDs in this patient population remains a source of controversy, it should be considered the definitive diagnostic tool given that neuromuscular patients are at risk to manifest more than one type of SRBD simultaneously [75].

Hypoventilation is commonly found in this patient population and assessed for via changes in awake and sleep carbon dioxide and oxygen arterial partial pressure measures. Differences in awake and sleep carbon dioxide arterial partial pressures are most commonly assessed using either transcutaneous or end-tidal carbon dioxide monitoring. The degree of hypoxemia is typically measured via pulse oximetry and quantified by the oxygen desaturation index (frequency of oxygen desaturation events per hour), nadir oxygen saturation, and time spent with oxygen saturation below 90%.

Isolated or concurrent sleep apnea is assessed for via the AHI. AHI is a measure of the number of apneas and hypopneas that last for at least 10 s/h of sleep. The following cutoffs are commonly used for classification of severity when diagnosing sleep apnea: 5–15 mild, 15–30 moderate, and >30 severe.

SRBDs of any type or combination are commonly associated with frequent arousals and significant disruption in sleep architecture. Electroencephalographic (EEG) sensors monitor and quantify disruptions to the four stages of sleep (N1, N2, N3, and REM). Non-REM sleep comprises stages N1-3 and typically composes 80% of total sleep time (TST). Stage REM composes approximately 20% TST and occurs more commonly in the latter half of the sleep period. In patients with SRBDs, the percent of stage N1 is typically increased (>10%) and the percentages of stage N3 (<15%) and stage REM (<15%) are typically decreased. The arousal index measures the number of cortical EEG arousals per hour of sleep. An arousal index >20 is abnormal, with values >40 typically viewed as representing severely fragmented sleep.

Treatment

The decision of when and how to initiate treatment of nocturnal respiratory dysfunction in the neuromuscular patient population is extremely challenging and requires particular attention to individual patient clinical course, testing results, and quality of life measures. Treatment options constitute a spectrum ranging from use of supplemental oxygen, to NPPV, to surgical tracheostomy and tracheostomy-assisted ventilation. NPPV will be the focus of this discussion and has proven itself as a valid alternative to more invasive (i.e., tracheostomy-assisted) therapy. While initially well documented for use in chronic obstructive pulmonary disease and obesity hypoventilation syndrome, use of NPPV in the neuromuscular population has become current standard practice. Although not functional as a definitive airway, NPPV can safely be used in lieu of, or as a bridge to, tracheostomy. Specifically, the use of NPPV has shown to improve quality of life, slow the rate of respiratory muscle decline, prolong the need for tracheostomy, and improve survival in patient populations such as ALS [48–50, 76].

NPPV is the pressurization of the upper airway via mask interface to allow assisted ventilation without the aid of a surrogate airway such as endotracheal tube or tracheostomy. Pressurization is provided via a pressure/volume-generating machine, which is connected to the mask interface. NPPV may be applied as a nocturnal, or an awake, treatment. In recent years, machines have become increasingly portable, adjustable, and tolerable in terms of noise and comfort. The most common pressurization modes generated by these machines include continuous positive air pressurization (CPAP) and bi-level positive airway pressurization (BPAP). CPAP is used when the predominant respiratory dysfunction is airway obstruction and constitutes a single continuous flow of pressure sufficient to overcome airway resistance by acting as a physiologic stent to maintain airway patency in inspiration and expiration. BPAP is used when the predominant respiratory dysfunction is hypoventilation and typically constitutes a fixed set expiratory pressure adequate to ensure airway patency accompanied by a higher inspiratory pressure to assist with ventilation. In this patient population, BPAP is almost always accompanied by a set backup rate to compensate for potential central apneas and ensure adequate ventilation. Additional modes of airway pressurization such as average volume assured pressure support (AVAPS) and adaptive servo-ventilation (ASV) are actively being developed and investigated and primarily consist of computer algorithm modifications to fixed BPAP. Data regarding the effectiveness of these newer NPPV modes is limited in this patient population.

Indications The decision to initiate NPPV is often a daunting task for providers. Current clinical practice parameters for the initiation of NPPV are both multiple in numbers and often confusing in their application. Further, clinical presentation is often insidious in this patient population and even experienced providers have been shown to underestimate the extent of nocturnal respiratory dysfunction and subsequent need for NPPV [77].

Consensus guidelines for initiation of NPPV in patients with restrictive lung disease, chronic obstructive lung disease, and nocturnal hypoventilation were originally published by the ACP in 1999 [64]. While not specifically based on neuromuscular patient population data, these guidelines are commonly applied to neuromuscular patients and have provided a platform for further disease specific guidelines. The criteria include:

Symptoms of SRBDs such as: morning headache, fatigue, daytime somnolence, dyspnea and one of the following

1. *A $PaCO_2$ level of ≥ 45 mmHg*;
2. *Nocturnal oximetry demonstrating oxygen saturation at ≤ 88% for five consecutive minutes*;
3. *A maximal inspiratory pressure of < − 60 cmH_2O; or*
4. *An FVC of < 50% predicted*

The ACP guidelines have also served as a platform for Medicare reimbursement guidelines with the following additional stipulations: chronic obstructive pulmonary disease is not a significant contributing factor; $PaCO_2$ is measured while awake and on patient's usual fraction of inspired oxygen (FIO_2); NPO is performed on patient's usual FIO_2.

Disease specific guidelines for assessment of respiratory insufficiency and timing of initiation of NPPV have been published based on data for specific neuromuscular disorders such as ALS and muscular dystrophy. ALS practice parameters from the American Academy of Neurology were published in 2009 and while similar to the ACP guidelines, include additional criteria of nasal inspiratory pressures and orthopnea for initiation of NPPV [78] (Fig. 5.2).

Consensus guidelines for the DMD patient population were published by the Center for Disease Control (CDC) in 2010 and differ from the ACP guidelines by the inclusion of baseline awake oxygen saturation and end-tidal carbon dioxide levels, AHI values, and absolute FVC inclusion criteria of < 30% [79]. The guidelines include:

NPPV is indicated in DMD patients with any of the following:

1. *Signs or symptoms of hypoventilation*;
2. *A baseline oxygen saturation < 95% and/or blood or end-tidal $PaCO_2$ > 45 mmHg while awake*;
3. *An* AHI *> 10/h on polysomnogram OR four or more episodes of oxygen saturation (SpO_2) < 92% OR drops in SpO_2 of at least 4%/h of sleep*

Contraindications Relative contraindications to use of NPPV include swallowing dysfunction, inability to clear secretions, bulbar involvement, and lack of patient motivation. Absolute contraindications include inability to achieve adequate mask-interface fit, inability of patient to remove mask-interface, and patient intolerance to treatment [80, 81].

Initiation and Titration The wide spectrum of clinical presentation and disease course in this patient population can create unique obstacles to the initiation and titration of NPPV. Ideally, initial exposure to therapy can occur in a sleep laboratory

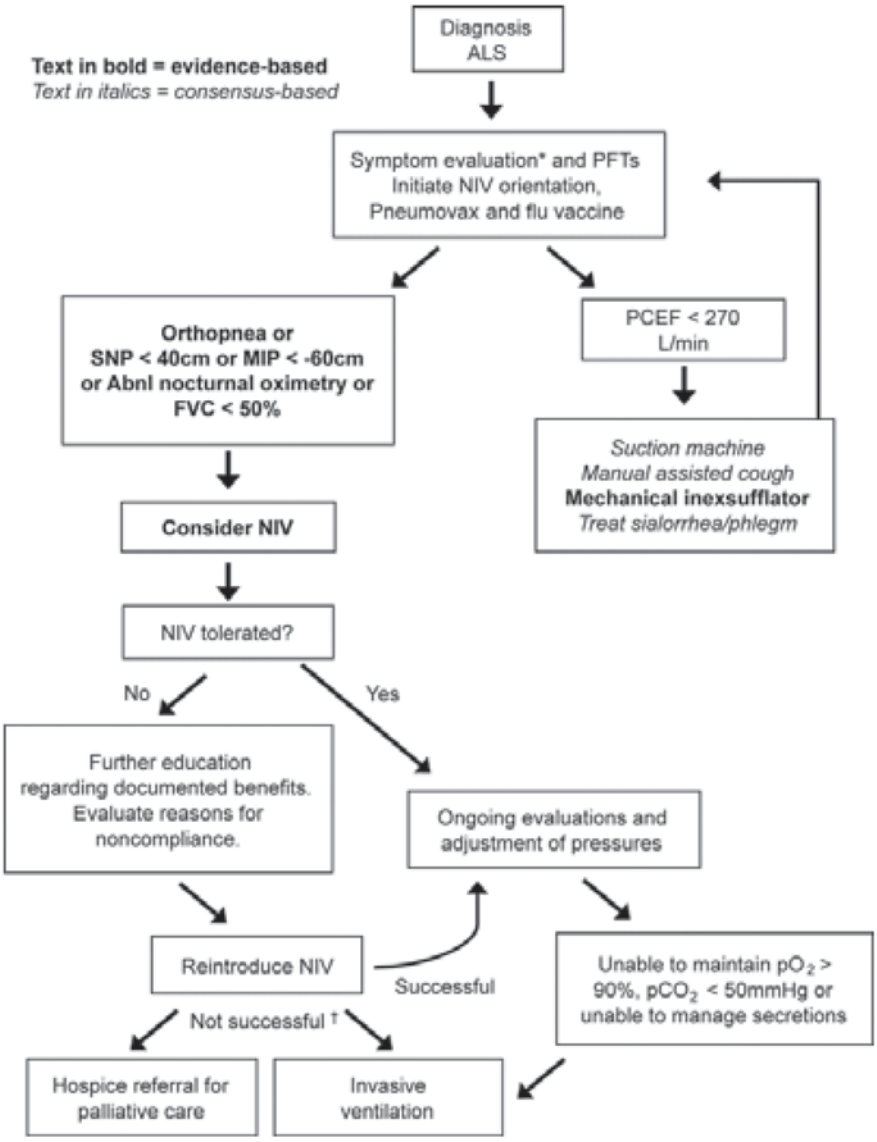

Fig. 5.2 Algorithm for respiratory management in ALS patients. (Miller [22])

or clinic setting. This allows adequate as well as an appropriate environment for education, mask fitting, titration, and patient desensitization. Given the profound weakness and disability associated with this population, patients commonly require hospital admission to ensure appropriate initiation of therapy.

Definitive titration is most accurately accomplished in a sleep laboratory and often requires a second night of PSG evaluation. However, if appropriate diagnostic

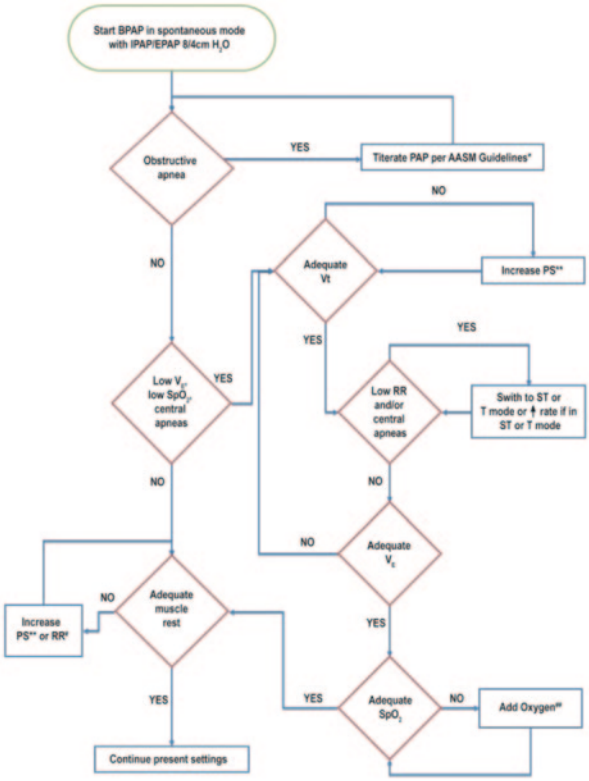

Fig. 5.3 Algorithm for NPPV titration protocol. (Berry [85])

criteria are met early in the PSG, titration may be performed during the same night in what is commonly referred to as a "split study." Outpatient or home titration via auto-titrating positive airway pressure machines (auto-PAP), have shown sufficient in uncomplicated patients with isolated OSA [82–84]. However, data for the use of auto-PAP machines to successfully titrate nocturnal hypoventilation in patients with non-OSA SRBDs is limited. The lack of carbon dioxide and oxygen monitoring by auto-PAP machines should at the minimum, be compensated for by use of nocturnal oximetry. Given the high prevalence of hypoventilation as well as combined SRBDs, the use of auto-PAP for titration in neuromuscular patients is viewed as suboptimal.

Sleep laboratory-based titrations in neuromuscular patients are typically based on guidelines from the American Academy of Sleep Medicine (AASM), which were published in 2010 for the titration of NPPV in patients with chronic alveolar hypoventilation [85] (Fig. 5.3).

Compliance Compliance with NPPV has shown to be a challenging limitation to therapy across all patient populations. Mask fit difficulties, discomfort, feelings of claustrophobia, and difficulty with swallowing are potentially magnified in the neuromuscular disease population.

Studies in the general OSA population have shown the quantity of NPPV usage within the first 30 days (and in particular the first week) of initiation to be strongly predictive of long-term compliance [86–88]. Improved NPPV adherence has been associated with patient education before, during or shortly after the initiation of CPAP therapy [89, 90]. Patient education focused on mask fit/adjustment, machine operation, and usage documentation is therefore a recommended practice parameter in all patients receiving NPPV therapy [91]. A randomized controlled trial in ALS patients demonstrated increased daily usage as well as improved quality of life measures in patients with early initiation of therapy [57, 78]. Further, compliance in ALS patients has shown to be improved with preserved bulbar function, preserved executive function, presence of orthopnea at therapy initiation [78].

While there is no definitive duration of nightly NPPV therapy necessary for maximal treatment benefit, studies in the general OSA population have shown greater than 6 h usage per night to achieve normal objective and self-reported measures of daytime sleepiness, and to improve memory and cognitive functioning [92–94]. While less data exist in the neuromuscular population, Lo Coco and colleagues demonstrated improved survival in ALS patients was independently related to NPPV use greater than or equal to 4 h daily [95]. As one would expect, increased compliance has been demonstrated in ALS patients with lesser bulbar involvement, and stronger nutritional status [95].

Summary

Neuromuscular disorders represent a broad spectrum of disease processes with a widely variable effect on clinical course and nocturnal respiration. It is crucial to consider each patient's clinical presentation when interpreting test result data implicating the need for ventilator assistance. Nocturnal noninvasive ventilation has been shown to improve quality of life and prolong life expectancy in patient populations such as ALS and DMD and likely carries similar benefit to patients with other neuromuscular diseases. While disease specific guidelines for the initiation of NPPV exist, the decision to initiate therapy is based on the combination of clinical suspicion for SRBD, patient symptoms, and evidence of daytime or nocturnal hypoventilation.

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Chapter 6
Nocturnal Noninvasive Ventilation in Children

Rakesh Bhattacharjee and David Gozal

Assessment of the historical trajectory of supportive ventilation in children would reveal a distinctive evolution of clinical practice over the past several decades. Classically, invasive mechanical ventilation, usually via a tracheostomy, was the mainstay management approach to disorders of ventilatory control, ranging from congenital central hypoventilation to infectious destruction of anterior horn cells, as is the case in poliomyelitis. However, with the advent of noninvasive ventilation in adults, its implementation in children was also initiated but has only recently emerged as an efficacious treatment of disordered breathing in children. This trend has particularly become apparent in the context of conditions in which supportive ventilation is only indicated at night, whereby the need for a permanent interface such as a tracheostomy can be obviated altogether, making the noninvasive approaches highly attractive.

Prior to any discussion of nocturnal noninvasive ventilation (nNIV) in children, it is imperative to acknowledge that familiarity with its use really stems from the vast experience of these devices in adults with sleep-disordered breathing (SDB). There is an abundance of research, as outlined elsewhere in this textbook, supporting its use in adults with SDB. Notwithstanding, the evidence, particularly from studies with large sample sizes, supporting nNIV use in managing SDB and other breathing disorders in children is sparse. Furthermore, despite the evidence from published studies, nNIV is not yet approved by the Food and Drug Administration for use in children weighing less than 30 kg.

In this chapter, we structure our discussion based on customary classifications of SDB in children, with the caveat that the treatment of these disorders overlaps to a large extent across the various conditions. We briefly introduce each of the major

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categories and conditions, and address their prevalence, challenges to diagnosis in children, and the efficacy of current treatment strategies including the indications for nNIV. We conclude with an analysis of the evidence that illustrates the unique hurdles that are emerging in the context of adherence among children using nNIV and finally present emerging evidence suggesting novel modalities that have become recently available.

Delineation of the specific indications for implementation of noninvasive ventilatory support in children has yet to be defined in a formal consensus statement, and there is clearly a pressing need for such guidelines as illustrated by the beneficial outcomes regarding neurocognitive deficits derived from use of nNIV in pediatric sleep apnea [1]. The indications for nocturnal noninvasive positive pressure ventilation are summarized in Table 6.1.

Before we specifically review the conditions associated with the potential need for noninvasive ventilatory support, a brief review of the equipment and specific issues pertaining to pediatric use merit attention.

Equipment

Interface Selection of the optimal interface is a critically important step aiming to secure patient compliance and effectiveness of treatment. The ideal interface should have minimal air leaks, and be very comfortable and easy to wear [2]. Multiple types of interfaces in pediatric use include nasal prongs, nasal masks, nasal pillows, oronasal masks, full-face masks, and helmets. Although mostly unpredictable, clinical factors affecting interface selection are patient age, neurological status, and the presence of pulmonary or facial abnormalities. For example, a nasal mask may not be appropriate for very young or uncooperative children considering the high probability of mouth air leaks. Similarly, the risk of emesis and aspiration in specific high-risk patients should be incorporated into the decision of implementing a full-face mask [3]. Infants and small children may optimally be treated with masks that have an appropriately calculated and sized dead space. In addition, we need to acknowledge that both mask type and size may have to be adjusted over time paralleling child somatic growth.

Circuit and Machine An open-system (single tubing) or closed-system (double tubing designated for inspiration and expiration) circuit is usually used and depends on the selection of the ventilator (i.e., time-cycled, pressure-limited, or volume-controlled). Volume-cycled ventilators provide the prescribed volume and will adjust the driving pressure as needed unless a high-pressure limit alarm is imposed. The major caveat to these systems is that they do not compensate for air leaks since the machine cannot differentiate between inspired gas and leaked gas, potentially resulting in reduced tidal volume delivery. In contrast, pressure-controlled machines compensate for small to medium air leaks. Pressure mode is usually preferred in

Table 6.1 Indications for nocturnal noninvasive positive pressure ventilation in children

Obstructive sleep apnea
Residual OSA in otherwise healthy children following adenotonsillectomy
Primary OSA due to factors other than adenotonsillar hypertrophy
Obesity
Macroglossia: Beckwith-Wiedemann syndrome, trisomy 21, and mucopolysaccharidosis
Midfacial hypoplasia syndromes: Crouzon, Apert, and Pfeiffer syndromes
Other facial skeletal defects: Pierre Robin sequence and Treacher Collins syndrome
Congenital or acquired upper airway hypotonia
Laryngomalacia, tracheomalacia, and laryngotracheobronchomalacia
Central apnea/hypoventilation
Congenital central hypoventilation
Congenital central hypoventilation syndrome (neonatal/early- and late-onset)
Rapid onset obesity, hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD)
Secondary to CNS structural anomalies: Chiari malformation type I and type II, hydrocephalus, and syringomyelia
Secondary to CNS injury during birth and cerebral palsy (severe asphyxia, CNS hemorrhage/stroke)
Other genetic conditions: Prader-Willi syndrome, Rett syndrome, familial dysautonomia, Joubert syndrome
Acquired central hypoventilation
CNS damage related to trauma, infection, bleeding, seizures, neoplasms, immune and post-infectious diseases, hypoxia/anoxia, storage diseases, metabolic diseases, and obesity
Neuromuscular disorders
Congenital neuropathies
E.g., spinal muscular atrophy types I, II, and III
Acquired neuropathies
Secondary to trauma, infection, immune, and postinfectious diseases
Metabolic diseases
Congenital myopathies
Duchenne and Becker muscular dystrophy, acid maltase deficiency, myotonic dystrophy, metabolic diseases
Acquired myopathies
Skeletal anomalies
Severe kyphoscoliosis, Jeune thoracic dystrophy
Lung and airway diseases
Cystic fibrosis
Bronchopulmonary dysplasia
Sickle cell disease
Acute asthma

OSA obstructive sleep apnea, *CNS* central nervous system

children due to the relatively large amount of wasted ventilation in the circuit. However, since the current noninvasive ventilators were designed for adults they are often not triggered by very small or weak children with low inspiratory flow rates or with high respiratory rates.

Modes

Continuous Positive Airway Pressure (CPAP) Positive pressure is delivered to the patient by continuous airflow and a pressure valve. This historically was the first method developed [4] to prevent airway closure throughout the respiratory cycle while improving functional residual capacity and reducing the work of breathing. In addition, CPAP normalizes pharyngeal dilator muscle activity during sleep in patients with obstructive sleep apnea (OSA) [5]. If cessation of breathing efforts (i.e., "central apnea") is a concern, CPAP is inadequate, and a titration study in the sleep laboratory or in hospital is required for an optimal mode and pressures to be defined.

Automatically Titrated Positive Airway Pressure (APAP) Here, the machine will continuously adjust delivery pressures as needed to eliminate defined respiratory events during sleep. Experience with APAP in children is scarce and not critically studied [6, 7].

Bi-level Positive Airway Pressure (BPAP) Ventilation BPAP is often prescribed in the management of central apnea/chronic hypoventilation in children [8]. Two fixed levels of pressure are delivered to the patient—a lower pressure during expiration (expiratory positive airway pressure; EPAP) and a higher pressure during inspiration (inspiratory positive airway pressure; IPAP)—thereby requiring triggering of the machine (assist, control, or assist-control modes are available in accordance with inherent issues pertaining to patient disease) by the patient and synchronization between the spontaneous respiration of the patient and the device. Concerning the latter, the inspiratory ramp slope and expiratory triggering valve setup may require specific adjustments in individualized situations [9].

Average Volume-Assured Pressure Support (AVAPS) This method combines volume- and pressure-controlled ventilation and was specifically developed for conditions during which BPAP with fixed pressure support may not sustain adequate ventilation over time. These recent modalities estimate the expiratory tidal volume and respond by adjusting the IPAP to preserve targeted alveolar ventilation [10]. To date, only one case report of AVAPS mode in children exists, which reported successful use in a 16-year-old child with congenital central hypoventilation syndrome (CCHS) [11].

Proportional-Assisted Ventilation Here, the volume or flow rate that the patient generates during inspiration is measured, and the ventilator will deliver inspiratory flow and pressure that closely tracks the child's spontaneous breathing effort [12]. Once determined by the clinician, the respiratory pattern is dialed (normal, obstructive, restrictive, or mixed) and all other machine variables are then programmed (CPAP, maximum pressure, maximum tidal volume, and percent assistance). Initial case-series studies in young infants and children with viral bronchiolitis and in premature infants appear promising in situations manifesting respiratory disturbances either during sleep, wakefulness, or both [13, 14].

Adaptive Servo-Ventilation (ASV) ASV was originally developed to treat Cheyne–Stokes breathing with central sleep apnea in adult patients with congestive heart failure, but no experience with ASV has been thus far reported in children with irregular breathing patterns [15]. We have recently implemented ASV in two children with Joubert syndrome who exhibited the characteristic and markedly erratic breathing patterns during sleep and waking with substantial improvements in overall gas exchange abnormalities [16, 17].

General Considerations

Air Leaks A major issue in nNIV is overcoming air leaks that result from mouth breathing or from poor interface selection and placement. Although the ventilators will compensate for leaks by increasing airflow, the presence of significant air leaks may lead to decreases in tidal volume delivery and to problems in triggering the ventilator, potentially compromising the child's respiratory status.

Humidification High flow rates of air and unidirectional inspiratory nasal airflow due to mouth leaks can lead to significant dryness of the nasal mucosa, potentially promoting substantial discomfort while also increasing the airway resistance [18]. Humidification of inspired gas, preferably with heated humidification, is an important consideration to optimize respiratory support, alleviate such nasal complications, and also to preserve mucociliary function. However, special attention to the proper care of the humidifiers is paramount to avoid potential risks of respiratory infection.

Oxygen Supplementation Supplemental oxygen can be provided to patients receiving nNIV in an effort to correct hypoxemia or when the patient does not tolerate higher pressures required to maintain adequate ventilation and oxygenation. We should emphasize that the FiO_2 that is generated by admixing oxygen to the circuit is generally unknown and potentially variable. Due to the uncertainty regarding the FiO_2 actually being provided to the patient, we advise the use of pulse oximetry monitoring for children who require supplemental oxygen with the nNIV.

Obstructive SDB in Children

Owing to heightened awareness to the potential ramifications of OSA in children, clinicians have become more inclined to screen children for snoring, the common presenting symptom of OSA. As a consequence, the prevalence of OSA in children has remarkably increased in recent years. It is estimated that 2–3 % of all children are affected with OSA, with a peak prevalence found in children aged between 2 and 8 years [19–26].

OSA is characterized by repeated episodes of prolonged increased upper airway resistance culminating in intermittent partial or complete obstruction of the upper airway during sleep. These events are accompanied by loud intermittent snoring, gasping during the night, and on occasion witnessed apneas. As a consequence of the disturbances provoked by periodic upper airway collapse, children with OSA develop an interruption to their normal sleep architecture as well as sustaining substantial alterations in normal gas exchange and ventilation, manifesting as recurrent, or decreases in oxygen saturation followed by rapid reoxygenation and episodic or sustained hypercapnia. Further, occlusion of the upper airway leads to large swings in intrathoracic pressures, which coupled with the effects of recurrent electrocortical arousals and episodic hypoxemia induce potent and sustained activation of sympathetic nervous system activity [27].

The net result of these various physiological disturbances is the emergence of several serious end organ morbidities in children afflicted with OSA, including neurocognitive and behavioral disturbances as well as cardiovascular and metabolic abnormalities [28–35]. For example, evidence from our laboratory has conclusively demonstrated that delays in the treatment of pediatric OSA may lead to persistent declines in cognitive function, as exemplified by reduced or failing academic performance [36]. Of equally significant concern, recent evidence points to the presence of cardiovascular morbidity in children with OSA [37]. Several studies have supported an association between pediatric OSA with endothelial dysfunction [38], a marker of subclinical cardiovascular disease, and systemic hypertension [39–42], pulmonary hypertension [43, 44], and myocardial left ventricular remodeling have all been reported [39, 44]. While these potential effects have only been recently described, the potential for even longer-term consequences of cardiovascular dysfunction in children in the context of OSA remains largely unknown. The potential for long-lasting consequences of OSA into adult life is particularly concerning since delays in the treatment of OSA including initiation of nNIV in children could plausibly result in a sustained dose-dependent effect for any of the morbidities cited.

Pathophysiology of OSA in Children

Prior to a discussion of the efficacy of treatment of childhood OSA, including the utility of nNIV, it is essential to summarily review the unique pathophysiological attributes of OSA in children. The cardinal abnormality associated with childhood OSA is the presence of hypertrophic adenotonsillar tissue. Enlargement of these tissues will reduce the anatomical patency of the upper airway and thus lead to exponential increases in pharyngeal resistance, ultimately resulting in episodic airway collapse during sleep, characteristic of OSA [45, 46]. While the presence of enlarged tonsils and adenoids does not uniformly and reliably predict the likelihood of OSA in children, [47] the concurrence of habitual snoring and adenotonsillar enlargement should serve as a major instigator of diagnostic inquiry to confirm or rule out the presence of OSA.

Notwithstanding, several other risk factors such as obesity, craniofacial, and neuromuscular elements may all independently contribute to the risk of OSA in children. The impact of obesity on the development of OSA in children is particularly topical given the extent of the obesity epidemic affecting children worldwide [48]. With obesity prevalence rates ranging from 7 to 22% of children in various Western countries, [49, 50] studies examining the prevalence of OSA have detected substantial increases in risk when obesity is concurrently present [51]. Indeed, for each increase of 1 kg/m^2 in BMI above the mean, the risk of OSA increases by 12% in children [52]. Consequently, multiple studies from all over the globe have consistently shown that the presence of obesity in children significantly increases the risk of OSA [53–56]. In fact, we have recently shown that the degree of adenotonsillar hypertrophy required is lesser in obese children at any given level of OSA severity [57]. Further complicating the scope of clinical practice, obesity-induced childhood OSA presents very differently from the classical OSA phenotype that is exclusively induced by adenotonsillar hypertrophy [58]. OSA in obese children strikingly resembles that of adult patients with OSA, who in their vast majority are obese, suggesting that similar mechanisms in adults and obese children lead to the clinical manifestations and morbid consequences of OSA in these patients.

Treatment of OSA in Children

In spite of robust progress in our knowledge on the complications of OSA, the same cannot be concluded in the context of a critical review of studies involving the treatment of OSA. In 2002, members of the American Academy of Pediatrics Task Force established that adenotonsillectomy should be considered as the first line treatment for pediatric OSA, and such assessment was based on descriptive uncontrolled patient series with no randomized studies being available [59]. After 10 years, this task force updated their recommendations, but no real changes emerged in their conclusions or the available evidence supporting them [60].

Notwithstanding the paucity of critically needed studies, the updated guidelines shed light into some of the potential limitations and pitfalls of adenotonsillectomy by providing a list of relative contraindications to this surgery (Fig. 6.1). Among these, the presence of small adenoids/tonsils (occupying < 25% of airway diameter for adenoids and + 1 size using common visual scales for tonsils [57]), particularly with the presence of concomitant morbid obesity with small adenoids/tonsils, the presence of submucosal cleft palate, and the presence of a bleeding dyscrasia that is refractory to treatment emerged. Similar to the 2002 guidelines, the more recent statement repeated the recommendation for follow-up evaluation after adenotonsillectomy including polysomnography for patients with persistent symptoms of residual obstructive SDB.

Current estimates aimed at predicting residual OSA following adenotonsillectomy have been based on four recent systematic meta-analyses, one large multicenter retrospective study, and one prospective randomized control study. In the

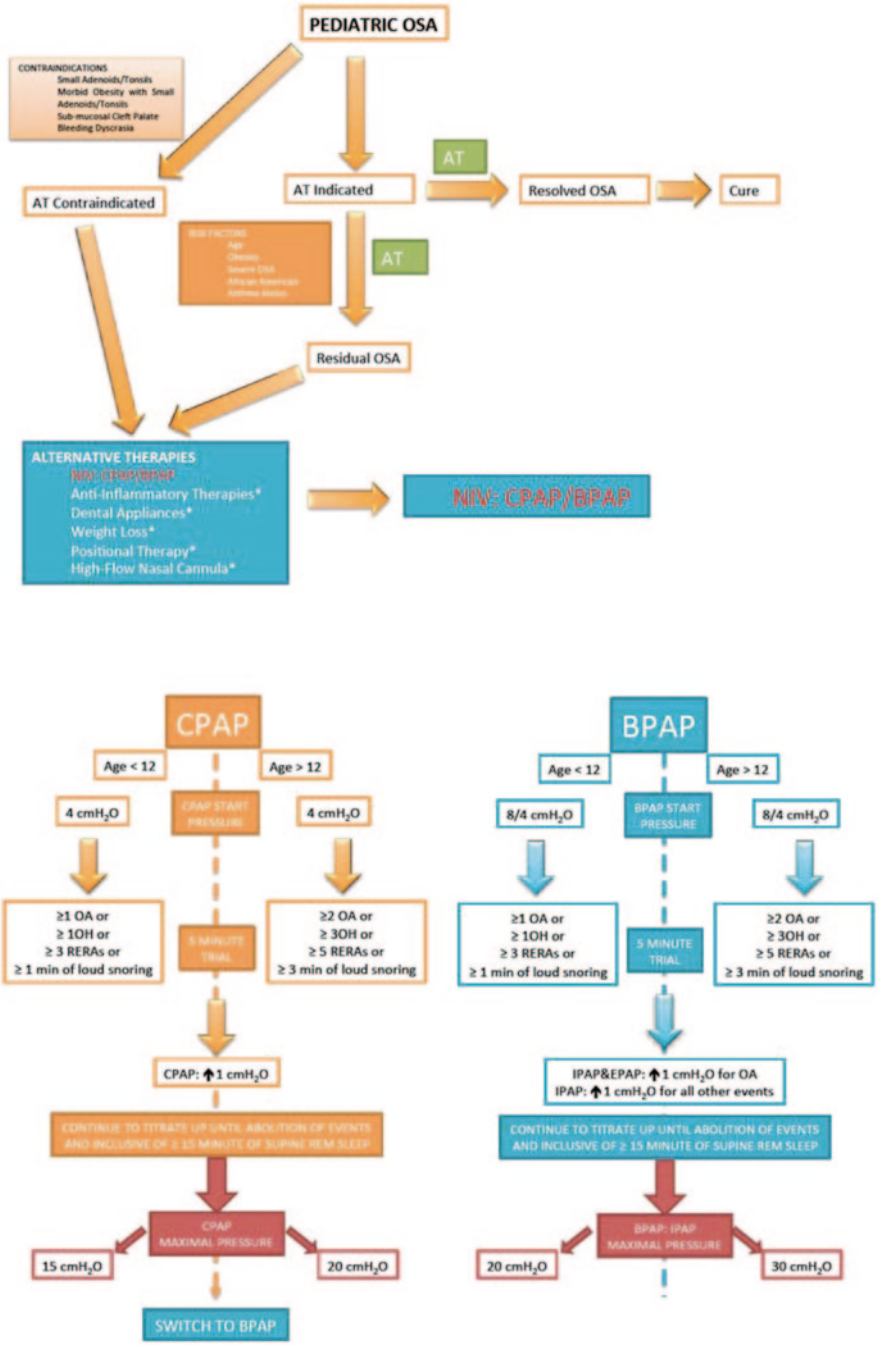

Fig. 6.1 Therapeutic algorithm for pediatric obstructive sleep apnea with titration protocol for nocturnal noninvasive ventilation. *OSA* obstructive sleep apnea, *AT* adenotonsillectomy, *NIV* noninvasive ventilation, *CPAP* continuous positive airway pressure, *BPAP* bi-level positive airway pressure, *IPAP* inspiratory positive airway pressure, *OA* obstructive apnea, *OH* obstructive hypopnea, *RERA* respiratory event related arousal. (Adapted from [144]; for a review of alternative therapies the reader is referred to reference [145])

first meta-analysis, we raised the concern that adenotonsillectomy may not be achieving as favorable outcomes as had been previously anticipated, with an estimated 15% failure rate [61]. Subsequently, Brietzke and Gallagher [62] critically reviewed 14 published studies and identified an overall "surgical success" rate of 82.9%. Unfortunately, as with the initial meta-analysis, this report included studies that had differing definitions of success, including many sleep studies that were technically suboptimal based on the standards of polysomnography outlined by the American Academy of Sleep Medicine (AASM) [63]. Expanding on this work, Friedman et al. [64] included nine additional studies with an emphasis on obese children. Using a weighted mean analysis, the mean apnea hypopnea index (AHI) improved from 18.6 to 4.9 events/h. Furthermore, using surgical success criteria of an AHI < 5/total sleep time (TST), only 66.2% normalized their sleep studies after the surgical procedure (95% CI 54.5–76.3%, $P = 0.007$), thereby indicating that > 30% of children had residual moderate to severe OSA following adenotonsillectomy. The major implication derived from this paper was to suggest that the presence of obesity in children diminishes the efficacy of adenotonsillectomy in the treatment of pediatric OSA. In the fourth and last available meta-analysis by Costa and Mitchell [65], the authors analyzed four studies that examined the efficacy of adenotonsillectomy exclusively among obese children with OSA. As a corollary to the previous meta-analyses, the presence of obesity curtailed the response to adenotonsillectomy with success emerging in only 38.5% of obese children and 51% of patients having a postoperative AHI > 5/h TST, that is the equivalent of moderate to severe residual OSA.

In a large multicenter retrospective study that included the participation of six pediatric sleep centers in the USA as well as two European pediatric sleep centers that routinely perform pre- and postoperative sleep studies, Bhattacharjee et al. [66] were able to critically evaluate potential demographic, clinical, and anthropometric confounding factors that may influence the postoperative AHI using multivariate logistic regression modeling approaches on a dataset that included 578 children. In this study, 27% of all children demonstrated complete resolution of OSA following adenotonsillectomy with a postoperative AHI < 1/h TST, and 22% had residual moderate to severe OSA with an AHI > 5/h TST. The strongest determining factors associated with residual OSA were older age, the presence of obesity, the presence of asthma, and finally the severity of underlying OSA prior to surgery (Fig. 6.1). The major contributions from this study were the improved delineation of groups at higher risk for surgical ineffectiveness who could therefore benefit from a postoperative polysomnogram (PSG) in order to ascertain either OSA resolution or residual OSA. In the context of a high prevalence of obesity in children, many children who undergo adenotonsillectomy for the treatment of OSA will be left with persistent SDB following surgery, and will therefore require additional treatment strategies including nNIV. Furthering the complexities of OSA in children, follow-up assessments in the large longitudinal cohort TuCASA study revealed that children with persistent OSA are at an elevated risk of developing obesity after 5 years [67].

Finally, in the single multicenter randomized control trial of adenotonsillectomy in children, involving 464 children (226 children undergoing surgery), it was found

that 79% of children undergoing adenotonsillectomy had successful resolution of OSA as defined by an AHI < 2/h TST, as compared with OSA resolution being recorded in 49% of control children who did not undergo any surgical intervention. Paralleling the finding from the aforementioned retrospective studies, the risk of residual OSA was again related to the presence of obesity and the underlying severity of SDB, but this study additionally determined that African-American children are particularly at high risk for residual OSA [68].

Therefore, even though the vast majority of children will demonstrate favorable responses to adenotonsillectomy in the treatment of OSA, the high prevalence of pediatric obesity would predict an ever increasing number of children [69] for whom adenotonsillectomy will either be contraindicated or unsuccessful. As such, a systematic implementation of approaches aiming to identify the large proportion of children with OSA in whom adenotonsillectomy will likely fail and who will require nonsurgical approaches [70] including nNIV as the mainstay of therapy is warranted. In children in whom adenotonsillectomy falls short of relieving obstructive breathing during sleep, including children with craniofacial anomalies, obesity, neuromuscular weakness, the application of nNIV (Fig. 6.1) including CPAP has expanded, particularly as our experience with these devices in treating children has grown. In one of the first reports in 1986 by Guilleminault and colleagues, nasal CPAP offered a novel alternative to tracheostomy in 10 young children with OSA [71]. In a review of practices from nine sleep centers across North America and one center in Europe, Marcus and colleagues [72] reported that as early as the mid-1990s CPAP was used, summarized in a series of 94 patients, ages 1–19 years. This cohort also included three children in whom an existing tracheostomy was successfully decannulated with the implementation of nNIV. In all but eight of the centers, nNIV represented the second line of treatment for OSA after adenotonsillectomy failed. In a similar study of 80 children, Waters and colleagues described a clinical protocol for introduction of CPAP to children including habituation procedures, as described above. In a study of 66 children, Masa and colleagues studied CPAP usage to treat OSA with an emphasis on close follow-up measures including telephone support, clinical assessments, and sleep studies at 1-month, 6-month, and 1-year intervals. Although adherence problems were clearly apparent, the feasibility of CPAP in a young pediatric population was documented. In studies by Downey et al., which included 18 children under the age of two, and McNamara et al., which included infants only, it was further confirmed that CPAP was an effective therapy in the youngest children with OSA.

Several recent studies have confirmed that BPAP in addition to CPAP can be successfully used to treat OSA in children. In a study by Marcus and colleagues [73], the efficacy of nNIV was examined in 29 children, of whom 13 were assigned CPAP and 16 were assigned to BPAP. While adherence was a concern due to a large proportion of dropouts, this study did not suggest any obvious differences in either CPAP or BPAP groups with respect to adherence or efficacy in treatment. Side effects were common in about 10–20% of children, primarily consisting of equipment or mask problems, symptoms related to mask leak, and skin erythema related to the mask. Symptoms of nasal congestion and/or epistaxis developed in 38% after 5 months of treatment.

Uong et al. [74] retrospectively examined 46 school-aged children and showed a significant reduction in AHI from 28.4 to 3.8/hr TST with the application of either CPAP or BPAP. Other parameters, including oxygen saturation nadir and elevated end tidal carbon dioxide levels also demonstrated significant improvements following the institution of nNIV. All symptoms of OSA included in the survey exhibited significant improvements following nNIV, including snoring, witnessed apnea enuresis, daytime somnolence, hyperactivity or behavioral problems, and deteriorating school performance. Adherence was available in 27 children, and adherence as defined by using nNIV for >4 h per night and ≥5 nights per week was only observed in 19 children (70%). In a randomized, double blind clinical trial comparing BPAP to CPAP in 56 consecutive children aged 2–16, Marcus et al. [75] randomized children in a 3:1 ratio of BPAP to CPAP. CPAP was shown to have equivalent efficacy to BPAP as the AHI was reduced from 22 to 2/h TST using CPAP, while BPAP improved the AHI from 18 to 2/h TST, with both treatment modalities resulting in small improvements in subjective sleepiness as measured by the modified Epworth Sleepiness Scale. While efficacy data in both CPAP and BPAP groups were promising, the low adherence rates with both CPAP and BPAP were discouraging.

The aforementioned studies all confirmed the polysomnographic efficacy of nNIV in the resolution of OSA; however, few studies have evaluated the efficacy of nNIV in alleviating the clinical symptoms of pediatric OSA. In a recent prospective study of 52 children, Marcus and colleagues employed surveys assessing neurobehavioral status, quality of life, subjective sleepiness, and surveillance of symptoms of attention deficit hyperactivity disorder (ADHD) at baseline and following 3 months in children with OSA who were treated with nNIV. In a contextual setting in which objectively measured adherence was suboptimal (mean adherence of 3 h/night), there were significant improvements in daytime sleepiness, symptoms of ADHD, and quality of life following 3 months of nNIV.

However, there is no doubt that the markedly limited wealth of information currently available in the setting of pediatric OSA treatment in general, and of nNIV use in particular, will require a concerted effort to address the most pressing and pending research and clinical issues if progress is to be made in the near future.

nNIV for Nocturnal Alveolar Hypoventilation in Children

Another major indication for the application of nNIV in children includes all of the extensive and markedly heterogeneous conditions that ultimately result in the emergence of nocturnal alveolar hypoventilation in children (Table 6.1). Salient conditions include the classic Congenital Central Hypoventilation Syndrome (CCHS) but also encompass congenital neuromuscular diseases, metabolic storage diseases including obesity, and musculoskeletal restriction of the thoracic cage as in the case of scoliosis or thoracic dystrophies. This marked variance in antecedents of nocturnal alveolar hypoventilation poses significant challenges to establishing universal practice parameters for the care of these children as the progression of disease and overall prognosis differ significantly.

As outlined by the International Classification of Sleep Disorders (ICSD-3; second edition) [76], nocturnal alveolar hypoventilation consists of reduced ventilation secondary to decreased tidal with ensuing isolated hypercapnia orhypercapnia, and as a manifestation of this variant of sleep-disturbed breathing, there often is accompanying sleep fragmentation related to increases in lighter sleep stage, transient arousals, and/or awakenings. Due to the muscular atonia of rapid eye movement (REM) sleep, in most disease states associated with nocturnal hypoventilation, the respiratory disturbance is most profound during REM sleep, except in CCHS, in which it is during non-rapid eye movement (NREM) stage 3 sleep that the more profound changes in ventilation are manifest.

The normative alveolar ventilatory parameters of children during sleep have only recently been defined. In a cross-sectional study of 542 children undergoing nocturnal polysomnography by Montgomery-Downs et al. [77], average nocturnal oxygen saturation, oxygen saturation nadir, and oxygen desaturation indices did not differ by age. Further, end-tidal carbon dioxide ($ETCO_2$) measurements captured by nocturnal polysomnography did not differ by age, with $ETCO_2$ being 40.7 mmHg. Twenty percent of the studies showed that children spent $\geq 50\%$ of TST with an $ETCO_2 \geq 45$ mmHg; 2.2% spent $\geq 50\%$ of TST with an $ETCO_2 \geq 50$ mmHg. These findings concur with previous smaller-sized studies assessing normative polysomnographic measures in children [78–80].

The ICSD-3 [76] establishes criteria for nocturnal hypoventilation largely based on oxygen saturation by pulse oximetry (SPO_2) during polysomnography, such that hypoventilation is defined by an SPO_2 during sleep of less than 90% for more than 5 min with a nadir of at least 85% or more than 30% of TST at an SPO_2 of less than 90%. Nocturnal hypoventilation is also defined by a sleeping arterial blood gas with a partial pressure of carbon dioxide (PCO_2) that is abnormally high or disproportionately higher than during wakefulness. The diagnostic criteria for children are exclusively defined by carbon dioxide monitoring measured during polysomnography. Specifically, the AASM scoring manual [63] defines alveolar hypoventilation during sleep as $>25\%$ of TST spent with a $PCO_2 > 50$ mmHg when measured by either the arterial PCO_2 or surrogate. Children, related largely to overall reduced pulmonary functional residual capacity, are especially prone to alveolar hypoventilation, leading to the recommendation for routine monitoring of carbon dioxide during pediatric polysomnography both during the diagnostic process as well as during the implementation of treatment [63].

Despite the aforementioned diagnostic criteria for alveolar hypoventilation, there is great variance in clinical practice regarding the parameters used for establishing nNIV as the mainstay of treatment of disorders associated with nocturnal hypoventilation in children. Recently, a task force put forth guidelines [9] for the treatment of hypoventilation syndromes in adults and children and largely focused on the titration of BPAP. While these efforts have provided a framework to the clinical practice regarding nNIV titration studies in disorders associated with nocturnal hypoventilation, they also stress the paucity of data concerning the timing of starting therapy, the standard of care for follow-up, and finally the efficacy of nNIV in treating nocturnal hypoventilation. Before we summarize the treatment of nocturnal hypoventilation, we here present a brief overview of the disorders of childhood that are associated with alveolar hypoventilation.

Nocturnal Hypoventilation in Neuromuscular Disorders: Pathophysiology

In the absence of large cross-sectional studies, the exact prevalence of alveolar hypoventilation has not been established in children with any of the more frequent neuromuscular disorders. For example, there are estimates that 27–62 % of children with Duchenne muscular dystrophy (DMD) display some form of SDB [81]. However, since there are no longitudinal assessments, such figures may be skewed and represent a later stage of disease, at a time when symptoms prompt referral to pulmonary services. The pathophysiology of SDB [82] in children with neuromuscular disorders is dependent mostly on the nature and severity of the underlying disorder, but is also affected by the patient's age, particularly if the disorder is progressive, and the type and extent of muscle involvement. Children with neuromuscular disorders have largely preserved central ventilatory drive with the exception of some children with myotonic dystrophy, in whom reduction in respiratory drive may be a component of the disease [83]. However, the overall loss of muscular tone, especially muscles that are integral to the respiratory system, begins an inexorable course that ultimately leads to profound disturbances of ventilation during sleep, even if respiratory muscle training and other rehabilitation approaches may slow down the process [84]. Furthermore, the atonia associated with REM sleep further accentuates the muscular weakness associated with neuromuscular disorders. Therefore, in conditions leading to intercostal muscle weakness, the loss of functional residual capacity (FRC) is augmented by the supine position of sleep, but this vulnerability during REM sleep leads to reduced oxygen reserves and an increased predisposition to carbon dioxide retention.

Neuromuscular disorders that amount to tonic deficits of the upper respiratory muscle such as in conditions of cerebral palsy, myotonic dystrophy, and sensory and motor neuropathies such as Charcot–Marie–Tooth or poliomyelitis are likely to contribute to the occurrence of obstructive SDB. Neuromuscular disorders such as DMD and Becker muscular dystrophy (BMD), mitochondrial myopathies, spinal muscular atrophy (SMA), cervical spine injuries, and metabolic and congenital myopathies are all associated with intercostal muscle weakness (sometimes preferentially affecting inspiratory or expiratory intercostals) that contribute to the pathogenesis of hypoventilation. In addition, certain disease states, including DMD and BMD, increase the risk of obesity or of disproportionate adipose tissue distribution in visceral and intramuscular regions even when BMI is preserved [85–87], and all children are at risk for adenotonsillar hypertrophy all of which further increase the risk for SDB. Taken together, the extent of SDB in children with neuromuscular disorders is largely contingent on the nature of the primary disease, more specifically the degree and nature of muscular insufficiency and the presence of disease-specific comorbidities [88]. In addition, related to intercostal muscular weakness, children with neuromuscular disorders often have an ineffective cough and ineffective airway clearance. Consequentially, pulmonary mucus plugging is a common occurrence in many children and predisposes children to recurrent pneumonias

and atelectasis that secondarily contribute to the onset of pulmonary scarring and respiratory insufficiency. Finally, the absence of sufficient muscle tone does not provide the necessary structural support to the ribcage, such that these children are often prone to impaired thoracic cage development manifesting as severe scoliosis, pectus excavatum, flattening of the antero–posterior chest diameter, and a funnel-shaped chest. As a consequence of these skeletal changes, there is a loss of chest wall compliance and subsequent reduction in pulmonary volumes including FRC, paradoxical breathing, and elevated work of breathing, all of which further predispose the child to nocturnal alveolar hypoventilation.

A complete review of the various neuromuscular disorders is beyond the scope of this chapter, but the reader is invited to peruse several reviews [82, 88, 89]. Nonetheless, while nNIV and invasive ventilation is the mainstay modality for treating SDB in these children, it is again emphasized that nocturnal alveolar hypoventilation in these children is not easy to detect and requires a high level of suspicion and also the implementation of systematic diagnostic approaches when possible while preserving individualized diagnostic and management decisions. Further, treatment of the nocturnal hypoventilation, once identified, is itself problematic.

Nocturnal Hypoventilation and Neuromuscular Disorders: Diagnosis

With the emergence of practice parameter guidelines related to DMD [81] and other congenital myopathies, it has been suggested that performing annual polysomnography to screen for nocturnal hypoventilation would be a sensitive and cost-effective approach with potentially improved outcomes. Since access to polysomnography poses a challenge to many children, the recommendations also encompassed the alternative use of overnight oximetry and continuous CO_2 monitoring (transcutaneous or end-tidal) or capillary blood gas testing in lieu of polysomnography in centers lacking pediatric polysomnography capabilities. Notwithstanding, clinicians are still advised to monitor for clinical symptoms of nocturnal alveolar hypoventilation (Table 6.2) during routine follow-up appointments. The American Thoracic Society [81] emphasizes that symptoms of SDB and sleep quality should be reviewed with each patient encounter. Finally, Gozal placed additional emphasis

Table 6.2 Clinical features of nocturnal alveolar hypoventilation in children

Dyspnea and/or shortness of breath
Diminished sleep quality: insomnia, frequent arousals, nightmares
Excessive daytime sleepiness
Orthopnea in patients with diaphragmatic dysfunction
Early morning or nocturnal headaches
Pulmonary complications: mucus plugging, atelectasis, recurrent pneumonia
Failure to thrive, reduced oral intake
Cor pulmonale

of the importance of a multidisciplinary approach to diagnosis and rehabilitation of patients with neuromuscular diseases including routine pulmonary function testing, nutritional, cardiac, orthopedic, and physical therapy assessments [88]. Such recommendations have gained substantial traction and are now widely implemented at major centers [90, 91].

The routine use of pulmonary function testing will often not only help tracking reductions in pulmonary volumes but is often an important adjunct for anticipation of nocturnal alveolar hypoventilation. For example, a forced expiratory volume in one second (FEV1) below 40 % predicted is moderately predictive of elevated base excess by 4 mmol/L, of an increased risk for the presence of PCO_2 above 54 mmHg, and for the occurrence of low daytime SpO_2 [92, 93].

Nocturnal Hypoventilation and Neuromuscular Disorders: Treatment

Most commonly, the initial treatment of hypoventilation in these children consists in the initiation and implementation of BPAP (Fig. 6.2). This approach has been shown to improve most parameters related to the presence of SDB, including severity of hypoxemia, the magnitude of carbon dioxide retention, as well as sleep efficiency, arousal index, sleep architecture, and overall sleep quality, with reductions in daytime sleepiness. Additionally, such nNIV usage is associated with a significant reduction in the frequency and severity of multiple morbidities, including a substantially lower number of hospitalizations and pneumonia episodes while improving quality of life, potentially prolonging survival.

In a study of nine infants/young children with SMA, Petrone and colleagues [94] found significant improvements in the oxygen desaturation index, mean transcutaneous CO_2, and thoracic abdominal muscular synchrony following just 10 days of BPAP. However, long-term outcomes of nNIV in children with neuromuscular disorders have been investigated in only a few small sized studies. Bach et al. [95] reported improvements in survival and fewer hospitalizations with nNIV in children with SMA. nNIV has been shown to be effective not only in reducing the frequency of pneumonia [96] but also in obviating the need for invasive ventilation, thereby promoting survival [97]. Mellies et al. [98] reported the long-term effects of nNIV on both nocturnal and diurnal gas exchange in 30 patients (mean age 12.3 years) with various neuromuscular disorders. This group reported improvements or normalization of nocturnal mean SpO_2 and transcutaneous PCO_2 as well as improvements in diurnal arterial tension of oxygen and carbon dioxide. In addition, this group reported significant reductions in nocturnal heart rate as well as improvements in sleep architecture. Similar improvements in gas exchange, prevention of atelectasis, and reductions in respiratory muscular work have been described in other long-term studies of children with neuromuscular disorders. As in other similar studies, Katz and colleagues retrospectively analyzed 15 children with various neuromuscular disorders and showed that nNIV led to significant reductions in hospitalization episodes, duration of hospitalizations, and admissions to

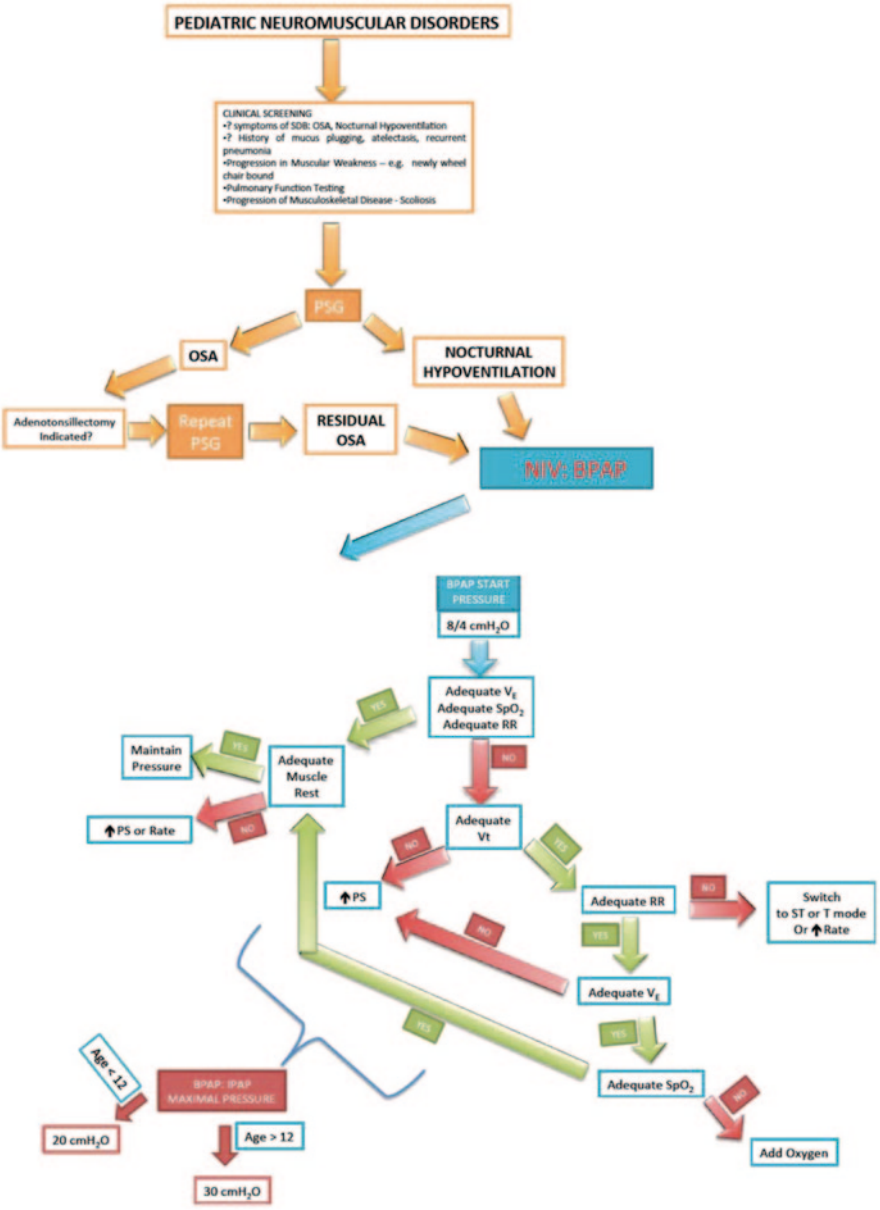

Fig. 6.2 Therapeutic algorithm for pediatric neuromuscular disorder with titration protocol for nNIV. *PSG* polysomnogram, *OSA* obstructive sleep apnea, *NIV* noninvasive ventilation, *BPAP* bi-level positive airway pressure, *IPAP* inspiratory positive airway pressure, V_E minute ventilation, *Vt* tidal volume, SpO_2 oxygen saturation, *RR* respiratory rate, *ST* spontaneous timed, *T* timed. (Adapted from [9])

the intensive care unit. In addition to improving the overall morbidity associated with neuromuscular disease, nNIV has shown to be efficacious in improving overall health quality in these children. In a retrospective review of 14 patients with various neuromuscular disorders, Young et al. [99] reported significant improvements in many symptoms of nocturnal hypoventilation in children aged 1.5–16 years using patient and parental questionnaires. There was a resolution of excessive daytime sleepiness in all children and significant improvements in the frequency of morning headaches. Quality of life was reported to be stable rather than steadily decline as would be anticipated by disease progression. Finally, these authors reported significant reduction in hospitalization rates and health-care costs following the institution of nNIV. Perez et al. further advocated nNIV therapy in 50 children with SMA or muscle myopathy as a method to improve rib cage development to further enhance pulmonary growth [100].

While the exact timing for nNIV initiation among children with neuromuscular disorders varies, the methods used for titration of nNIV parallel the recommendations as set out by the consensus guidelines [9]. In general, it is not advocated to use oxygen alone in the management of nocturnal alveolar hypoventilation, and if oxygen is added in addition to nNIV, this should be done in a carefully performed overnight polysomnography test (Fig. 6.2). Technological advances in nNIV have undoubtedly led to advances in the treatment of young children with neuromuscular disorders. Mask sizes now exist for infants as small as 4 kg. There has been an enhancement in the triggering sensitivity of several BPAP devices that now allow for more synchronized and less effort-dependent initiation of inspiration and overall ventilation in children. Notwithstanding, triggering and cycling problems, do remain significant issues in children on nNIV particularly when implemented in very young children and infants.

Nocturnal Hypoventilation: Central Hypoventilation Syndromes

a. Congenital Central Hypoventilation Syndrome (CCHS)

CCHS, a condition best defined as an idiopathic failure of automatic control of breathing, was first described in 1970 [101]. Whereas CCHS is classically considered a life threatening condition, the discovery of the genetic origin of the disease has revealed a much wider array of severity than originally thought. The primary manifestation is that of sleep-associated respiratory insufficiency and markedly impaired ventilatory response to hypercapnia and/or hypoxemia [102, 103]. Unlike the aforementioned neuromuscular disorders of hypoventilation, the pathophysiological hallmark of CCHS is hypoventilation that is most profound during quiet stage 3 NREM sleep, a sleep stage most classically associated with the automatic neural control of sleep. The variability of ventilatory insufficiency in CCHS can range from mild nocturnal hypoventilation to respiratory failure accompanied with sleep-related apneas and hypoventilation observed even during wakefulness.

In addition to profound disturbances of ventilation, CCHS is associated with broader impairment of the autonomic nervous system, Hirschsprung's disease, and neural crest derived tumors [104–108].

The putative-affected gene underlying CCHS, paired-link homeobox 2B (PHOX2B), has been described by Amiel and colleagues [109]. This gene plays a critical role in the embryologic development of the autonomic nervous system [110]. Mutations related to polyalanine expansions and nonpolyalanine repeat mutations have been characterized in CCHS [111, 112] and further recent evidence has led to an ability to predict phenotype including the severity of impaired ventilatory control with the underlying genotype, specifically the nature and extent of mutations in PHOX2B.

The cardinal features of CCHS, particularly early onset CCHS, are the presence of sleep-associated alveolar hypoventilation during quiet sleep and a presentation of symptoms during the first year of life [113]. In addition, a failed response to hypercapneic ventilatory challenges is typical. However, it has become increasingly apparent through enhanced diagnostic testing, including genotype identification, that milder forms of CCHS exist, including only mild alveolar hypoventilation during sleep, and as such the presentation may occur much later in life [114].

The treatment of CCHS is largely contingent on the underlying severity of ventilatory insufficiency. Despite the lack of evidence from large-sample-sized studies due to the exceptionally rare nature of this disease, there have been several published case reports and case series outlining various successful strategies of ventilation. In the context of severe alveolar hypoventilation during both wakefulness and sleep, the mainstay of treatment has been invasive ventilation using a permanent tracheostomy. However, there has been successful transition to nNIV particularly later in childhood (typically 4–7 years of age), particularly in cases where the burden of ventilator insufficiency is limited to sleep [102]. Further, recent evidence has also suggested successful application of nNIV in early childhood including young infants with CCHS [115–122].

b. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation (ROHHAD)

The condition termed ROHHAD is a novel disorder, even though it was first suggested as a separate entity in 1965 [123]. ROHHAD is characterized by a period of normal breathing patterns and growth during early life that is then accompanied by the sudden onset of hypothalamic dysfunction leading to hyperphagia and rapid weight gain. This is followed by development of autonomic dysregulation and later alveolar hypoventilation. The timing of alveolar hypoventilation varies with a median onset during early childhood (6 years of age) [124]. Unlike CCHS, there is currently no determinative genotype; however, the strong association with neural crest tumors implicates a very similar pathophysiological mechanism to CCHS, even if the gene or genes involved do not include PHOX2B. The multisystem nature of ROHHAD demands a multidisciplinary therapeutic approach and it is suggested that stabilization of central alveolar hypoventilation is best achieved by a pediatric sleep physician and/or pulmonologist [125]. We are not aware of any longitudinal

studies examining the efficacy of nNIV in children with ROHHAD; however, it is apparent that there are a subset of children with ROHHAD who are managed with continuous ventilation and some in whom nNIV represents an attractive paradigm, as supportive ventilation is usually indicated only at night [126, 127].

Central Sleep Apnea in Children

The etiology of central sleep apnea in children is variable ranging from neoplasms of the central nervous system [128], compression of the medullary respiratory centers related to a Chiari malformation type I [129–131], central neurological disorders including Rett syndrome [132], and can also be present in the context of more phenotypes of the normal physiological variant of periodic breathing [133]. While agreements in diagnosis and management recommendations in the context of OSA have overall been published, there is a scarcity of such algorithms for evaluation and treatment of central sleep apnea in children. To our knowledge, there are no published studies examining the efficacy of nNIV in treating pediatric central sleep apnea.

Response to Treatment: nNIV Adherence

The extent of the cumulative evidence regarding adherence in children is remarkable for its paucity, not surprisingly considering the relatively short experience of such noninvasive ventilatory support modalities in the pediatric age range. There have been very few studies evaluating nNIV adherence in children using objective criteria [74, 134]. Even when adherence in the hospital appears to be optimal, the overall utilization in the home appears to be quite different with substantial problems in adherence emerging [73, 135]. Here again, we will emphasize that noninvasive ventilatory support is not approved by the Food and Drug Administration for children younger than 7 years of age or weighing less than 40 lb (18 kg), even if off-label use does not seem to impose any incremental risk even in very young children at home [136]. The three major adherence measures we employ include the number of hours of actual use as a proportion of the duration of sleep, the number of nights per week using $\geq$6 h/night, and the overall total duration of use (months to years) [137]. A major problem with adherence estimates is that many studies are based on subjective reports, mostly overestimating actual usage [138], therefore stressing the importance of objective adherence monitoring in children. Factors affecting CPAP adherence have included the underlying disease characteristics and severity, psychosocial factors, socioeconomic status and parental education levels, implementation and titration procedures, mask type, pressure discomfort, perceived benefit, and nasal and ocular symptoms [134, 135, 138]. Indeed, the approach to improving adherence in children is multifactorial, including educational, technologi-

cal, and psychosocial facets of using nightly NIV [139]. Many children requiring nNIV have underlying chronic illnesses or developmental delays that may impose an additional layer of difficulties in optimizing long-term adherence. Many of these children will object to the caregiver efforts and may develop conditioned anxiety because of poorly fitting equipment and repeated association of the sight, sound, and sensation of nNIV with the discomfort from the mask, struggle, or both [140]. Considering the fact that parental assessment of nNIV use markedly overestimates actual use, efforts to improve adherence are more likely to fail in the context of such misperception, particularly among adolescents [141]. We and others will traditionally implement a period of acclimatization in the home environment as a useful strategy to achieve improved adherence and outcomes. Most studies have assessed adherence for only the first 3–6 months of treatment, and therefore data for long-term adherence are lacking. Nonetheless, identification of adherence, as early as in the first week of therapy, is predictive of long-term adherence, thereby implying that compliance therapy should commence as early as possible [142]. In settings of noncompliance, we recommend behavioral interventions using child life therapists and biobehavioral psychological techniques [143]. We routinely implement a period of home acclimatization to the equipment whereby children are provided with a practice mask and headgear to practice, and a gradual application of low-pressure therapy (5 cm H_2O) is then used for 2 weeks while awake and then while asleep to help the child habituate to the intervention. Once the child accepts low pressures through the night as indicated by the digital monitoring card in the machine, an overnight laboratory titration study is performed to determine the optimal pressures required. Finally, when comparing BPAP to CPAP with regard to adherence data in a small, randomized, double-blinded trial of 56 children, Marcus et al. reported no differences in adherence with either technology, further illustrating the multidimensional facets of nNIV adherence. Since children continue to grow, the pressure setting requirements may change and should be therefore periodically ascertained with titration polysomnography. Ensuring adequate pressure settings in nNIV to restore normal SDB likely contributes to enhancing long-term adherence.

Summary

We have shown that while nNIV treatment of SDB in many children would be considered “off-label,” there is certainly a plethora of indications supporting the use of nNIV in children of all ages. The paucity of longitudinal and large cohort-sized studies remains the central limitation in the field and precludes the promulgation of evidence-based standards of care for all children treated with nNIV. In the context of increasing experience in the implementation of nNIV in children, the push for universal standards of care will likely require multicenter investigational approaches in which outcomes of nNIV for each distinct indication will need to be carefully examined. Until then, the approach to managing a child with nNIV is perhaps most appropriately assumed by experienced pediatric sleep physicians.

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Chapter 7
Nocturnal Noninvasive Ventilation and Adjuncts in Disorders of Breathing Control

Robert Joseph Thomas

Ventilation management for central sleep apnea syndromes is challenging. Respiratory rate, volume and rhythms are such primordial life processes that they do not take kindly to external manipulation. In this chapter, the term "non-invasive ventilation" refers to positive airway pressure therapies for disorders of respiratory control characterized by abnormally high or low respiratory chemosensitivity. The focus here is primarily disorders of high chemosensitivity, [1] which can be conceptualized as "High Chemosensitivity Sleep Apnea" (HCSA) for convenience and includes central sleep apnea, periodic breathing, ventilation-induced respiratory instability, and complex sleep apnea (Fig. 7.1). The problem of opiate-induced sleep apnea will also be discussed; other disorders of reduced ventilatory chemosensitivity are discussed elsewhere in this book.

Sleep and Respiratory Control

Non-rapid eye movement (NREM) sleep unmasks a highly sensitive hypocapnia-induced apneic threshold, whereby apnea is initiated by small transient reductions in arterial CO_2 partial pressure ($PaCO_2$) below eupnoea, and respiratory rhythm is not restored until $PaCO_2$ has risen significantly above eupneic levels [2–10]. The CO_2 reserve (the difference in $PaCO_2$ between eupnoea and the apneic threshold, determined by plant gain (the change in blood gasses in relation to change in ventilation) and controller gain (the change in ventilation/respiratory driuve in relation to change in O_2/CO_2; the ventilatory responsiveness to CO_2 above eupnoea) is a key determinant of breathing instability in sleep. The CO_2 reserve varies inversely with both plant gain and the slope of the ventilatory response to reduced CO_2 below eupnoea. The reserve is highly labile in NREM sleep [4]. Reductions in cerebrovascular

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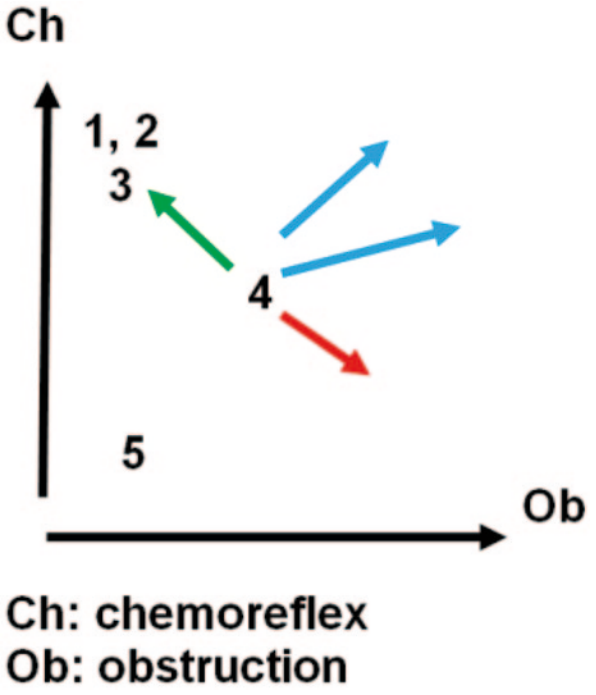

Fig. 7.1 Spectrum of sleep apnea (*SA*) syndromes along the obstruction vs. chemoreflex axis. *1* idiopathic central sleep apnea (ICSA). *2* high-altitude SA. *3* congestive heart failure with nearly pure Cheyne-Stokes breathing. *4* NREM-dominant obstructive SA. *5* hypoventilation syndromes. *6* REM-dominant SA. There is an intrinsic dynamism in this group. Examples: CPAP can shift towards central apnea (*green* arrow, may reach threshold for currently defined complex SA); acetazolamide, O_2 or CO_2 can shift to a more pure obstructive phenotype and thus CPAP responsiveness (*red* arrow); the worst outcome could be both worsening obstruction and heightened chemosensitivity (*blue* arrows), such as weight gain + congestive heart failure (the latter group can demonstrate the whole range of obstruction and chemosensitivity)

responsiveness to CO_2 result in a gain in chemoreflex control of sleep-breathing, and may also play an important role in mediating respiratory instability during sleep [11–13]. Both central (especially the ventral medullary surface) and peripheral (especially carotid body) chemoreceptors are known to mediate chemoreflex control of respiration [7, 14–17]. During the wake state, top-down influences including from the cortex are important determinants of ventilation. During sleep, the system largely functions automatically during NREM sleep, while REM sleep seems to have unique respiration characteristics. Studies that have tried to dissociate the central and peripheral components seem to suggest that rapid responses are dependent on the peripheral chemoreceptors [7, 9, 18].

Respiratory Chemoreflex Enhancement and Disease

A primary increase in the slope of the respiratory chemoreflexes is best described with the hypercapnic ventilatory response. The quintessential disorder is "idiopathic central sleep apnea" (ICSA)—a rare sleep disorder, where the single consistent abnormality is an increased slope of the hypercapnic response [19–22]. An increase that is at least partially reversible in hypoxic and hypercapnic ventilatory responses occurs in obstructive sleep apnea syndromes [23]. Hypoxia, heart failure, or increased pulmonary vascular pressures all increase the slope of the CO_2 response below eupnoea and narrow the CO_2 reserve despite an accompanying hyperventilation and reduced plant gain [4]. An absence of the normal rise in CO_2 (which may be determined by end-tidal measurements using a non-vented oronasal mask or blood gas analysis) at sleep onset is also characteristic of central sleep apnea syndromes [10]. There is recent evidence that patients with "mixed" sleep apnea, that is, showing a substantial central sleep apnea component admixed with the obstructive components, have increased CO_2 response slopes below eupnea and a narrow CO_2 reserve during sleep but not differences in airway collapsibility [24]. In this study, patients with conventional central sleep apnea were excluded. A substantial component of obstructive sleep apnea severity is mediated by enhanced chemosensitivity [25–30]. Partial responders to upper airway surgery have been reported to have enhanced chemoreflexes [31].

Trait Versus State Components of the Respiratory Chemoreflex

A fundamental question is whether we are dealing with a transient phenomenon or a disease pathophysiology unlikely to remit. There is ample evidence of ***genetic/trait*** effects on respiratory chemoreflexes, although the effects on sleep-respiration were not evaluated in many of these reports [32–50]. Certain mice and rat strains are highly susceptible (or resistant) to periodic breathing following hypoxic exposure [41, 51]. Several knockout mice have altered (usually blunted) hypoxic [52–61] and hypercapnic [62] sensitivity. Evidence for genetic/trait effects in humans include: (1) Individual differences in hypoxic ventilatory sensitivity and its correlation with altitude-induced periodic breathing [63]. (2) Familial clustering of chemoreflex sensitivity [35, 38, 39, 49, 50, 64–67]. (3) Ventilatory instability during sleep onset in healthy individuals being greater in those with high peripheral chemosensitivity [68].

State effects are also important: (1) Hypoxic ventilatory responses to sustained hypoxia including at altitude [69–75]. (2) Increased prevalence of mixed forms of sleep apnea poststroke, in heart failure and increased chemoreflex sensitivity in periodic breathing associated with congestive heart failure or poststroke [16, 76]. (3) A reduction of periodic breathing occurring following cardiac transplantation

[77, 78]. (4) An increase of central apneas occuring with age [77–79]. However, chemoreflexes have been reported to be reduced in the elderly, [80–82] so that the mechanisms may be more complicated. (5) Post-tracheostomy central sleep apnea that reduces in severity over time [83, 84]. (6) Recent evidence from a dog model of acute pulmonary venous hypertension suggesting that increases in left ventricular end-diastolic pressure (LVEDP) may reduce CO_2 reserve [85]. Of possible relevance, systolic and diastolic cardiac dysfunction is common in severe sleep apnea, [86, 87] but obesity, age, and hypertension are confounders [88]. (7) A 30 % overnight increase in chemoreflex sensitivities having been reported in sleep apnea, whereas in the non-apnea group there was a significant overnight reduction in chemoreflex thresholds (approximately 5 %), without changes in sensitivities [89]. (8) Changes in hypercapnic ventilatory response (HCVR) (reduced sensitivity) having been reported following therapy of obstructive [90–92] but not central sleep apnea [90–92]. Reduction in hypoxic ventilatory response (HVR) but not HCVR was recently reported following 4 weeks positive airway pressure therapy for obstructive sleep apnea [93], while NREM CO_2 reserves improves within a month [23].

Men have a higher awake hypercapnic ventilatory response, lighter and more easily disrupted sleep, and develop apnea with much smaller changes in CO_2 than women, which explains higher prevalence of central sleep apnea syndromes among men [94–96]

Polysomnographic Recognition of NREM-Dominant Obstructive Sleep Apnea

The first description of central apneas following continuous positive airway pressure (CPAP) treatment probably came from Marrone et al. who reported the occurrence of central apneas, hypopneas, periodic breathing, and prolonged oxygen desaturations in patients who were started on CPAP. These events occurred in NREM and almost exclusively after arousals or wakefulness periods [97]. The concept was revived in the mid 2000s, with an emphasis of the NREM dominance of disease [98]. The term “complexity” in the context of sleep-disordered breathing was first applied to articulate the problems of conflicting therapeutic principles, with upper airway support for obstructed breathing amplifying respiratory chemosensitivity [99]. It was subsequently proposed that the development of central apnea during titration of CPAP is a “defining characteristic” of complex sleep apnea, with a threshold of 5 or greater central apneas and hypopneas per hour of sleep making up greater than 50 % of all respiratory events [100]. This was then adopted by centers for medicare services and most insurers in the United States. As discussed below, this definition is a core cause of controversy in the field. Though associated with CPAP treatment in the classic description, this phenom-

enon has also been observed with non-positive airway pressure (PAP) treatments for OSA, including tracheostomy, maxillomandibular advancement surgery, mandibular advancement devices, and other forms of surgical relief [101–103]. Although in most patients, the central apneas emerged only after application after CPAP [99], there is an argument to expand the definition to include emergence of central events in situations other than CPAP therapy.

In this obstructive sleep apnea subset, the demands on the respiratory control systems expose control instabilities and present themselves as a NREM-dominant sleep apnea phenotype [98]. Consequences include a poor response to CPAP, [98] fragmented sleep that is disproportionate to the effects of sleep apnea, and a strong association with anxiety, depression, and hypertension [102]. The polysomnographic phenotype is more reminiscent of the type of sleep apnea seen at high altitude (short cycle time, 25–30 s) [104] than in congestive heart failure [105].

Scoring of respiratory events in sleep apnea patients have traditionally been biased to an obstructive phenotype, though the recent (2012) update of the 2007 American Academy of Sleep Medicine (AASM) guidelines has proposed criteria for scoring "central" hypopneas and short sequences of periodic breathing/Cheyne-Stokes breathing [106]. The guidelines state that "central" hypopneas should not be scored in the presence of flow-limitation, but obstruction is a common feature of central events, [107] even at simulated altitude, [108] the latter being a relatively pure model of chemoreflex-driven sleep apnea. Direct visualization of the upper airway shows collapse at the nadir of the cycle to be common even in polysomnographic "central" respiratory events [109]. Expiratory pharyngeal narrowing occurs during central hypocapnic hypopnea, [110] directly supporting the concept that the presence of flow-limitation alone cannot be used to distinguish obstructive and central hypopneas [108]. Complex sleep apnea as currently "defined" requires a central apnea-hypopnea index ≥ 5/h of sleep with centrally mediated respiratory events constituting ≥ 50 % of all respiratory events during CPAP titration for obstructive sleep apnea, in those who do not fulfill criteria for primary central sleep apnea or periodic breathing on the diagnostic polysomnogram. However, publications of complex apnea did not score "central" hypopneas or periodic breathing. ***Thus, descriptions of low (< 5 %) persistence of "complex apnea" may not be accurate, as this is usually based on scoring central apneas alone, and not central hypopneas or periodic breathing*** [111, 112]. In our center, at least 15–20 % of obstructive sleep apnea not related to congestive heart failure is recognized to be NREM-dominant. The guidelines for recognition of "Cheyne-Stokes breathing" also require a cycle duration of at least 40 s, but we have shown that even shorter cycle times in the range of 20–25 s is typical of NREM-dominant sleep apnea, [98] reminiscent of high altitude periodic breathing. ***The most characteristic feature of chemoreflex driving is not the morphology of individual events but NREM-dominance and timing/morphology of sequential events (nearly identical) in a consecutive series of events*** [113] (Figs. 7.2, 7.3).

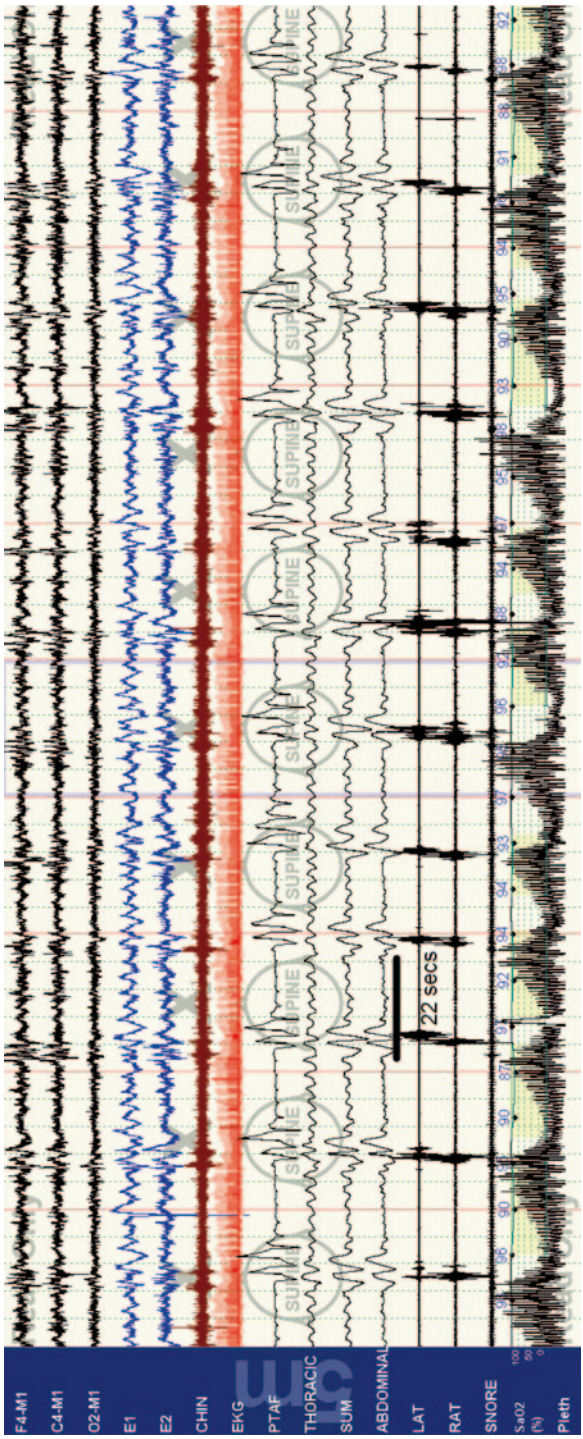

Fig. 7.2 Polysomnographic phenotype of chemoreflex driving of sleep apnea. By conventional scoring criteria, these are obstructive respiratory events. However, closer inspection should reveal the following features that are characteristic of NREM-dominant obstructive sleep apnea, which is a presentation of chemoreflex-driven sleep apnea. Note: (1) Self-similar/clone-like respiratory events and pathological oscillations, including hypopneas, electromyographic tone rise and fall, electroencephalographic arousals, and in the finger plethysmographic signal. (2) The respiratory events are short cycle, averaging 20–22 s, strongly reminiscent of high altitude periodic breathing cycle times. Oxygenation is mildly impaired due to the short cycle time of respiratory event—there is not enough time to develop deep desaturations unless cardiopulmonary reserve is impaired. This pattern, if recognized, has an increased risk of positive pressure-induced or amplified respiratory instability

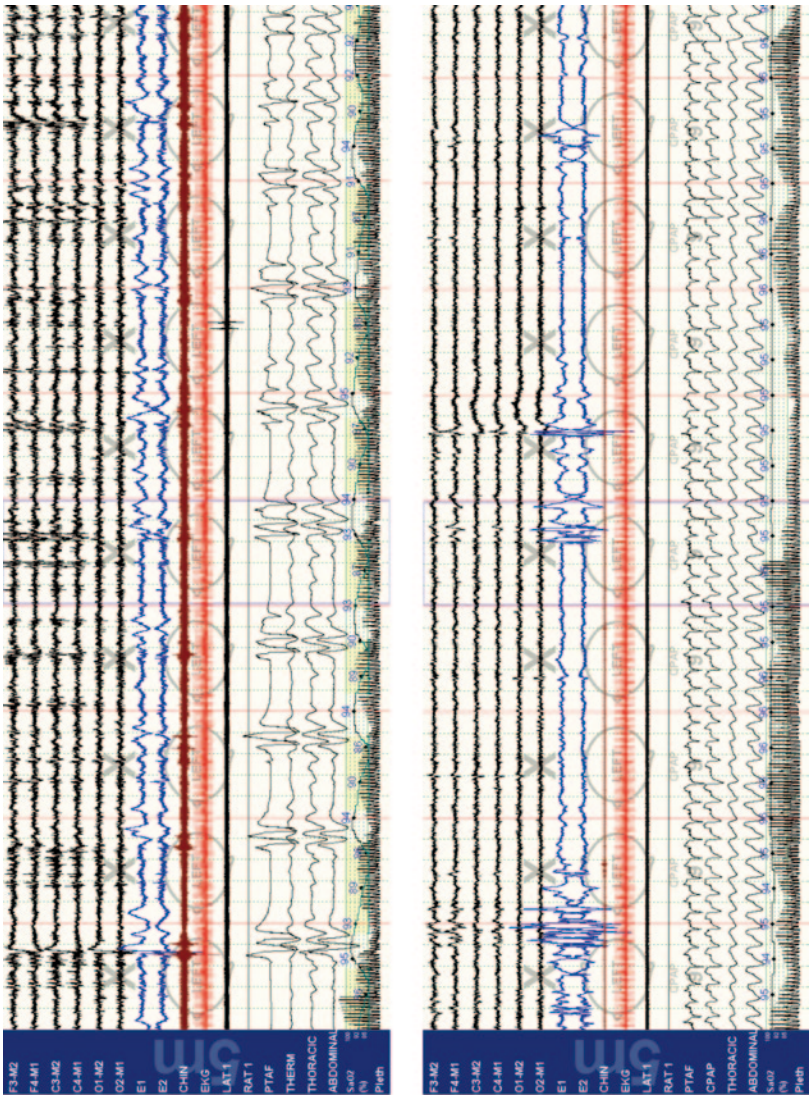

Fig. 7.3 Polysomnographic phenotype of chemoreflex driving of sleep apnea: REM vs. NREM differences. Note (*upper*, **a**) short cycle respiratory events with a self-similar morphology and timing, yet "obstructive" by any criteria. When the same subject enters REM sleep (*lower*, **b**), the respiratory events "disappear". This sequence is highly reminiscent of periodic breathing at high altitude. Body position here is unchanged

The ICSD-3 Contribution: Lumping vs. Splitting

The recently published *International Classification of Sleep Disorders*, 3rd Edition has a new category of treatment-emergent CSA (TE-CSA) [114]. The requirement is for a central apnea index of 5 or more/hour of sleep and the central events

greater than 50% of all scored events. The term complex apnea has been avoided, but the classifications schema allows multiple diagnoses in the same patient, e.g., TE-CAS, OSA and periodic breathing, or periodic breathing, and OSA. This is a "splitting" approach driven by event morphology, which has already been noted to have serious limitations (such that scoring central hypopneas are "optional"), while the term "complex apnea" is a lumping driven by pathophysiology. The merits of the approaches can be debated, but the ICSD-3, based on classic scoring approaches, likely under-recognizes the contribution of enhanced respiratory chemoreflexes to pathogenesis of sleep apnea, which is an important issue as treatment approaches and criteria for treatment success are impacted. More data will settle the issue, but for now the author suggests keeping an open mind, recognizing NREM-dominance, and other tell-tale signs of respiratory chemoreflex activation. These signs include short cycle (30 s or less) of respiratory events, band-like oxygen desaturation (several consecutive desaturation points being identical), periodic breathing regardless of flow-limitation, and EEG arousals in the middle of the respiratory recovery sequence [115]. In general, induction of central apneas and thus meeting the criteria for TE-CSA is not required to recognize strong respiratory chemoreflex driving of sleep apnea.

Quantification of Pathological Chemoreflex Activation During Sleep

How can the effects of an enhanced respiratory chemoreflex be quantified? Daytime testing such as hypoxic and hypercapnic ventilatory responses, measurements of muscle sympathetic nerve activity, serum or 24-h urine catecholamine levels, and heart rate variability measures are not precise enough in individual subjects but can distinguish groups. During sleep, assessment of the output of the respiratory chemoreflexes can take two general approaches. In one approach, that of "provocation," various maneuvers are used to induce instability during periods of stability [27, 116]. These include the use of proportional assist ventilation, [117, 118] partial obstruction by pressure dial down, [29] and using bilevel-ventilation to induce hypocapnia [10]. An alternate approach is that of "spectral mapping," which has a focus on low frequency oscillations that dominate light or fragmented sleep in health and disease [119, 120]. The core principle is that when the respiratory chemoreflexes are hyper-responsive, the induced metronomic autonomic/respiratory/hemodynamic oscillations demonstrate a narrow-band feature on spectral analysis (highly limited dispersion of frequencies) [113]. Such patterns are typical of congestive heart failure- associated periodic breathing.

Clinical Implications of Pathological Respiratory Chemoreflex Activation During Sleep

Several studies have estimated the prevalence of complex sleep apnea syndrome (central sleep apnea >5/hr on CPAP) to be in the range of 13–15% in the general sleep center patient population [100, 121–124]. Endo et al. reported prevalence of complex sleep apnea in 5% of Japanese patients, which is lower than reported prevalence in USA and Australia [125]. These patients were mostly male and had maintenance insomnia complaints [124]. They had disturbed sleep and excessive daytime sleepiness [126]. Risk factors for high chemosensitivity forms of sleep apnea (idiopathic central sleep apnea, complex apnea, periodic breathing) include male sex, history of cardiac disease and central sleep apnea on baseline polysomnogram [121]. Although in some patients the apnea-hypopnea index improved over time, many maintained a persistently elevated index with abnormal oximetry. These patients tend to be leaner and sleepier. They also report more air hunger, a sensation of "dyspnea" which may reflect ventilator-patient asynchrony or awakenings at the end of a central apnea, and CPAP mask removal. Other risk factors include higher age, higher baseline apnea-hypopnea index and central apnea index, hypertension, coronary artery disease, stroke and congestive heart failure [127]. In another large retrospective study, severity of sleep apnea and use of opioids were noted to be potential risk factors for complex sleep apnea [112]. However, patients with positive pressure-emergent complex apnea are clinically heterogeneous and one third of patients do not have any risk factors prior to sleep studies [127]. Compliance with CPAP is low and residual machine-detected apnea-hypopnea index high in patients with NREM-dominant sleep apnea.

Natural History of Pathological Respiratory Chemoreflex Activation During Sleep

It is not clear what proportion of complex sleep apnea patients improve over time with continued CPAP treatment. Dernaika et al. in a prospective case-control study documented disappearance of central sleep apnea activity with CPAP in 86% (12/14) of patients over 2–3 months. However, this finding may not be generally applicable because of small size and their exclusion criteria [128]. Seven of their initial 21 patients were CPAP intolerant or lost to follow-up which suggests possible complex sleep apnea in these patients. Similar findings were reported in a study by Kuzniar et al. [122]. In the largest prospective study performed to date, Cassel et al. reported resolution of complex apnea in some patients, but also reported de novo appearance of the pattern in patients who did not have such characteristics initially [129]. Ultimately, it comes down to the criteria for "persistence"—wave form analysis from current generation positive pressure devices provide us a unique tool to quantify persistent periodic breathing or central apneas and answer this question

conclusively. It does seem that persistence of pure central apneas at a high frequency decreases over time [112]. In this study, a strict definition (flat line flow and effort on the polysomnogram) of residual central disease (no scoring of central hypopneas or periodic breathing) was used.

Treatment of Pathological Respiratory Chemoreflex Activation During Sleep

The core goals of treatment of sleep apnea syndromes are normalization of sleep architecture and sleep respiration, including oxygenation and ventilation. Only by addressing upper airway obstruction, respiratory control dysregulation, and sleep fragmentation propensity is successful treatment of HCSA achievable. Each patient is unique in the contribution of these individual elements and the phenotype should drive therapeutic decision making. Weight loss and good sleep hygiene play an important role in the management. Weight loss can reduce the positive pressure requirements and in turn pressure-related hypocapnia and respiratory instability. Sleep onset instability is amplified in patients with apnea in general, and can be especially prominent in those with HCSA syndromes. Poor sleep hygiene or a mismatch between social and biological sleep times (such as in patients with delayed circadian phase syndrome) can increase sleep fragmentation, sleep-wake transitions, and potentially adversely and disproportionately impact HCSA management.

Positive Pressure Therapies—Adaptive Ventilation

More often than not, CPAP is ineffective in patients with HCSA syndromes. (Fig. 7.4). Supporting ventilation during central apneas and stabilizing PCO_2 fluctuations has proven successful in treating central and complex sleep apnea. Adaptive Servo-ventilation (ASV) devices are adaptive bilevel positive airway pressure devices introduced in the last decade for treatment of central and complex sleep apnea syndromes. Non-randomized evaluations show the two USA-marketed devices to be equally effective:, the VPAP-AdaptSV® (ResMed Corp, San Diego, CA) and BiPAP-AutoSV® (Phillips-Respironics, Murrayville, PA) [130]. Use of adaptive ventilation in complex apnea patients and central sleep apne/periodic breathing in patients with congestive heart failure (CHF) improved sleep apnea as well as cardiac function parameters [131]. Treatment with ASV is clearly better tolerated than CPAP in patient with TE-CSA or complex sleep apnea more broadly defined, and in patient with congestive heart failure. In these patient groups, adaptive ventilation is more effective in suppressing central apneas and improving oxygenation than CPAP, but residual disease remains high and positive effects on sleepiness, quality of life, and sleep architecture are less impressive [132]. The criteria for success and the respiratory event scoring criteria (usually 4% desaturation association for

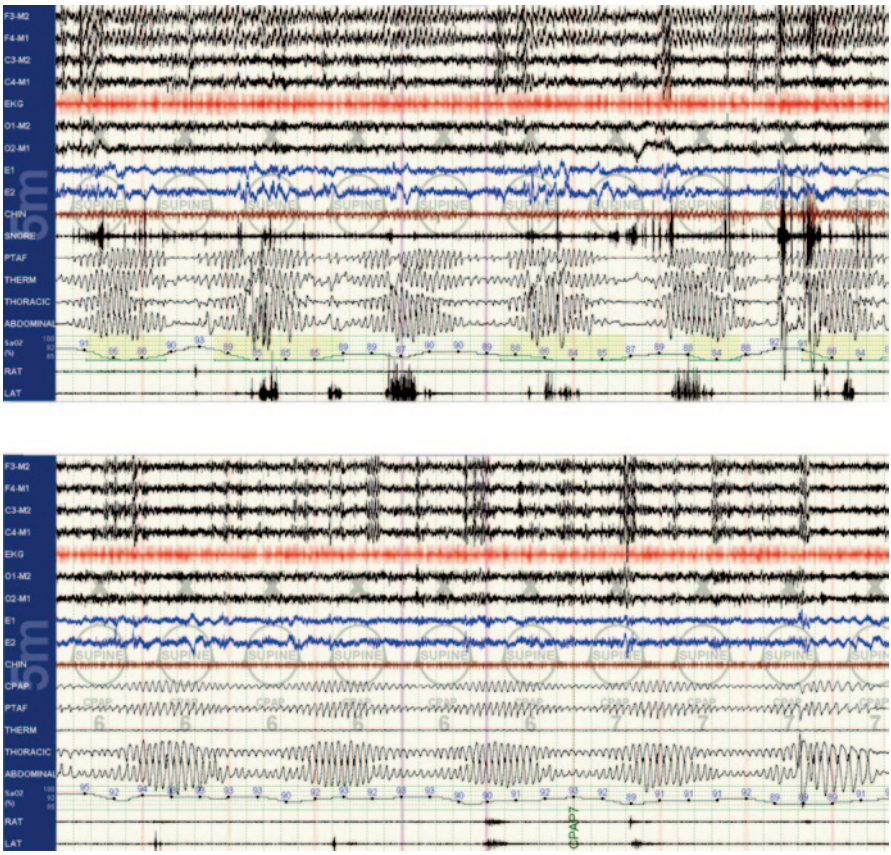

Fig. 7.4 Periodic breathing/Cheyne-Stokes respiration with obstruction and CPAP effects. Note (*upper*, **a**) long cycle periodic breathing in this patient with congestive heart failure. Snoring is seen during respiratory events; narrowing of the airway is common in such patients. There is minor ongoing respiratory effort, enough to drive upper airway vibrations. When CPAP is applied (*lower*, **b**), the basic long cycle periodic breathing pattern persists

hypopneas) can overestimate effectiveness. Two recent reviews provide in-depth summaries of current device algorithms and clinical utilization [133, 134]. These powerful devices allow a range of adjustments, have complex algorithms, and are used in patients with respiratory dyscontrol, where breathing rhythms span the obstructive, central, and ataxic spectrum. Substantial theoretical knowledge, hands-on practice with devices, and skills in recognition of polysomnographic patterns are required for optimal use of these devices (Box 7.1). The results of the Servo Ventilation in Heart Failure trial (SERVE-HF), with lack of benefit and increase in mortality in patients with a low ejection fraction or Cheyne-Stokes breathing suggest the need to better understand patterns and implications of pressure cycling / patient-ventilator desynchrony and other adverse consequences of adaptive ventilation, including hypocapnia and arousals in vulnerable patients, such as those with reduced ejection fraction.

How to Titrate Adaptive Ventilation

One option is to simply allow the device algorithm to function "wide open". A physician could request this mode for part of the night. For the Adapt SV that would mean an EPAP minimum of 4 and maximum of 15 cms H_2O, and a minimum/maximum pressure support of 5 and 15 cms H_2O respectively. For the BiPAP Auto SV that would mean an EPAP minimum/maximum of 4 and 20 cms H_2O, a minimum pressure support of 4 cms and maximum pressure support of 25 cms H_2O, also setting the inspiratory-maximum pressure of 25 cms H_2O. At the end of the titration, the following targets are to be achieved, and thus the technician's efforts need to be directed to provide the following information.

1. What is the optimal expiratory support? This may be a challenge in those who have chemoreflex-mediated disease in NREM sleep and obstructive events in REM sleep. In that instance, higher EPAP than needed in NREM sleep or cautious use of narrow range auto-EPAP may be considered.
2. What is the minimum pressure support that does not trigger respiratory instability? A reasonable default is 3 cms H_2O for both adaptive ventilators. If this level of inspiratory support worsens periodic breathing or central apnea and the pattern is maintained despite use of adequate adaptive space, several approaches are open: changing mode of the AV (see next paragraph), non-supine positioning, adding supplemental O_2, use of a NV mask, or moving back to CPAP (often with adjuncts—O_2, NV mask, non-supine positioning).
3. What is the optimal mode of the AV? My personal experience in the sleep laboratory is that the degree of device-induced pressure cycling is worse when the Adapt SV is used with a 0 minimum support (the "minimum maximum" is still 5 cms H_2O; thus, 3 cms is H_2O is preferred as minimum pressure support). However, more titrations need to be done with the mode to be sure of efficacy or lack of it. The BiPAP Auto SV with a 0 inspiratory minimum pressure support does not seems to be a problem, but is not clearly superior.
4. What should these modes be called? It is arbitrary, but Mode I uses "some" minimum inspiratory pressure support and Mode II uses none. I choose these as above because it is the mode more likely to be actually used.
5. What is the minimum inspiratory pressure support and what inspiratory pressure support is required to treat inspiratory flow limitation or snoring? The Adapt SV is a default of 5, maximum of 25. The BiPAP Auto SV minimum is zero, the maximum pressure possible is 25 cms H_2O. The minimum EPAP for the Auto SV is 4 cms; the minimum EPAP for the Adapt SV is 3 cms.
6. Is body positioning critical? A subset of patients is absolutely uncontrollable with any current modality, singly or in combination, during unstable supine N2 sleep.
7. Was supplemental O2 required to stabilize respiratory rhythm?

8. If a NV approach was used, was additional dead space/Enhanced Expiratory Rebreathing Space required, and what was the ETCO2 at baseline/NREM sleep and REM sleep at optimal settings?
9. Was sleep fragmentation an independent problem?
10. I personally think that the auto EPAP function is largely not helpful; the issue is rarely inadequate EPAP or indeterminable EPAP. Moreover, while auto-EPAP is "finding its way" the adaptive function also tries to chase its own targets leading to desynchrony with patient effort. Moderate EPAP (e.g., 5, 6, or 7) is reasonable to start.
11. Increase pressure support minimum for inspiratory flow-limitation and snoring. If no improvement after 3–4 cms increase, reduce to 3 cms, increase EPAP, and repeat sequence.
12. Pressure support maximum is increased to increase adaptive "power"—if pressure cycling increases and persists, reduce this component.
13. When using EERS or O2 with adaptive ventilation—stabilization efforts can alternate between gas/pressure steps.
14. Rate control: auto function in BiPAP Auto SV and the native rate of Adapt SV are reasonable. Speeding or slowing of the patient's native rate by 3–4 or more breaths per minute can be a sign of developing desynchrony.

Devices

The ResMed Adapt SV [135–139] provides a baseline degree of ventilatory support. The subject's ventilation is servo controlled with a high-gain integral controller (0.3 cm H_2O per L/min per second, clipped to 4–10 cm H_2O) to equal a moving target ventilation of 90% of the long-term average ventilation (time constant 3 min). If the subject suddenly ceases all central respiratory effort, machine support (i.e., pressure swing amplitude) will increase from the minimum of 4 cm H_2O up to whatever is required to maintain ventilation at about 90% of the long-term average (up to a maximum of 10 cm H_2O, reached in approximately 12 s). In the CPAP mode the pressure can be set at 4–20 cm H_2O. In the ASV and ASV auto mode EPAP may be set as: 4–15 cm H_2O; pressure support (PS): 0–20 cm H_2O, but the pressure will not exceed 25 cm H_2O. The Auto mode is an auto EPAP. The previous restrictions to PS, such as a minimum support of 3 cm, have been removed with the most recent versions of the software. Algorithm changes will likely continue, to improve patient-ventilator synchrony, such as to dealing with slow breathing rates (current back-up default is 15/minute) and slew rates (maximum rate at which target ventilation can rise, currently 0.01389 L min/sec) [133].

The Philips Respironics BiPAP autoSV Advanced (flow-targeted dynamic bilevel positive pressure ventilator) provides PAP support to sustain upper-airway patency [140–142]. The current version is the "Advanced", which has auto-CPAP and thus an EPAP minimum and maximum setting. The maximum inspiratory support level is up to 30 cm H_2O minus the expiratory pressure. The expiratory pressure automatically adjusts within the available (or prescribed) range (4–25 cm H_2O). Expiratory

pressures can also be set at fixed levels if desired. The algorithm's automatic backup rate is based on calculations performed on a moving window of the last 12 spontaneous breaths. The flow-targeted dynamic Bilevel PAP device modulates the maximum and minimum PS above the EPAP as required to maintain a target peak inspiratory airflow: when the device detects normal breathing, flow-targeted dynamic BPAP operates like conventional CPAP by providing the minimal PS; when the patient does not maintain the target peak inspiratory airflow, the device increases the PS up to a maximum IPAP, which can be set by the user. Peak flow is captured on a breath-by-breath basis and is monitored over a moving 4-min window; as one breath is added, the initial breath falls off. At every point within this 4-min period an average peak flow is calculated, and the peak flow target is established around that average and is based on the patient's needs. The device also provides an automatic backup rate should sustained apnea be detected. To avoid hyperventilating the patient and to promote spontaneous breathing, the target inspiratory flow is set to below the mean inspiratory flow during spontaneous breathing by the patient and the timing of the backup rate begins with time delay and is set to a slower rate than the average respiratory rate of the patient. The current version of the device (BiPAP Auto SV Advanced) allows expiratory pressure relief, where the pressure drops during early expiration in an attempt to improve patient comfort, and rise time (period of time in milliseconds for the pressure to increase to 67% of the difference from end EPAP to maximum inspiratory pressure) when the pressure relief mode is not enabled [133].

The Weinmann SOMN*Ovent* CR is available in Europe and combines auto and adaptive pressure [143]. The pressure is measured using a pressure sensor, snoring is calculated based on the high-frequency variations of the pressure signal, and the flow is determined based on pressure and blower parameters. The minute ventilation is compared with the average minute ventilation in a moving window and is focused by 50% on the last 2 min and by 50% on the previous time. The treatment mode is called *anticyclic modulated ventilation*. Apneas are defined by a cessation of breathing for more than 10 s. Hypopneas are detected if the minute ventilation is reduced by 40% for at least two breaths as compared to the average minute ventilation or if the peak flow is reduced by 50% as compared to the average peak flow. Obstructive and central events are discriminated based on the recognition of flattening of the flow curve and on the reaction on additional PS: obstructions are detected by an increased need for respiratory support with flattening or snoring or by time-cycled breath insufficient to generate flow. The device applies three pressure levels: the IPAP, which represents the pressure level during inspiration; the EPAP, which represents the pressure level in the early expiration; and the end-expiratory positive airway pressure (EEPAP). The EEPAP regulation is based on the cumulative sum of obstructions within a 2-min epoch, not on single events. During periodic hypopneas the algorithm increases the difference between IPAP and EPAP continuously to raise the tidal volume. During hyperventilation the difference between IPAP and EPAP is reduced and can reach CPAP level (zero difference between IPAP and EPAP). During apneas, mandatory breaths are applied automatically. The frequency of these breaths depends on the baseline respiratory frequency of the patients. The physician can choose a manually fixed instead of automatic backup frequency. In addition, the device uses pressure relief during expiration in the course of normal breathing.

Recognition and Scoring of Respiratory Abnormality During Adaptive Ventilation

Scoring respiratory events during adaptive ventilation needs to use the pressure output signal from the ventilator. This is roughly equal and opposite the patient's abnormality. The flow and effort signals combine patient and ventilator contributions and give a false sense of success. See Fig. 7.5 for excessive "pressure cycling," which is the response of the adaptive ventilator to ongoing periodic breathing. When pressure cycling persists, sleep fragmentation is usually severe even if respiration is "improved." This pattern means than periodic breathing pathology is ongoing, necessitating the continued pressure response.

Challenges of Titration with Adaptive Ventilation

1. Treating upper airway obstruction can induce or worsen periodic breathing and central apneas, even with these ventilators.
2. Using the auto EPAP module allows the inspiratory component of the algorithm to induce respiratory oscillations during the EPAP titration period that can in turn cause flow-limitation—thus triggering inappropriate auto-CPAP responses. My default recommendation is to not use this functionality, but manually titrate EPAP. However, others recommend using the auto EPAP mode, and individual sleep laboratories can choose one approach over the other as the initial option.
3. Excessive minimum inspiratory support will induce hypocapnia and respiratory instability, which will trigger the back-up rate and induce patient-ventilator desynchrony.
4. Excessive maximum inspiratory pressures may induce pressure discomfort and arousals, besides hypocapnia.
5. Inadequate minimum or maximum inspiratory pressures will cause inspiratory airflow obstruction and futile triggering of the algorithm.
6. Inadequate "span" of inspiratory maximum and minimum pressures (the "adaptive space") will stifle the adaptive algorithm.
7. With all adaptive ventilation approaches, there is a distinct risk of trading-off airflow and oxygenation/ventilation improvements for sleep quality. This risk is not specific to adaptive ventilators per se, but true for other non-invasive ventilation approaches.
8. Occasionally, periodic breathing is induced during REM sleep as obstructions or the normal tidal volume fluctuations of the state trigger the adaptive algorithms. The best response is to increase EPAP first, then IPAP, or if there are no arousals, to just leave it be.
9. One of the most complex functions of adaptive ventilation is the inspiration to expiration switch. Manufacturers use some combination of "human physiological limits," rate of change in inspiratory flow, detected respiratory rate or other proprietary algorithms.

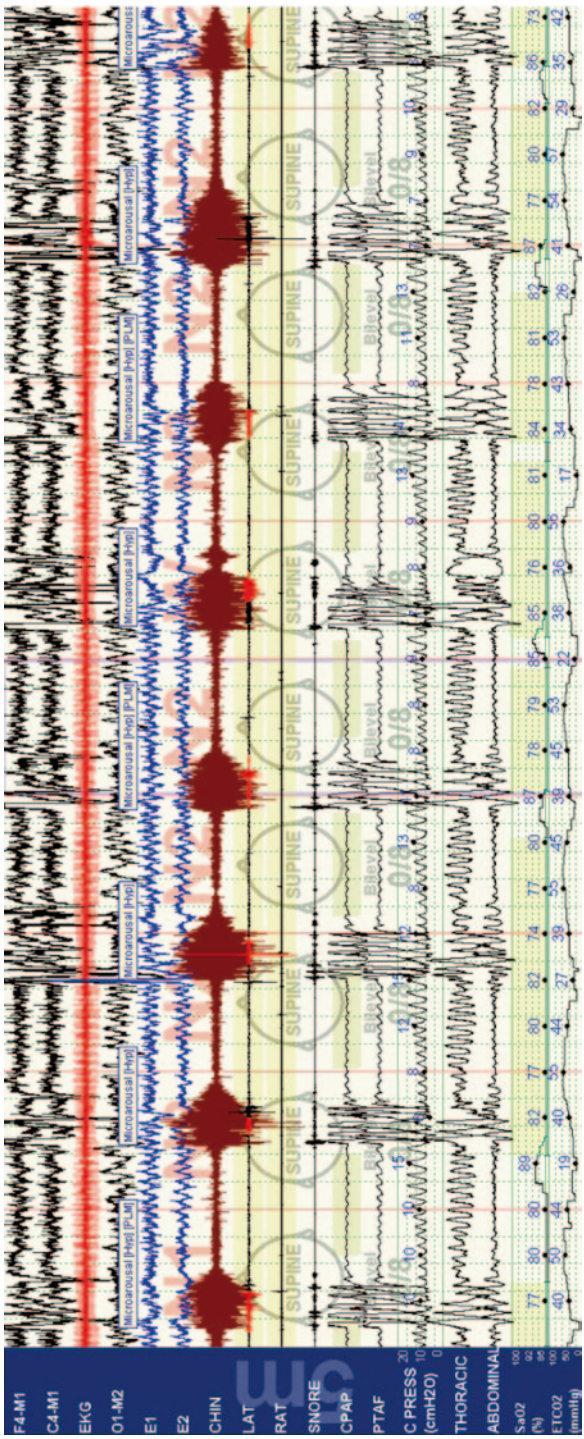

Fig. 7.5 Pressure cycling with adaptive ventilation. The snapshot shows uncontrolled periodic breathing which is unresponsive to all modes of positive pressure, including adaptive ventilation. The ResMed Adapt SV has a characteristic waveform that requires measuring and display of the device's pressure output (C PRESS in the snapshot above) that is best described as "pressure cycling." While such cycling is expected and appropriate at the start of implementation of adaptive ventilation, persistence reflects inability of the device to convert periodic breathing to stable breathing. i.e., the device keeps responding to periodic breathing rather than treating the underlying pathology. Supplemental oxygen, non-supine positioning, acetazolamide and a non-vented mask/enhanced expiratory rebreathing space (dead space added to positive pressure ventilation) can all reduce or eliminate pressure cycling. Mild pressure cycling without associated arousals is seen when the adaptive ventilation treatment is successful. The Phillips-Respironics BiPAP Auto SV is somewhat less prone to pressure cycling, and when it does, the saw-tooth pressure waveform is not seen. See Fig. 7.6 for a comparison of CPAP and both adaptive ventilators in the same patient

Minimization of Hypocapnia

The use of supplemental CO_2 for hypocapnic central sleep apnea syndromes is old news. That CO_2 can stabilize respiration has been known for decades, but high concentrations fragment sleeps by inducing arousals secondary to respiratory stimulation and sympathoexcitation [144, 145]. The key challenge has been delivery of CO_2 in a clinically adequate, tolerated, and precise manner. Prevention of hypocapnia is a critical stabilizing factor in sleep respiratory control. "Minimization of hypocapnia" is also physiologically a more appropriate phrase that "induction of hypercapnia" as the latter is utterly unnecessary. The key is holding the CO_2 steady and just above the NREM sleep CO_2 threshold—protecting the CO_2 reserve.

A recent study by Xie et al. is one of the best demonstrations of the power of CO_2 modulation in treating sleep apnea syndromes [146]. Twenty-six patients with obstructive sleep apnea (AHI 42 ± 5 events/hour with 92 % of apneas obstructive) were treated with O_2 supplementation, an isocapnic rebreathing system in which CO_2 was added only during hyperpnea to prevent transient hypocapnia, and a continuous rebreathing system. Each patient's controller gain below eupnea was measured, as was CO_2 reserve, plant gain, and passive upper airway closing pressure. With isocapnic rebreathing, 14/26 reduced their apnea-hypopnea index (AHI) to 31 ± 6 % of control ($p < 0.01$) (responders); 12/26 did not show significant change (non-responder). The responders vs. non-responders had a greater controller gain, a smaller CO_2 reserve but no differences in Pcrit. Hypercapnic rebreathing (+4.2 ± 1 mmHg $PETCO_2$) reduced AHI to 15 ± 4 % of control ($P < 0.001$) in 17/21 subjects with a wide range of CO_2 reserve. Hyperoxia (SaO_2 ~ 95–98 %) reduced AHI to 36 ± 11 % of control in 7/19 OSA patients tested.

Thus, there is strong evidence from multiple studies over the years that manipulation of arterial CO_2 levels might provide an alternative treatment strategy. Addition of a closed volume (space) to exhale increases rebreathing of the exhaled air and results in a rapid increase in arterial CO_2 levels and an increased tidal volume and respiratory rate. This is similar to breathing into a bag when trying to treat anxiety-induced hyperventilation. Increased amounts (> 300 mL) manifestly feel uncomfortable from both CO_2 retention and volume effects. The concept has been used in mechanical ventilation to reduce hypocapnia for several years and more recently has been successfully used to treat central sleep apnea and Cheyne-Stokes respiration in heart failure. None of these uses combine it with positive airway pressure.

We have shown that keeping CO_2 above the apnea threshold with the use of enhanced expiratory rebreathing space (EERS) is an effective adjunct to continuous positive airway pressure therapy in patients with pressure-induced respiratory instability across CSA and periodic breathing phenotypes [102]. The EERS approach is also a useful adjunct to adaptive ventilation, which is described later in this chapter. Enhanced xpiratory rebreathing space is the dead space concept applied to pressure ventilation. Positive airway pressure therapy usually induces mild relative to pretreatment hypocapnia. Central apneas and periodic breathing can be generated when the arterial PCO_2 level falls below that required to stimulate respiration. This

level is referred to as the *apnea threshold*. Hypocapnia at or near the apnea or CO_2 control threshold destabilizes sleep-breathing control, resulting in periodic breathing patterns of various severities and morphological characteristics. Preventing hypocapnia is a powerful stabilizing influence on sleep-breathing control, regardless of the presence of hypoxia. Atmospheric CO_2 levels are near zero, therefore the CO_2 levels in the blood are the result of the balance between metabolism in the patient and blow-off during breathing.

The clinical effect of using EERS is gratifying and this approach is now routinely available in our sleep laboratory to use with CPAP or adaptive ventilation, as requested by the physician (Fig. 7.6, 7.7). We described in our original report improved clinical tolerance, compliance and sustained clinical improvement monitored over period of several months by adding EERS to CPAP [102]; since our original publication, we have successfully added EERS to adaptive ventilation in the sleep laboratory and for home use (unpublished). EERS was initially evaluated and used in a subgroup of patients who had stopped using CPAP, and in whom effective treatment was salvaged with the use of EERS. The fundamental idea is that sub-tidal volume dead space would be adequate when the upper airway was also supported, i.e., a synergism between positive pressure and prevention of hypocapnia. Control was achieved with minimal increase in CO_2 (0–0.5 mm Hg) which we speculate, judging by the beneficial effects seen within 20–30 s, is due to the effect on carotid chemoreceptors.

There is strictly no true dead space when this concept is used with mask pressure ventilation. Mixing, turbulence, and leaks ensure variable degrees of effective rebreathing (thus the suggested term *enhanced expiratory rebreathing space*). There is, however, a reduction in ventilatory blow-off, with remarkable clinical effectiveness. There is no, or minimal, increase in inspiratory CO_2 because of the positive pressure-induced washout. One important practical effect of using positive airway pressure with enhanced expiratory rebreathing space is that the respiratory rate seems unchanged, and the subject does not notice any significant discomfort. This is not surprising, given the known effects of positive pressure support on relieving shortness of breath in mechanically ventilated patients. Such symptoms minimization is obviously important when considering use in patients who are already short of breath, such as in heart failure.

The physiological target for titrations with enhanced expiratory rebreathing space is to maintain $ETCO_2$ at the low normal range for sleep. Normal sleep results in an increase of 2–8 mm Hg in $ETCO_2$. With this technique the target is to keep the $ETCO_2$ in the high 30 s to low 40 s, the lower end of normal for patients with hypocapnic central sleep apnea and periodic breathing. Those with central and mixed sleep-disordered breathing show a prominent tendency to hypocapnia during sleep.

The primary monitoring is that of $ETCO_2$ with a mainstream CO_2 sensor at the mask. Transcutaneous CO_2 may usefully complement end-tidal measures but is not critical for treatment of hypocapnic central/complex sleep apnea. Transcutaneous measurements can have a role in hypercapnic central apnea management. A biocalibration of $ETCO_2$ is done before sleep study (1–2 min rested steady breathing, average final 10 breaths), with a nonvented (NV) mask and 50, 100, and 150 mL add-

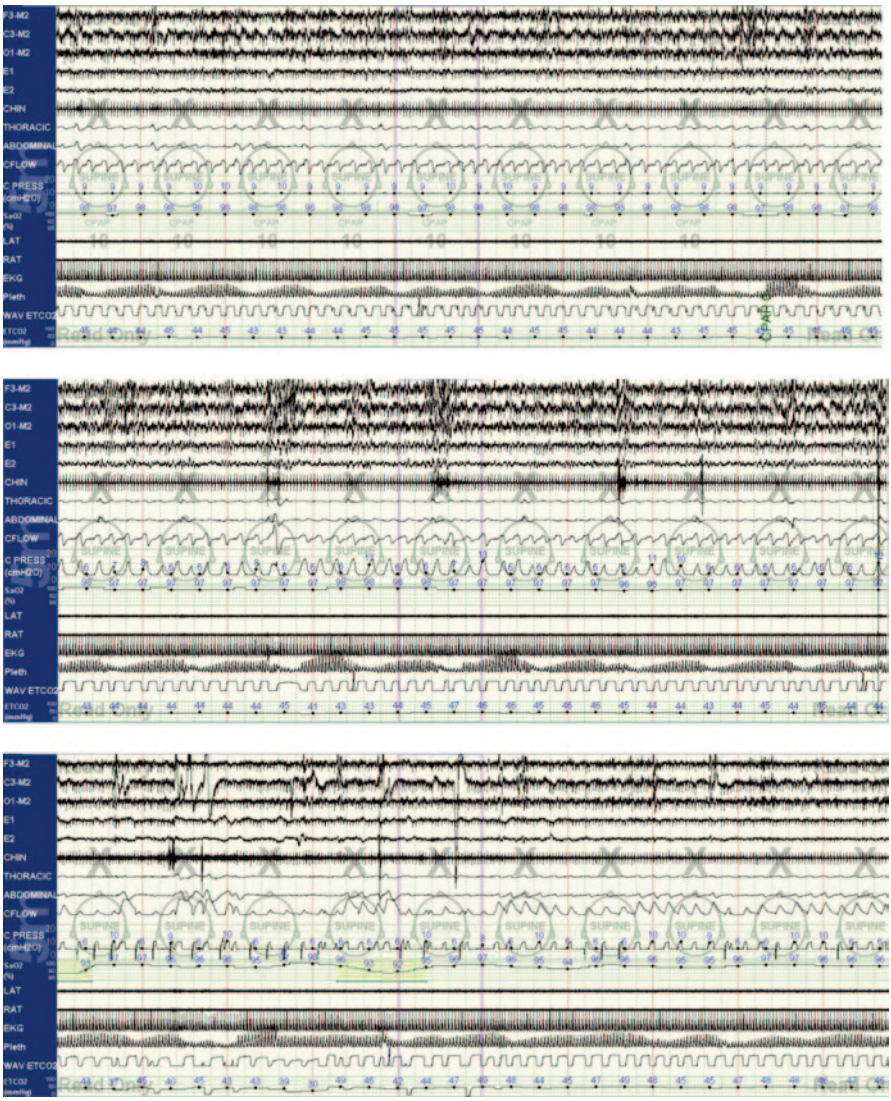

Fig. 7.6 Relative efficacy of EERS + CPAP, ResMed Adapt SV or Phillips-Respironics BiPAP Auto SV Advanced in the same patient. The upper panel shows CPAP efficacy, with the end-tidal CO_2 held to the mid-1940s. This patient had failed prior positive pressure titrations with induction of central sleep apnea. The middle panel shows relative efficacy of the Adapt SV—pressure cycling (the CPRESS channel) is mild but there are recurrent arousals. The lower panel shows that in this patient, the Auto SV Advanced in the worst. Note severe sleep fragmentation, the flip-flop between patient and machine supported breaths on the CPRESS channel, and the poorly controlled residual apnea

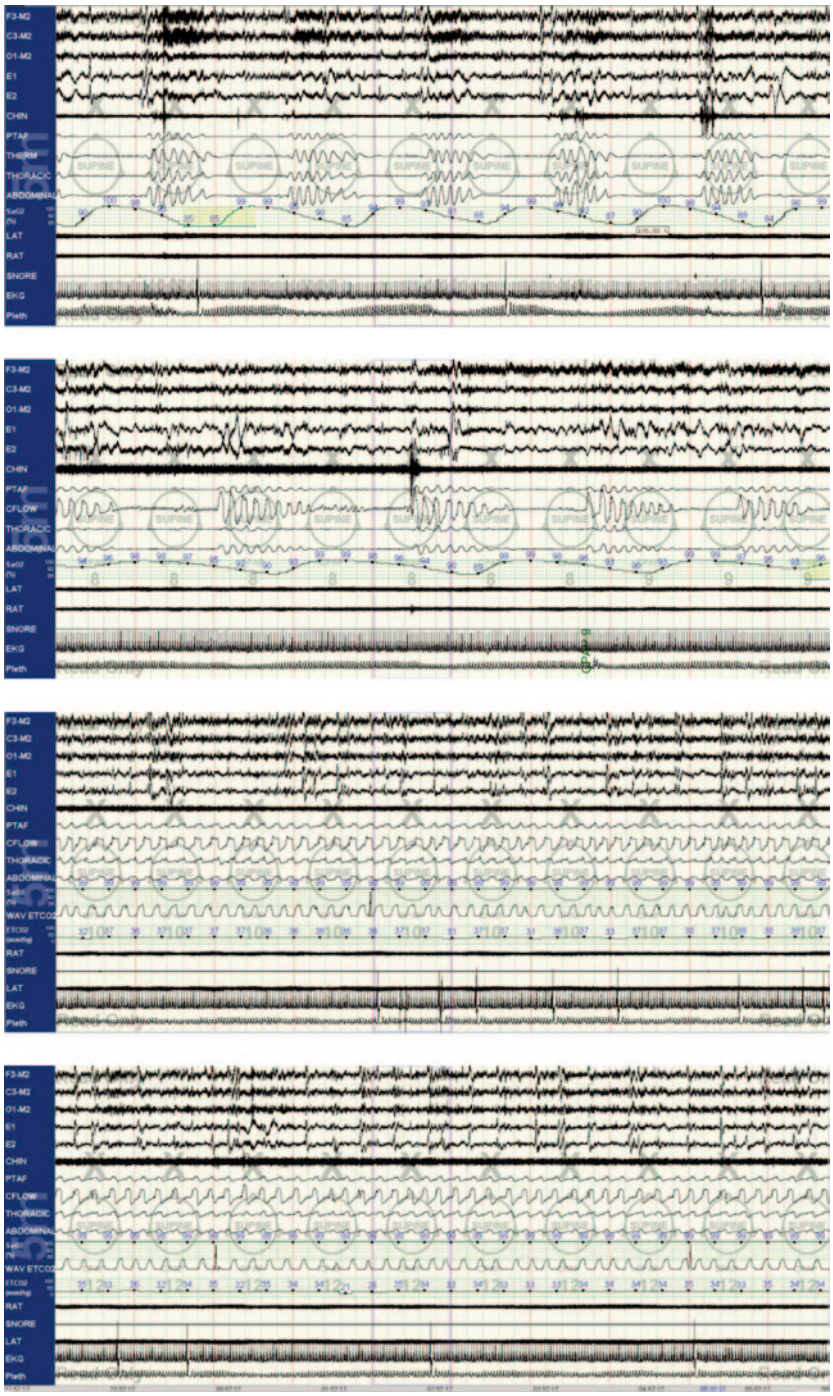

Fig. 7.7 Efficacy of dead space/EERS used with CPAP. From top: *1* Diagnostic polysomnogram component of a split night study. Note classic severe Cheyne-Stokes breathing. *2* Effect of continuous positive airway pressure—cycle time lengthening but no improvement in fundamental

Table 7.1 Determination of starting enhanced expiratory rebreathing space volume

Starting dead space condition	Baseline "wake" $ETCO_2$[a]	Suggested starting EERS
$ETCO_2$ with NV mask only[a] and ≥45 mm Hg with 150 mL EERS	≤40	50 mL
$ETCO_2$ with NV mask only[a] and ≥45 mm Hg with 100 mL EERS	≤40	0 or 50 mL
$ETCO_2$ with NV mask only[a] and ≥45 mm Hg with 50 mL EERS	≤40	NV mask only
$ETCO_2$ with NV mask only[a] and ≥50 mm Hg with 50 mL EERS	40–45	NV mask only
$ETCO_2$ with NV mask only[a] and ≤50 mm Hg with 50 mL EERS	40–45	NV mask only
$ETCO_2$ with NV mask only[a] and ≤50 mm Hg with 100 mL EERS	40–45	0 or 50 mL
$ETCO_2$ with NV mask only[a] and ≤50 mm Hg with 150 mL EERS	40–45	0 or 50 mL
$ETCO_2$ with NV mask only[a]	≥45	Physician approval

EERS Enhanced expiratory rebreathing space; *ET* end-tidal; *NV* nonvented
[a] is resting CO_2 during biocalibration

ed dead space. The biocalibration is used to determine the starting EERS volume and is summarized in Table 7.1**.** The CO_2 targets are to keep the $ETCO_2$ below 50 mm Hg during sleep and not greater than 5 mm Hg increase from wake. If transcutaneous CO_2 is monitored, the target is to keep at less than 50 mm Hg or limit increases to 5 mm Hg from baseline. The latter approach is somewhat approximate, because sleep baseline $ETCO_2$ without an NV mask on the patient, will probably not be known and it is unclear how much time is required for equilibration after sleep onset.

The mask-fitting clinic at the Beth Israel Deaconess Medical Center has modified a large number of masks. Specific masks, methods to convert to NV, and appropriate connectors are available on request (contact Dr. Thomas at rthomas1@bidmc.harvard.edu) and are tabulated with mask-specific PowerPoint files. The nonvented configuration, including the safety valve, adds 60–100 mL of dead space (including the intra-mask space), and this "NV alone" usually means about 60–100 mL of dead space/EERS compared to a vented mask. What this means in practical terms is that adding further EERS is often not necessary any more.

respiratory pattern. *3* Addition of 50 cc of dead space/EERS to CPAP using a non-vented mask configuration. Note stabilization of respiration and residual flow limitation. $ETCO_2$ is about 37 mm Hg. *4* Final pressure, 12 cms, with normalization of nearly all flow-limitation and maintained stabilization of respiration. $ETCO_2$ signal shows a partial loss of plateau due to increased leak at the higher pressure

There are two approaches to titration of EERS, "forward" and "backward." In the forward approach, incremental options are considered with positive airway pressure first with a vented mask, then converting to a nonvented mask, then adding rebreathing space (e.g., 50 mL, then 100 mL, etc.), O_2. In the backward approach, maximal stabilization is provided at the outset, starting at 50 mL "dead space" (which seem to be adequate for most) and 2 L/min O_2. After obtaining control in REM/stable and unstable NREM sleep, the O_2 and CO_2 modulations can be progressively withdrawn to assess the minimum requirement. The concept of stable vs. unstable NREM sleep is discussed later in this chapter. Typically, with successful levels of dead space, O_2 is not critical but can be a useful backup, because consistent good seals at home are hard to maintain. Obtaining a plateau on the $ETCO_2$ signal ensures effectiveness (i.e., the seal is adequate) and accuracy of the reading. An alternate approach is to simply start with a non-vented mask and no added EERS and titrate as required.

CO_2 manipulation can also be done by bleeding CO_2 in to the circuit by a more precisely controlled flow-independent method. Thomas et al. reported successful treatment of mixed obstructive and central sleep apnea using a proprietary device, the positive airway pressure gas modulator (PAPGAM), which delivers precisely controlled concentrations of oxygen and CO_2. In this small case series, 6 patients with average AHI of 43/h on CPAP improved with reduction of AHI to 4.5/h with addition of 0.5−1% using PAPGAM [147]. However, translating this finding to patient care requires the development of a device approved for clinical use.

Oxygen

Nasal O_2 has a long history of use to treat central sleep apnea and periodic breathing [148, 149]. Adding oxygen to CPAP may result in better control of complex apnea, with reduction in responsiveness of peripheral chemoreceptors and the loop gain [150]. The limitations include the long term cost and difficulty with reimbursement in "non hypoxic" patients. A recent study in a Veteran's population showed that O_2 has beneficial effects, but the polysomnographic changes were delayed by as much as an hour or more [151]. One change to be aware is that of respiratory event cycle length—which can lengthen with the use of O_2. Such a change may "reduce" the respiratory event index but not imply a true stabilization of respiration. Use of O_2 also negates use of desaturation link to score hypopneas. It should be noted that hypoxemia levels used to initiate O_2 therapy are not the threshold for evaluating supplemental O_2—moving saturations from the mid to the high 90s can be beneficial. Use of O_2 is off-label for central apnea syndromes. Supplemental O_2 can thus usefully be a component of a multi-modal multi-step approach to management of HCSA syndromes.

Sleep Stabilization—"Stable" vs. "Unstable" NREM Sleep

Most patients, including older individuals or those on benzodiazepines/sedative drugs, exhibit periods of sleep that are not scored as NREM stage 3 (N3) by conventional criteria (or any modification thereof) but clearly have ample low amplitude delta frequency waves. Respiration is usually quite stable during this period (functionally, think of it as slow wave sleep), and if recognized, the same precautions as during conventionally scored slow wave sleep apply. Those who study the cyclic alternating pattern (CAP) will recognize this type of "stable" NREM sleep as predominantly non-CAP [152]. In fact, for the purpose of titration, dividing sleep into stable and unstable NREM sleep (or non-CAP/CAP) and REM works well, better than N1–N3 and REM sleep. It may be easier to recognize stable and unstable NREM sleep from non-electroencephalographic signals, such as respiration, heart rate variability, and respiratory amplitude modulation of the electrocardiogram [153]. The stability of this non-CAP or slow wave-like (frequency but not amplitude) sleep can cause a false sense of security (of treatment efficacy); it is also important not to change pressures if this state is recognized (unless obstructions and flow limitation are quite overt). Airflow can look absolutely normal in this state, and then rather abruptly (often within a minute) a switch to being quite abnormal may occur. Such switches of stable/unstable state are spontaneous, and disease or treatment needs to deal with this dynamic.

Sleep fragmentation propensity can be recognized by prolonged (more than 5–10 min) sleep-wake transitional instability. The same pattern can be seen if the laboratory bedtime is before the internal biological night. The subset of patient with higher likelihood to respond to sleep stabilization are those with persistent low efficiency (less than 70%) and increased stage N1 (greater than 15%) during the positive pressure titration study and those with prominent post-arousal instability (1–2 min of periodic breathing after individual arousals). Recognizing the sleep fragmentation phenotype can be challenging during the study, it is often more readily evident after the study is scored. If the fragmentation phenotype is recognized, the following are options: (1) reduce pressure (watch for evidence of increased obstruction) or change mode; (2) allow the patient to take a break, until subjective sleepiness is noted, to allow better expression of homeostatic sleep drive; (3) trigger the physician-directed drug option if available (see below).

The core concept is to use sedatives that can induce stable NREM sleep. While the conventional approach avoids sedatives in "obstructive sleep apnea," these drugs can be used safely in NREM-dominant apnea, as here arousals further destabilize sleep and thus can worsen sleep apnea severity. In fact eszopiclone can improve sleep apnea in those with a low arousal threshold [154]. Arousals from sleep and frequent sleep stage transitions can both induce, and increase the severity of, central and complex sleep apnea. The proposed mechanisms are arousal induced hypocapnia, reduction of upper airway resistance upon arousal and increased neural output to respiratory centers in wake. Triazolam, temazepam, zolpidem, and clonazepam have all been shown to reduce central apnea activity [155–158]. We selectively use hypnotics with good clinical results in patients with the sleep fragmentation phenotype. Short-acting sedatives can be part of a "lab pharmacology protocol" (Fig. 7.8). The use of sedatives in sleep apnea patients is off-label, and appropriate cautions

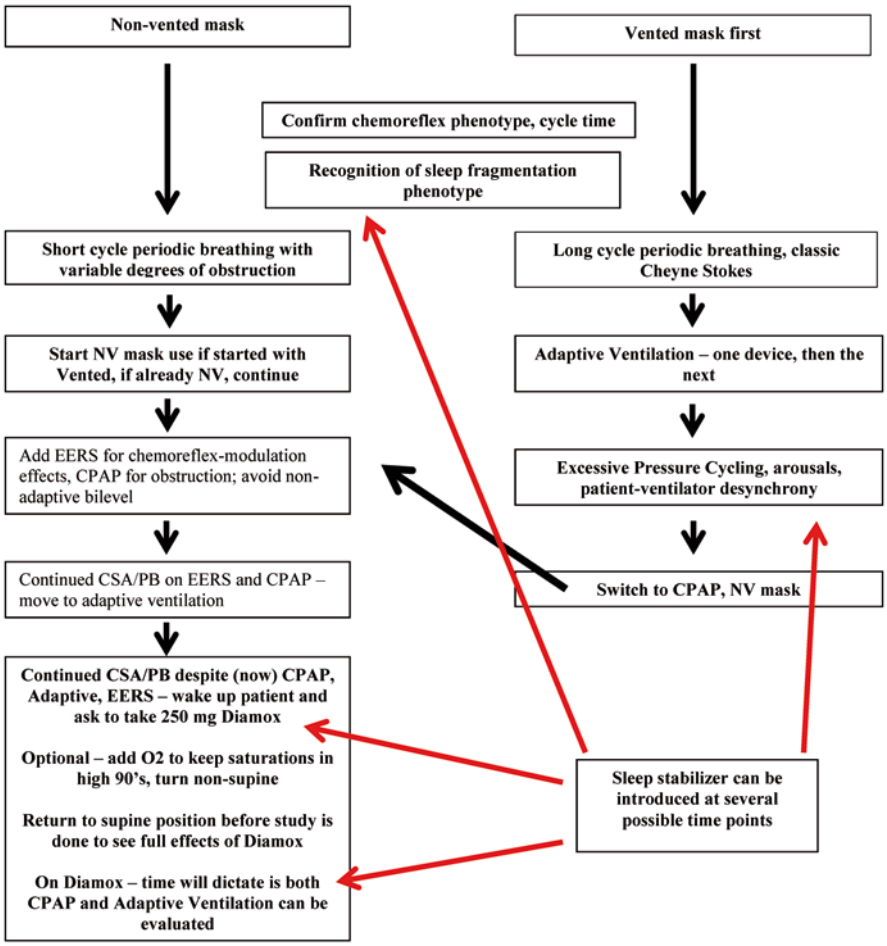

Fig. 7.8 A logical clinical-laboratory approach to treatment of hypocapnic central sleep apnea—stop when treatment is successful at any point. This figure describes a schema including pharmacological probing for phenotype-driven sleep apnea management in the sleep laboratory. It assumes that either central apnea and periodic breathing are evident in a diagnostic assessment, or the patient has already failed an attempt at positive pressure titration. However, the protocol can even be initiated during a first split night if risk for chemoreflex-apnea is high, such as heart failure. The "sleep stabilizer" could be zolpidem or a longer acting option with the risk of next-day hang over; assuring a designated driver to return home is important. Acetazolamide dose is 250 mg. A second option for acetazolamide us is to start 5 days before the sleep study, 125 mg for 3 nights and then 250 mg, 1 h before bedtime

(hang-over, potential of worsening apnea, cognitive impairment, and next day driving difficulty) are essential. The author restricts this use to NREM-dominant apnea patients, typically starting with zolpidem or eszopiclone, and moving to a classic benzodiazepine if this initial approach is not effective. The logic behind the use of sedatives in sleep apnea is discussed in a recent review [159].

The most recent addition to the anti-insomnia armamentarium, suvorexant, is a dual orexin receptor agonist [160, 161]. The drug increases total sleep time and improves sleep maintenance, but effect on sleep and respiratory stability as conceptualized above are unknown. However, orexin has sensitizing effects on the respiratory chemoreflex, [162, 163] raising an intriguing possibility of dual efficacy in HCSA syndromes with substantial post-apnea treatment residual sleep fragmentation.

Opioid Dose Reduction

Opioids use is a risk factor for development of ataxic breathing (Fig. 7.9) and central sleep apneas [164–166]. Decreasing the dose of opiates may help reduce central apneas [167, 168]. In most patients stopping opiates entirely is not possible. The pathophysiology involves modulation of hypoxic and hypercapnic ventilatory responses, [169] but opiate receptors are found throughout the respiratory control pathways. Opiate-induced ataxic breathing is quite sensitive to CO_2 levels—with ready induction of central apnea and worsening of dysrhythmic breathing with continuous or nonadaptive bilevel positive pressure ventilation. These patients tend to show mild hypercapnia, with end-tidal CO_2's in the high 40's to low 50's. Using a NV mask and EERS as needed to hold CO_2 in the mid-40's can be useful. We have found the use of acetazolamide to be of consistent benefit in patients with opiate-induced central/ataxic sleep apnea. Adaptive ventilation is a double-edged sword in these patients—being able to both enable stable breathing [170] and at times markedly destabilize breathing or simply be ineffective [171]. Experimental evidence of modulation α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by ampakines suggests potential for opiate-induced sleep apnea [172, 173].

Carbonic Anhydrase Inhibition

Acetazolamide, a diuretic and carbonic anhydrase inhibitor, diminishes the ventilatory response of the peripheral chemoreceptors to hypoxia, decreases loop gain, and reduces the ventilatory response to arousals [28, 174–176]. In animal models, it has been shown to lower the $PETCO_2$ apnea threshold and widen the difference between the eupneic and $PETCO_2$ thresholds [6]. Acetazolamide has been used in treating central apneas and Cheyne-Stokes breathing in patients with and without CHF [177]. While the results may be statistically significant, the degree of residual sleep apnea is unacceptable as sole long-term therapy. The drug can convert those with mixed obstructive and central sleep apnea to mostly obstructive (the reverse of CPAP-induced central sleep apnea). The drug is now part of our algorithm for management of HCSA. Those with short-cycle (30 s or less) periodic breathing not responding to EERS are the best candidates, as in this subset, the time constant of the adaptive ventilators seems too long to optimally entrain. Carbonic anhydrase

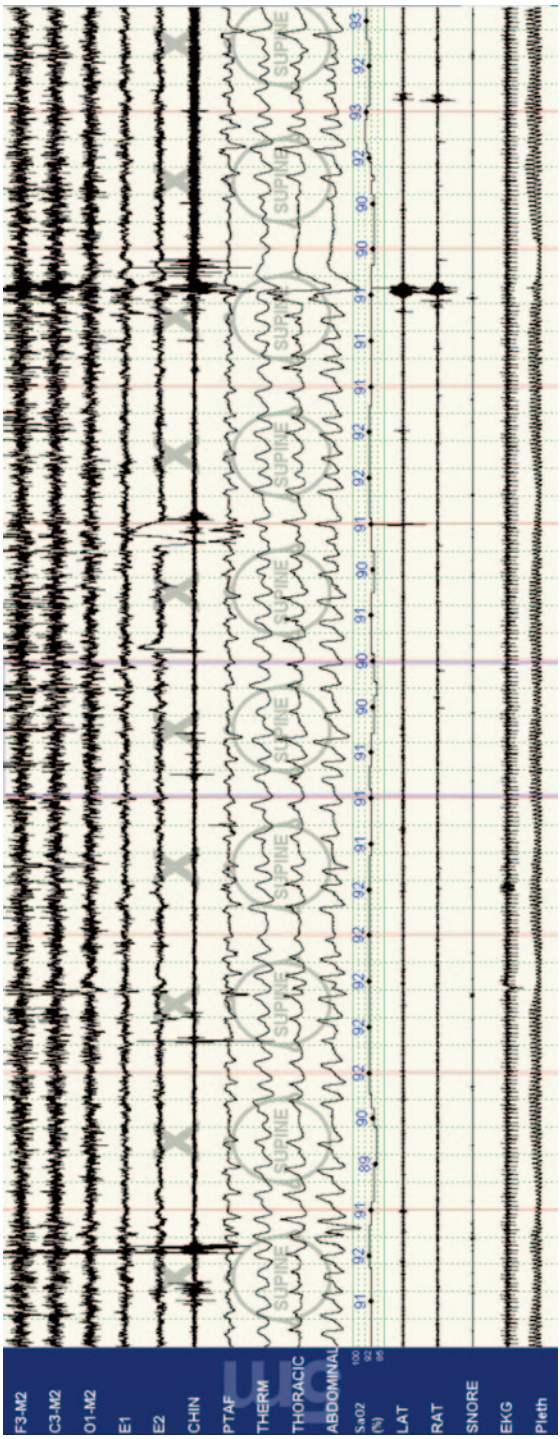

Fig. 7.9 Opiate-induced sleep apnea—subtle features. This 5-minute snapshot shows the core effects of opiate-induced sleep apnea: ataxic respiration, post-arousal instability and variable degrees of obstructive features such as flow-limitation. Note the varying duty cycles due to variability primarily in the expiratory phase. Periodic breathing can be present but it is rarely as "pure" as that seen at high altitude (*short cycle*) or congestive heart failure (*long cycle*). If end-tidal CO_2 is monitored, these patients tend to be mildly hypercapnic

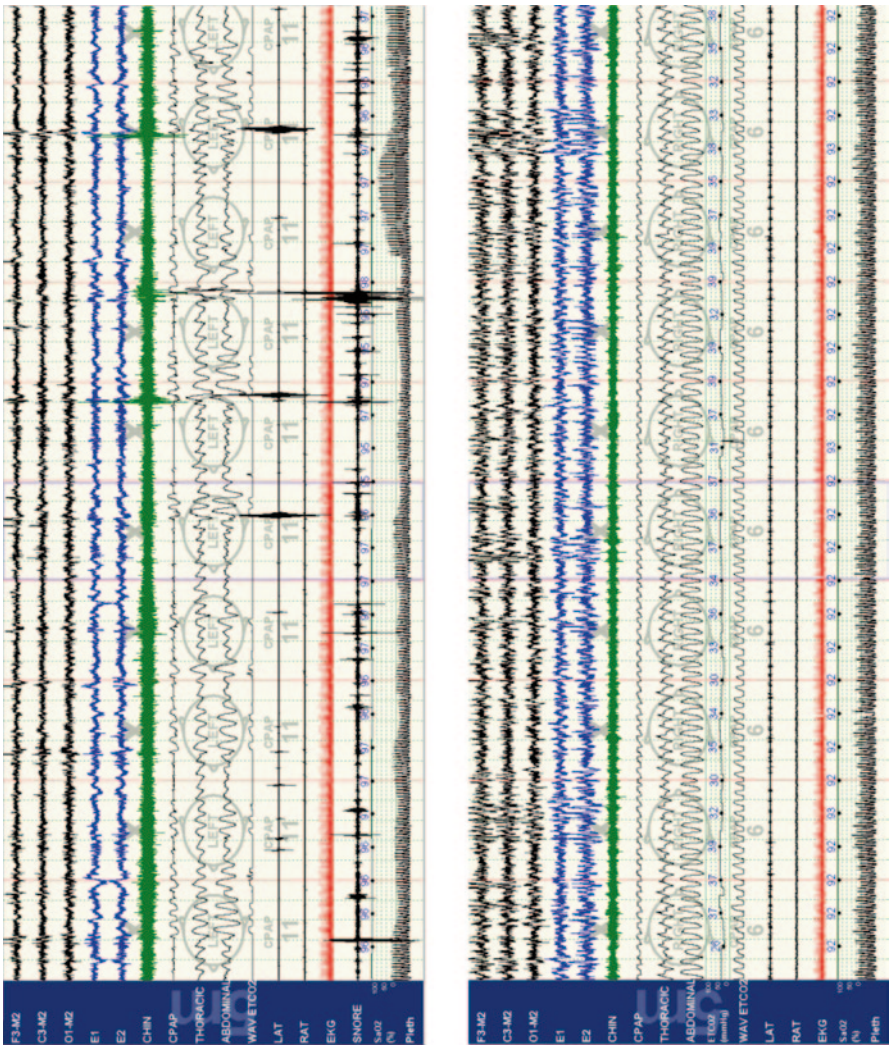

Fig. 7.10 Synergism between acetazolamide and dead space EERS. Note (*upper*) persistent periodic breathing across a range of pressures, with and without dead space/EERS. The lower trace is from a return to the sleep laboratory but now using acetazolamide 250 mg 1 h before bedtime, along with a NV mask alone, which provides about 70 cc of dead space within the mask and connecting tubing. Note complete resolution of sleep apnea at relatively low pressures. When there is ongoing periodic breathing, respiratory events frequently have flow limitation and other obstructive features. This typically results in evaluation of higher CPAP pressures, "chasing" the abnormality

inhibition with acetazolamide or topiramate can be part of a "lab pharmacology protocol," and can be used with a non-vented mask/EERS (Fig. 7.10, 7.11). Acetazolamide has been successfully used as CPAP adjuncts at high-altitude to prevent new altitude-related periodic breathing despite use of CPAP [178, 179]. Zonisamide

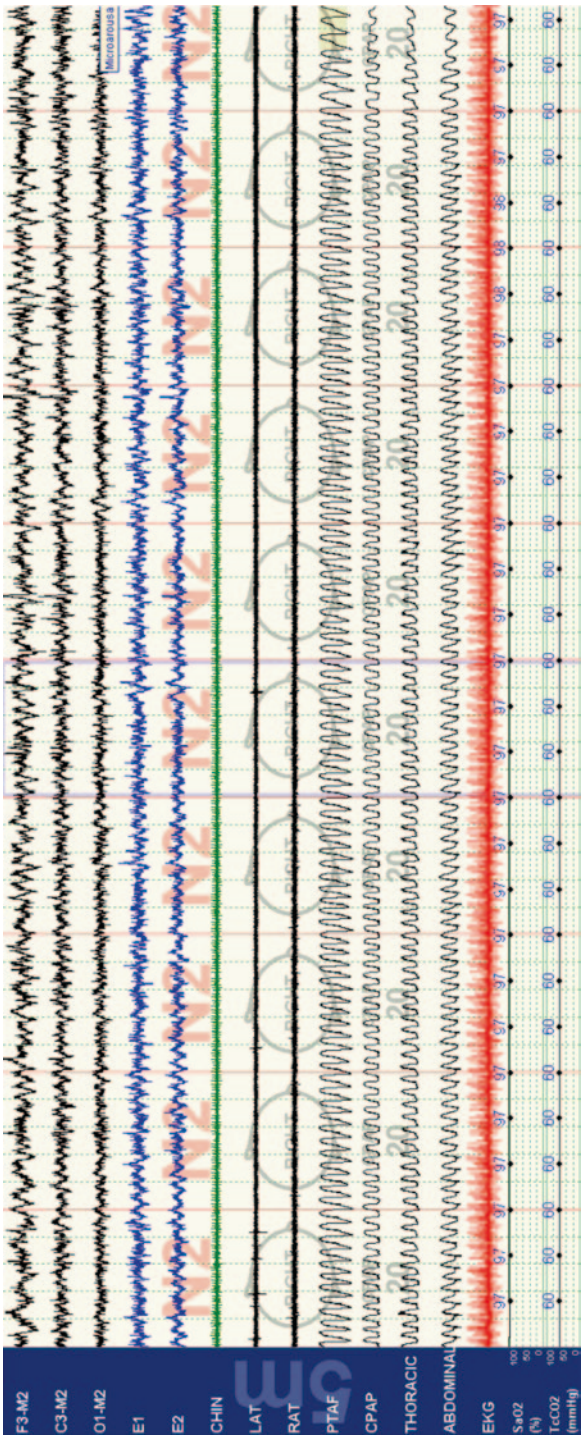

Fig. 7.11 Stabilization of mixed sleep apnea with acetazolamide (synergism with EERS). The same patient as in Fig. 7.5 now returns to the sleep laboratory on 250 mg of acetazolamide taken one hour before bedtime. With CPAP, a NV mask and 20 cms CPAP, control of sleep disordered breathing is achieved. Note transcutaneous CO_2 is 60—it is rare instance that hypercapnic individuals exhibit periodic breathing but this was once such instance

[180] and topiramate [181] each have carbonic anhydrase inhibitory effects, and could in theory be used in the place of acetazolamide. It is not known if the neuronal effects would have an impact on respiratory control integration.

Clonidine

A single report describes a potential role for clonidine as adjunctive therapy for hypocapnic central sleep apnea syndromes [182]. In a study of 10 healthy subjects (4 females) (age 22.3 ± 3.0 years; BMI 25.5 ± 3.4 kg/m^2), subjects were randomized to receive placebo or 0.1 mg/45 kg of clonidine on 2 separate nights. Ventilation and upper airway resistance were monitored during wakefulness and sleep. Two separate experiments were performed. In one (8 subjects), CO_2 reserve, hypocapnic apneic threshold and hypocapnic ventilatory responses were determined using noninvasive hyperventilation to induce hypocapnia. In a second protocol, peripheral hypocapnic ventilatory response was determined by NIV using short (3 breaths) hyperventilation. Clonidine decreased the systolic blood pressure by 12 ± 10 mmHg but did not affect baseline ventilation or upper airway resistance during wakefulness or sleep. Clonidine was associated with a decreased hypocapnic apneic threshold relative to placebo (37.3 ± 3.3 mmHg vs. 39.7 ± 3.4 mmHg, increased CO_2 reserve (−3.8 ± 1.3 mmHg vs. −2.8 ± 1.2 mmHg), and decreased hypocapnic ventilatory responses (1.6 ± 0.6 L min/mmHg vs. 2.5 ± 1.3 L min/mmHg). Administration of clonidine did not decrease peripheral ventilatory responses. The hypotensive effect will likely reduce enthusiasm for clinical use, but the concept has merit.

Androgen Blockade

Testosterone reduces the NREM sleep CO_2 reserve, and the 5-α reductase inhibitor finasteride can increase it. In a study of 14 healthy males treated with finasteride for 1 month, [183] the apnea threshold decreased (38.9 ± 0.6 mm Hg vs.37.7 ± 0.9 mm Hg, $P = 0.02$) and the CO_2 reserve increased (−2.5 ± 0.3 mm Hg vs. −3.8 ± 0.5 mm Hg, $P = 0.003$), with a significantly lower NREM sleep hypocapnic ventilatory response. However, long-term 5-α reductase inhibition will have adverse effects and benefits in patients with central sleep apnea syndromes remains to be demonstrated.

Targeting Carotid Body Function

Data on the role of carotid chemoreceptors in arousal and loop gain augmentation leads to a suggestion of an invasive intervention in treatment of autonomic imbalance in chemoreflex-driven sleep apnea syndromes [184]. Experiments in lambs

show that carotid body denervation attenuates arousals during airway obstruction, hypoxemia and hypercapnia, [185–187] while in rabbit model of CHF, the same procedure prevented periodic breathing and improving cardiac function [188]. Chemical inhibition of H_2S (gaseous signal transmitted in carotid body) in a rodent model of CHF nearly normalized chemosensitivity and breathing instability [189]. A case report of unilateral carotid body denervation in a man with systolic heart failure and moderate CSA showed that chemosensitivity and SA severity were reduced and shifted to an obstructive phenotype at 2 months post treatment, accompanied by an improvement in quality of life [190]. Although above findings are intriguing, concerns regarding hypoventilation and loss of the needed hypoxemic sensitivity in setting of cardiorespiratory illness with denervation are real [191, 192, 192] as is the development of clinically significant OSA [193, 194]. An ongoing trial of carotid body denervation in a group of CHF patients may provide some answers to relative risk to benefit ration in this approach (NCT01653821).

Nasal Expiratory Positive Pressure

Nasal expiratory positive airway pressure (Provent™, Ventus Medical), another device with a simple design marketed for use in patients with mild OSA, may also be useful in treating central and complex apnea (Fig. 7.12). This device helps generate auto PEEP and increased tracheal tug via increased lung volumes, which may relieve obstructive sleep apnea; efficacy is variable and unpredictable [195]. In our center, about 25% show acceptable benefits when evaluated during polysomnography. This effect of Provent™ can be enhanced by acetazolamide, similar to the use of the drug with CPAP [179]. We speculate that Provent™, while providing increased nasal expiratory resistance, also mildly increases the $PaCO_2$ as reflected in end tidal which may stabilize chemoreflex driven breathing instability [195].

Oral Appliances

In patients who chose oral appliances as first line treatment, it is important to be aware that central apneas can also emerge in these settings [196]. At our center we have used these devices in PAP- intolerant complex apnea patients with reasonable success. Residual sleep apnea is typical, and requires adjunctive therapy. Oral appliances are less likely, it seems, to induce hypocapnia, but treatment of obstruction is less precise. “Cocktails” that are currently being used by our patients include oral appliance + acetazolamide, or a benzodiazepine, or supplemental oxygen. One specific use of an oral appliance is with positive pressure, to reduce pressure requirements [197, 198].

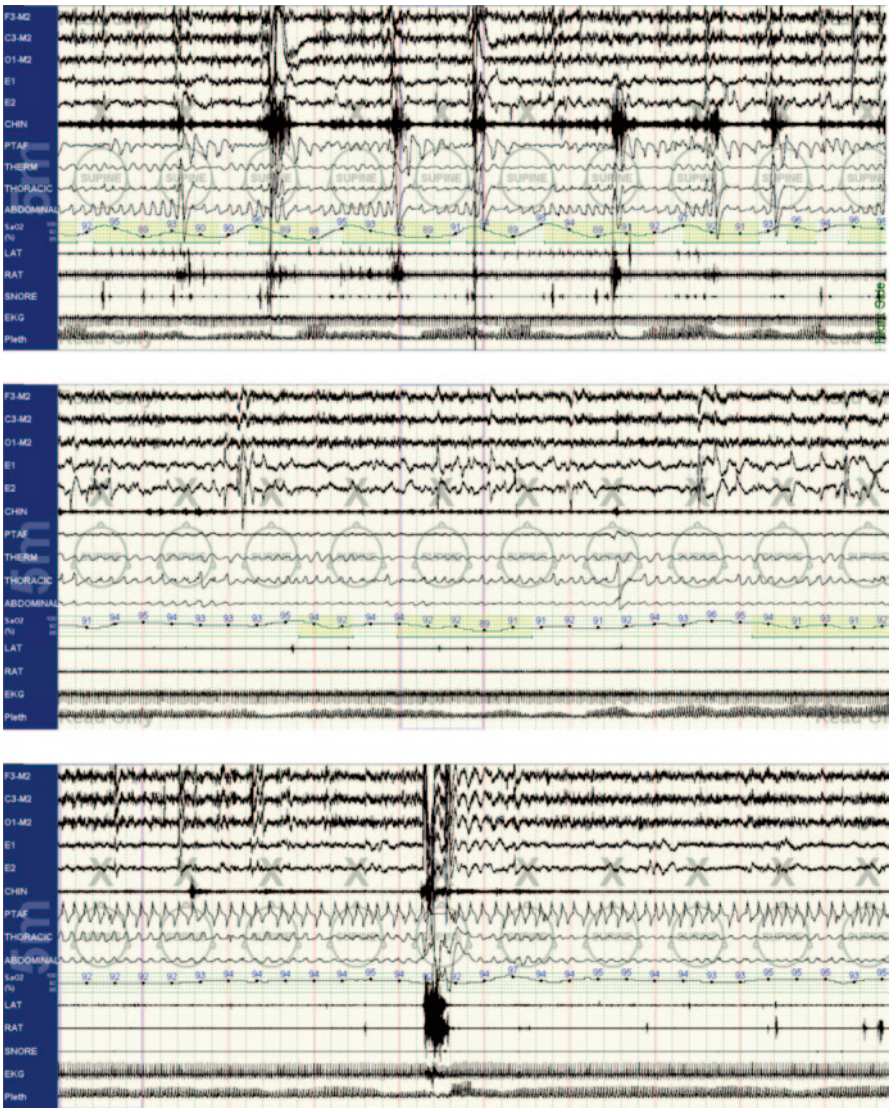

Fig. 7.12 Efficacy of Provent™ in NREM dominant apnea with periodic breathing. From *top*: *1* NREM stage with repetitive short-cycle (about 30 s) mostly obstructive hypopneas, with some periodic breathing features. *2* Same patient, still supine, REM sleep—note near disappearance of respiratory abnormality, suggesting strong chemoreflex driving as pathology. *3* Efficacy of Provent™, shown across a transition from NREM to REM sleep

Winx®/Oral (Negative) Pressure Therapy

This new approach uses a mouth piece to apply gentle negative intraoral suction that moves the tongue and soft palate anteriorly, opening and stabilizing the airway. As positive pressure is not applied, theoretically there is less hypocapnia induction.

There is no apparent reason why Winx® could not be used with, for example, acetazolamide, to provide complementary and synergistic effects on sleep-breathing, or Winx® + nasal oxygen, or Winx® + Provent™, or indeed Winx® + dead space. I have tried all these options in the sleep laboratory and they seem to have potential for benefit in individual patients.

Body Position Manipulation

A subset of central and complex apnea appears to be position dependent. These patients are "unfixable devils" while supine and "angels when non-supine" (personal observation). The reasons include upper airway and lung volume effects, the latter perhaps altering plant grain unfavorably when supine. Positional effects in central apnea syndromes have been reported in patients with classic Cheyne-Stokes respiration in the setting of heart failure [199, 200]. Sleeping on the side is also an important adjunctive treatment to reduce positive pressure requirements which may cause less CO_2 blow off and respiratory instability.

A second effect of body position is on fluid redistribution from the caudal to cranial parts of the body [201–205]. The effect is rapid, associated with increased neck circumference, and hypocapnia from increased lung water in those with central apnea. While a rostral fluid shift facilitating upper airway obstruction is intuitive, one report supported promoting central sleep apnea by augmenting ventilation and lowering transcutaneous CO_2. Therapeutic manipulation is currently clunky but a wedge pillow or pillows are options, besides optimal medical management of management of edema/fluid overload states.

Phrenic Nerve Stimulation

Transvenous phrenic nerve stimulation is in clinical trials for central sleep apnea. In one published study, [206] a prospective, non-randomized, acute study determined the feasibility of using unilateral transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure patients. Patients underwent phrenic nerve stimulation from either the right brachiocephalic vein or the left brachiocephalic or pericardiophrenic vein. The stimulation duration, reported in 16 subjects, was 251 ± 71 min. Stimulation resulted in a significant improvement in the apnea-hypopnea index [median (inter-quartile range); 45 (39–59) vs. 23 (12–27), central apnea index [27 (11–38) vs. 1 (0–5), arousal index [32 (20–42) vs. 12 (9–27), and ODI4 % [31 (22–36) vs. 14 (7–20) events/h. Further data on long term efficacy, response predictive criteria, impact on sleep quality, quality of life/sleepiness, and neurohumoral activation, are awaited.

Targeting Residual Sleep Apnea Following Other Anti-Obstructive Treatments

Residual sleep apnea from a highly activated respiratory chemoreflex can probably occur after major weight loss including bariatric surgery (noted by the author), and hypoglossal nerve stimulation. Adjunctive therapy with acetazolamide is a logical approach, and possibly supplemental oxygen.

Recognizing Persistent and Emergent Periodic Breathing and Central Sleep Apnea During Positive Pressure Therapy

Current generation positive pressure devices are equivalent to a mini sleep laboratory at the patient's bedside, in term of the precision and sophistication of data gathering and transmission [207]. Leak, residual events, and waveform (flow over time) data are available either through wireless transmission or via reading data on data cards. As this level of information is new, what is "normal" respiration during long-term ventilation management for the HCSA syndromes remains to be defined (Fig. 7.13); different manufacturers use different detection thresholds

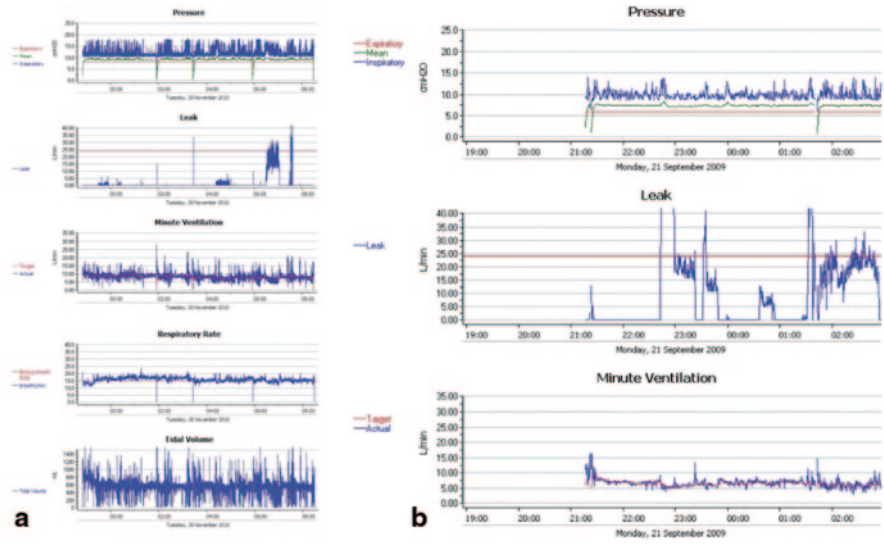

Fig. 7.13 **a** and **b** Determining efficacy of adaptive ventilation. Current generation adaptive ventilators provide a large amount of useful physiological data, including tidal volume, residual machine-detected events, respiratory rate, minute ventilation, and pressure outputs of the device. The latter is critical—if there is excessive and persistent (week and months of therapy) pressure cycling, then there is residual periodic breathing (i.e., need for pressure cycling). Figure "**a**" shows poorly controlled disease, note the variability of the computed metrics, and "**b**" shows well controlled disease in a different patient—note the stability of metrics across the treatment interval, even though leak is less stable

[207]. Moreover, machine-derived phenotypes are yet to be validated in terms of accuracy or clinical significance. Machine-generated residual event index is useful when high (over 5–10) in suggesting a need for intervention, especially in symptomatic individuals, but undetected events remain a problem (personal observation; Fig. 7.14). Several factors may challenge accurate automated event detection—including detection thresholds, lack of identified associated features such as arousals, and the time constant. The latter is probably especially important—during treatment, the rate of change of the flow signal may take a longer duration to evolve (relative to a diagnostic assessment) and the required % change may not occur during the algorithm's sampling window. User adaptive/adjustable analysis windows and thresholds may be useful, and manufacturers should consider providing physicians this flexibility.

NonInvasive Ventilation for Hypercapnic Respiratory Failure

A hypoactive respiratory chemoreflex results in hypoventilation syndromes. Bilevel ventilation is the standard noninvasive ventilation approach, and guidelines for polysomnographic characterization and treatment are available. Besides standard bilevel pressure devices, with and without back-up rate capability, a new generation of devices provides a pressure-driven volume targeted mode. Devices in which this functionality are available include some of the home ventilators, the Phillips-Respironics AVAPS-AE (average volume assured positive pressure) and the ResMed IVAPS (Intelligent Volume Assured Pressure Support). A tidal volume can be prescribed, and the devices attempt to maintain this target by varying the pressure between minimum and maximum set pressure support. These devices are specifically designed for hypoventilation management. The pressures can be constrained or left relatively wide open, but within those constrains the device will attempt to reach the target tidal volume. If this target is excessive, the pressure fluctuations can cause arousals and patient-ventilator synchrony difficulty. If the target is insufficient, hypoventilation will persist. Tracking transcutaneous and possibly end-tidal CO_2 using a non-vented mask is necessary to know the effect on ventilation, though a non-vented mask can increase CO_2 by increasing dead space. The devices allows manipulation of inspiratory time (usually 1–1.2 s), I/E time ratios (inspiration is typically 30% of the cycle), rise time (in 100 ms increments). Using these options requires substantial hands-on experience and careful attention to patient comfort, oxygenation/ventilation/sleep quality, and signs of abnormal synchrony. An example of a manufacturer's starting recommendations are to set the target tidal volume to 8 ml/kg of ideal weight, IPAP limits Max: 25 cm H_20 depending on patient pathology and Min: EPAP + 4 cm H_20, set respiratory rate 2–3 BPM below resting respiratory rate, and set inspiratory time and rise time to patient comfort (e.g., 1 s and 300 ms respectively). However, therapy is best guided by simultaneous integrated evaluation of oximetry, sleep quality flow and carbon

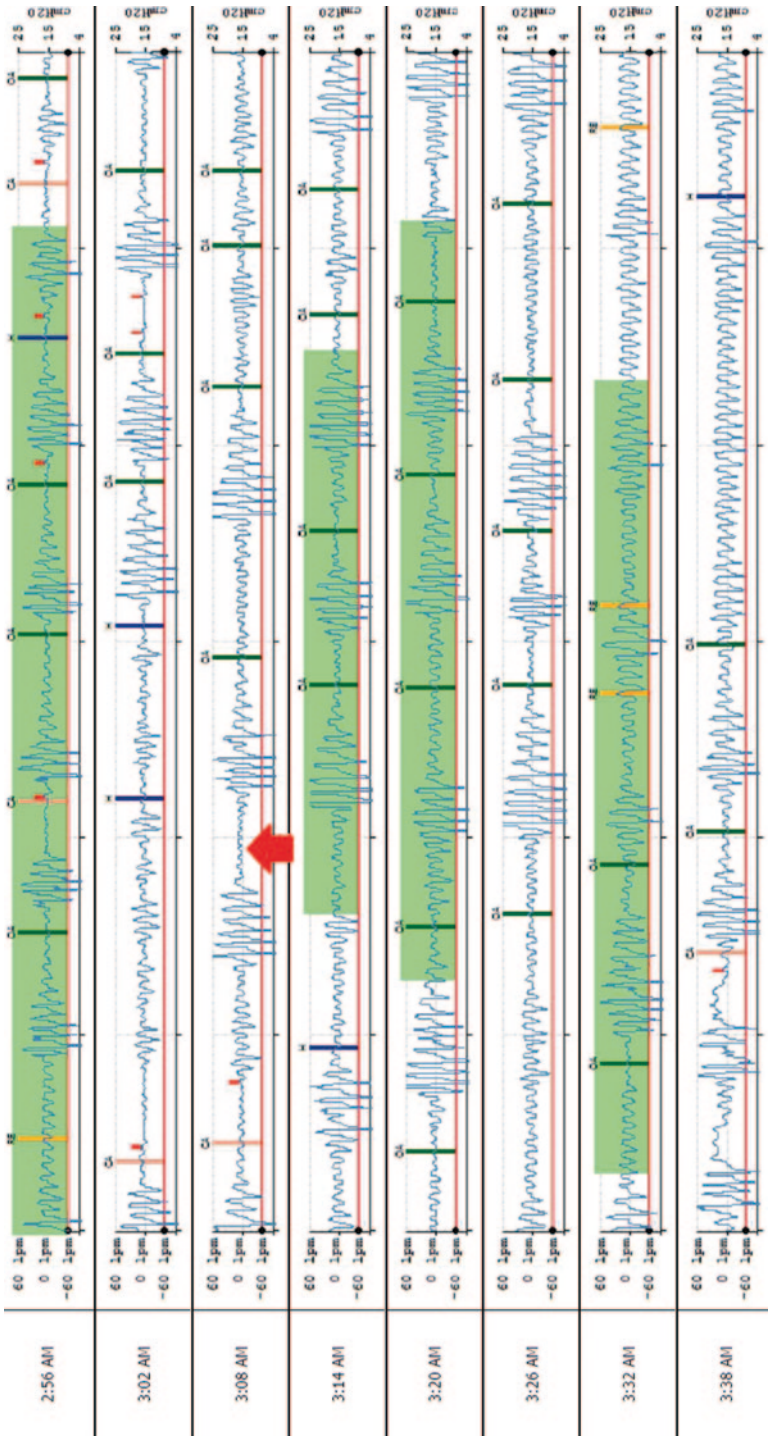

Fig. 7.14 Residual sleep apnea during therapy—detection and phenotype challenges. The snapshot from Phillis-Respironics EncoreAnywhere™ shows respiratory event detected by the device algorithm, but also note the untagged events (example, *red arrow* head), and the residual

dioxide. Published data do not yet show a consistent superiority in terms of sleep quality or blood gasses, [208–210] but with transcutaneous CO_2 to guide therapy in addition to the standard polysomnogram montage, it is the author's experience that improvement over standard bilevel ventilation is achievable, especially in patients with neuromuscular disorders. Intuitively, these devices should not be appropriate for the HCSA syndromes, but in rare instances, I have found a conservative tidal volume target to aid in management of a specific subset of patients who have mild to moderate hypercapnia but a strong tendency to positive-pressure induced ventilatory instability. In these patients, acetazolamide is a useful adjunct.

Summary

Enhanced or dysregulated respiratory chemoreflexes have a profound impact on sleep-breathing and the polygraphic patterns that emerge. There is an increasingly array of treatment options, on and off-label, singly or in combination, that can be used to enhance system stability. Three major components need to be adequately phenotyped and targeted—upper airway, respiratory control, and sleep fragmentation/consolidation.

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periodic-breathing like waveforms. The green bands are machine-tagged periodic breathing. This patient did have complex sleep apnea, and the addition of acetazolamide to CPAP/non-vented mask treatment largely stabilized ventilation and minimized periodic breathing

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Chapter 8
Noninvasive Positive Pressure Ventilation: Systems for Tracking Adherence and Efficacy

Patrick J. Strollo and John M. Coleman

Introduction

With the development of intensive care units, noninvasive positive pressure ventilation (NPPV) has been increasingly utilized as an option to forestall or avoid intubation in the setting of acute respiratory failure. Today, it is generally accepted that NPPV is useful in acute respiratory failure and has been shown especially beneficial in treating acute or chronic respiratory failure for chronic obstructive pulmonary disease (COPD), acute pulmonary edema, and post-extubation respiratory failure [1–10]. The use of NPPV, including nocturnal NPPV, in chronic respiratory failure is expanding. There is value in the treatment of hypoventilation in patients with neuromuscular disease (Amyotrophic Lateral Sclerosis (ALS), Muscular Dystrophy (MD), and paraplegia). These patients generally demonstrate excellent acceptance and adherence to therapy that is associated with improvement in symptoms of dyspnea and complications of hypercapnia [11]. Other types of chronic respiratory failure, in particular COPD, have been associated with equivocal benefits.

To date there have been no studies examining the use of data management in NPPV regarding its impact on patience acceptance, adherence, and comfort in patients who are prescribed NPPV for these conditions. The goal of this chapter is to review the various types of tracking programs for NPPV. We discuss the potential value of monitoring patient acceptance and adherence and the different technologies that can be used for tracking. We examine the use of tracking and adherence in the various types of chronic respiratory failure and provide some speculation relating to the future directions of NPPV and accompanying systems to track adherence

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and efficacy in patients prescribed acute and chronic NPPV for respiratory insufficiency and failure.

Noninvasive Positive Pressure Ventilation

Before assessing patient acceptance and adherence to NPPV, the clinician can take steps to optimize the chances of patient acceptance of the therapy. There are several key characteristics of the NPPV experience that contribute to a patient's acceptance of the therapy including the interface, the mode of ventilation, and the degree of unintentional leak.

Interfaces are devices that connect the ventilator tubing to the face and facilitate the entry of the pressurized gas into the upper airway. There are various types of interfaces, including nasal and oronasal masks, but ultimately the most effective mask is chosen based on the patient preference and the absence of significant unintentional leak with therapy. Nasal masks are triangular and fit over the nose, frequently distributing pressure over the bridge of the nose in order to achieve an adequate seal (Fig. 8.1). They are available from a variety of manufacturers and are fabricated in a number of sizes. Nasal masks are frequently better tolerated in patients with chronic respiratory failure and in patients with claustrophobia [12]. Full-face masks cover both the nose and the mouth (Fig. 8.2). This interface is more

Fig. 8.1 Image of nasal continuous positive airway pressure (*CPAP*) interface. (Care of ResMed)

Fig. 8.2 Oronasal face mask for NPPV. (ResMed)

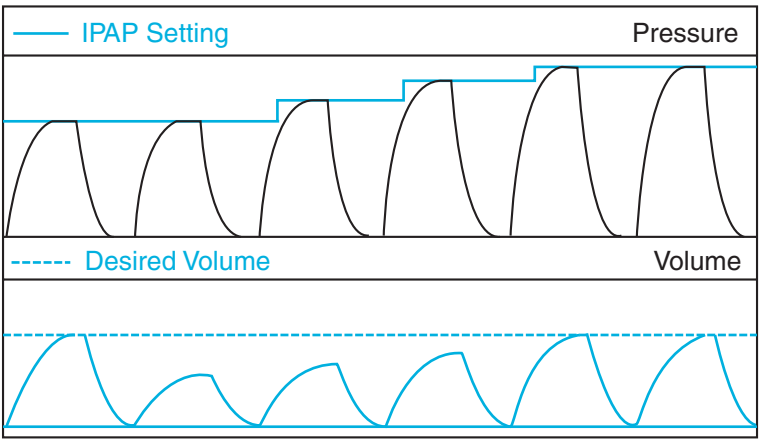

Fig. 8.3 Waveform for average volume-assured pressure support (*AVAPS*™) mode: waveform analysis of the changes in inspiratory positive airway pressure (*IPAP*) to meet the desired and preset tidal volume. (Courtesy of Philips-Respironics)

commonly used in patients in the hospital with acute respiratory failure, but can also be used in chronic respiratory failure. While this interface is particularly effective in minimizing unintentional leak, it is more commonly associated with claustrophobia as well as difficulty with speech, eating, and coughing. Regardless of the interface chosen, proper fit is key to increasing patient acceptance and adherence.

NPPV commonly employs either volume- or pressure-targeted ventilation. With volume-targeted ventilation, a fixed tidal volume is determined, and the ventilator will generate a pressure to achieve that tidal volume. This will lead to a variable pressure in the airways depending on the compliance and resistance of the respiratory system as well as patient effort. A major disadvantage of this system is that the patient's potentially varying ventilatory requirements are not taken into account; the patient always receives the same predetermined tidal volume. In addition, if there is a leak, there will be no increase in the flow rate to compensate, which will lower the generated pressure, in turn reducing the delivered tidal volume. Volume-targeted ventilation is frequently utilized as average volume-assured pressure support (AVAPS™) and intelligent volume-assured pressure support (iVAPS™).

AVAPS™ was developed to ensure the delivery of targeted tidal volume, using an algorithm that automatically adjusts pressure support to meet the changing patient needs while maintaining the target tidal volume (Fig. 8.3).

iVAPS™ targets minute ventilation, accounting for anatomical dead space, and uses a backup rate to improve patient synchrony and comfort. This system automatically adjusts the level of pressure support to achieve and maintain target minute ventilation (Fig. 8.4). Both devices utilize a pneumotachometer internal to the machine to monitor and adjust their respective algorithms.

In pressure-targeted ventilation, the device is set to deliver a predefined positive pressure with variable airflow to maintain a constant airway pressure. Under these circumstances, the volume delivered is not fixed and depends on interactions between the ventilator, the patient's respiratory system (specifically airway

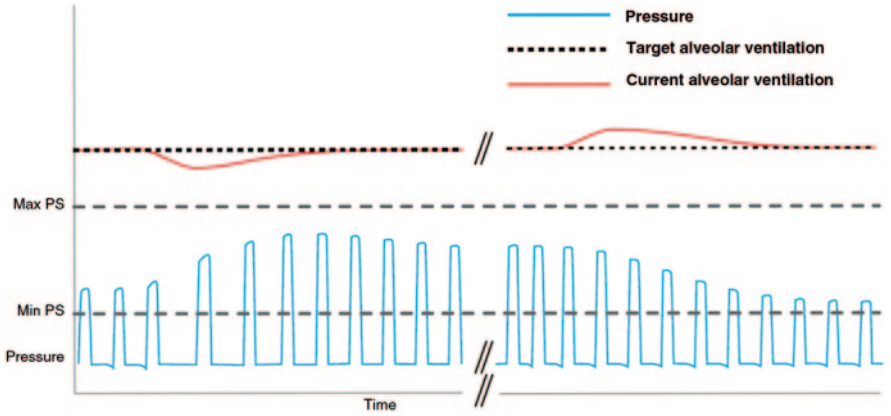

Fig. 8.4 Waveform analysis for intelligent volume-assured pressure support (*iVAPS*™): waveform analysis of the changes in inspiratory positive airway pressure (*IPAP*) to meet the desired and preset alveolar ventilation. (Courtesy of ResMed)

Table 8.1 Comparison of different options for home ventilation

	Trilogy	Stellar 150	LTV
Modes of ventilation	PC, VC, bi-level	PC, VC	PC, VC, PS, AC/SIMV
Portable	Yes	Yes	Yes
Data download capabilities	Yes	Yes	No
Supplemental O_2	Yes	Yes	Yes
Backup rate	Yes	Yes	Yes

PC pressure control, *VC* volume control, *PS* pressure support, *AC* assist control, *SIMV* synchronized intermittent mandatory ventilation

resistance and compliance), and the degree of unintentional leak. While the tidal volume and therefore the minute ventilation are variable under these conditions, it does allow for compensation for leaks. Traditional bi-level positive pressure ventilation (variable positive airway pressure, VPAP™, or bi-level positive airway pressure, BiPAP™) utilizes pressure-targeted ventilation using a preset fixed inspiratory and expiratory pressure level.

Some patients with chronic respiratory failure will require tracheotomy and use of home ventilation. Devices compatible with home ventilation via tracheotomy are illustrated in Table 8.1.

Indications for Noninvasive Positive Pressure Ventilation

It is well established that NPPV is beneficial in the acute care setting, with potential to reduce hospital morbidity, reduce intubation rates, facilitate liberation from mechanical ventilation, and decrease hospital length of stay [11]. Numerous studies,

including randomized controlled trials (RCT) using NPPV in acute exacerbations of COPD, have demonstrated effectiveness. Continuous positive airway pressure (CPAP) alone has also been shown to be effective in avoiding intubation in patients with acute pulmonary edema [5]. The utility of NPPV in acute hypoxemic respiratory failure is not as clear and requires further investigation.

NPPV in selected chronic respiratory failure phenotypes has been demonstrated to stabilize ventilation and gas exchange, and improve daytime symptoms. The two major types of chronic hypercapnic respiratory failure we focus on in this chapter are restrictive thoracic/lung disease (neuromuscular disease, kyphoscoliosis, obesity hypoventilation syndrome) and obstructive lung disease (COPD).

Restrictive Thoracic/Lung Disease NPPV for restrictive thoracic/lung disease has been successfully utilized for decades. It is well established that the use of NPPV improves gas exchange and symptoms in patients with restrictive lung disease. Bach and Ellis demonstrated improvement in daytime gas exchange and symptoms of hypercapnia including fatigue, daytime hypersomnolence, and morning headaches with NPPV [1, 13]. The seminal paper was published in 1998 by Dr. Simonds and her colleagues [11]. This was an uncontrolled observational study examining the role of NPPV in chronic respiratory failure with survival, gas exchange, and quality of life as the outcomes. All patients had an average arterial pCO_2 of approximately 77 mmHg and average arterial pO_2 of approximately 56 mmHg breathing ambient air. They were nonambulatory, and therapy was initiated in the hospital for nocturnal use. Arterial pO_2 and pCO_2 levels improved significantly on NPPV, and these improvements were maintained over time as the patient continued to use NPPV (Fig. 8.5). A favorable impact on survival was observed (Fig. 8.6).

These observational studies demonstrated the benefits of NPPV in chronic respiratory failure, presumably allowing rest for the respiratory muscles, with improvement in gas exchange, lung compliance, lung volume, and mortality.

Indications and contraindications for NPPV in restrictive lung disease are listed below.

Indications [14–16]

1. Symptoms: morning headaches, daytime hypersomnolence, dyspnea
2. Signs: right heart failure or cor pulmonale
3. Gas exchange/ventilatory abnormalities:
   (a) Daytime arterial $pCO_2 > 45$ mmHg
   (b) Nocturnal oxygen desaturation $< 90\%$ for ≥ 5 min
4. Other:
   (a) Recovery from acute respiratory failure with persistent CO2 retention
   (b) Multiple hospitalizations for acute respiratory failure

Contraindications

1. Inability to protect airway: impaired cough or swallowing
2. Excessive airway secretions
3. Need for continuous ventilatory assistance
4. Inability to comprehend therapy

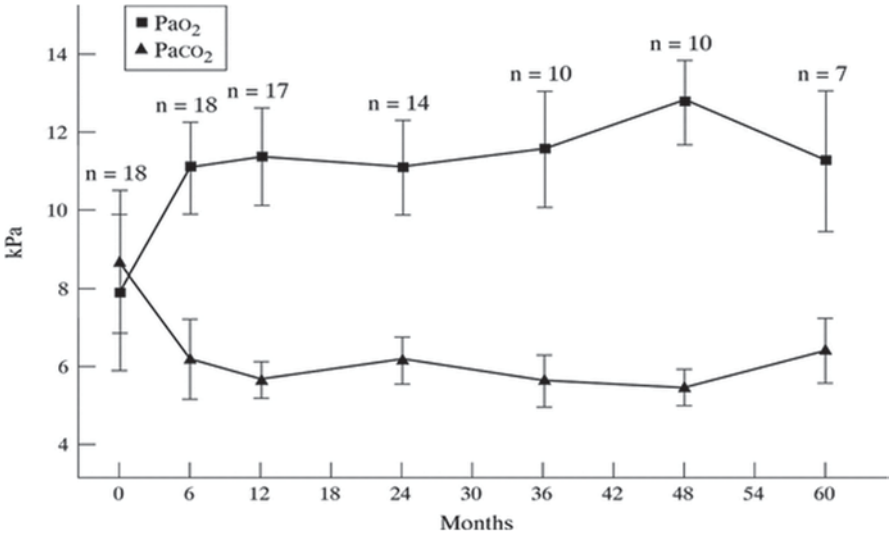

Fig. 8.5 Results of noninvasive ventilation in patients with chronic respiratory failure from neuromuscular disease in 18 patients. There was a decrease in baseline arterial pCO_2 levels (pCO_2 77 → 40–50 mmHg), while also improving oxygenation (pO_2 56 mmHg → 80–90 mmHg) [1]. *PaO_2* arterial partial pressure of oxygen, *$PaCO_2$* arterial partial pressure of carbon dioxide

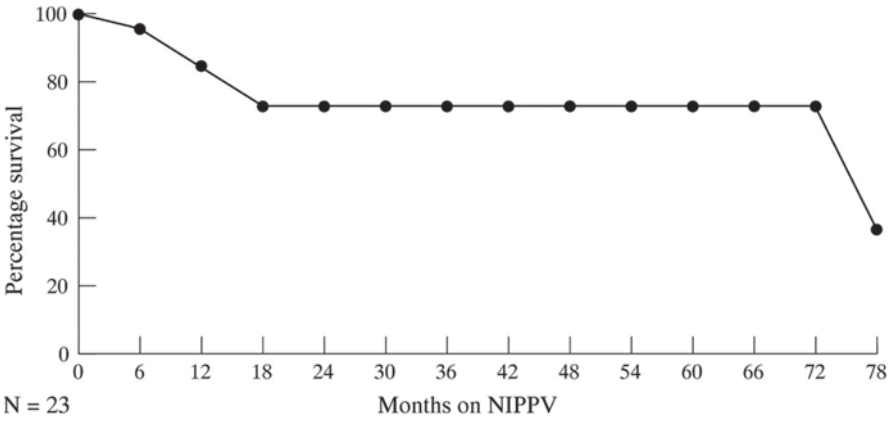

Fig. 8.6 Decline in mortality in 23 patients with chronic respiratory failure from neuromuscular disease using noninvasive positive airway pressure ventilation (*NIPPV* here). With the use of NIPPV, there is an initial slight decrease in survival (1-year survival 85%), but then there is a plateau in mortality from year 2 to 5, maintained at 73% with the use of NIPPV [11]

Obstructive Lung Disease The utility of NPPV therapy in obstructive lung disease is not as clear as in patients with restrictive lung disease. The literature supports the use of NPPV in acute or chronic respiratory failure in patients with obstructive lung disease (mostly COPD) by reducing the need for mechanical ventilation as well as by improving mortality and hospital length of stay. In one RCT, Plant et al. assessed the impact of NPPV in 236 participants with COPD exacerbations and respiratory acidosis (pH 7.25–7.35). NPPV demonstrated a reduced need for intubation (15 vs. 27 %, $p = 0.02$) and a more rapid improvement in respiratory acidosis [17].

The impact of NPPV in chronic respiratory failure for stable severe COPD has been inconsistent. One of the largest RCTs examining the role of NPPV in chronic respiratory failure for COPD was performed by McEvoy et al. [18]. In this study, 144 patients were assigned to either nocturnal NPPV and long-term oxygen therapy (LTOT) or LTOT alone. Participants on NPPV used a mean inspiratory positive airway pressure (IPAP) of 13 cm H_2O and mean expiratory positive airway pressure (EPAP) of 5 cm H_2O. Average objective adherence was 4.5 h a night. No difference in arterial pCO_2 or forced expiratory volume in 1 s (FEV1) was found between the two groups in 12 months of follow-up (Table 8.2 and Fig. 8.7). The study did identify a minimal survival advantage in participants with NPPV + LTOT over participants with LTOT alone, but this was at the expense of questionnaire-associated poorer general and mental health, and less vigor. Recently, Köhnlein et al. demonstrated a survival advantage of 1 year in patients with stable hypercapnic COPD patients randomized to NPPV versus usual care [19]. The survival benefit was only realized if the participants accepted therapy, and awake arterial pCO_2 was decreased by 20 % from baseline.

Table 8.2 Comparison of arterial pCO_2 (arterial partial pressure of carbon dioxide, *PaCO*$_2$) and forced expiratory volume in 1 s (*FEV1*) levels when treated either with noninvasive ventilation (*NIV*) and long-term oxygen therapy (*LTOT*) versus LTOT alone. There was no statistically significant difference in either arterial pCO_2 levels or FEV1 after either 6 or 12 months of therapy with NIV therapy when compared to LTOT [18]

		Baseline	6 months	12 months
$PaCO_2$ (mmHg)	LTOT	54.2 (52.0–56.4)	55.1 (52.1–58.1)	52.2 (49.5–54.9)
		$n = 45$	$n = 43$	$n = 29$
	NIV+LTOT	54.1 (51.7–56.5)	52.9 (50.5–55.3)	53.2 (50.6–55.8)
		$n = 54$	$n = 44$	$n = 43$
$FEV_{1.0}$ (% pred)	LTOT	23.9 (21.9–25.9)	23.4 (21.4–25.4)	26.3 (24.1–28.5)
		$n = 51$	$n = 47$	$n = 38$
	NIV+LTOT	25.3 (22.3–28.3)	24.9 (21.7–28.1)	24.1 (21.1–27.1)
		$n = 58$	$n = 56$	$n = 47$

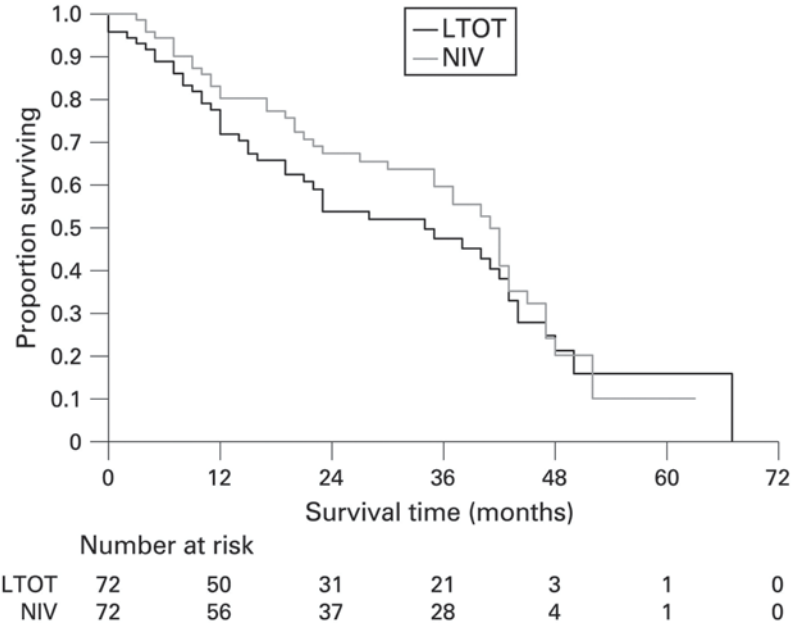

Fig. 8.7 Survival advantage: Use of noninvasive ventilation (*NIV*) + long-term oxygen therapy (*LTOT*) showed a minimal survival advantage when compared to LTOT alone [2]

Current indications for NPPV in obstructive lung disease due to COPD are listed below.

Indications [16]

1. Symptoms: fatigue, hypersomnolence, dyspnea
2. Gas exchange/ventilatory abnormalities:
   (a) Arterial $pCO_2 > 55$ mmHg
   (b) Arterial pCO_2 50–54 mmHg AND O_2 saturation < 88 % for > 10 % monitoring time
3. Pharmacologic therapy failure with maximal bronchodilators and steroids

Initiating Therapy

We have discussed the different modes of ventilation, types of NPPV, and the indications for initiating therapy. With the exception of the Köhnlein [19] report, no definite blueprint for success exists, and favorable outcomes depend on multiple variables.

Initiation of NPPV can be initiated in an inpatient or outpatient setting. Patients with restrictive lung disease or neuromuscular disease with chronic respiratory failure and who are followed by pulmonary physicians are likely to be monitored for alveolar hypoventilation (hypercapnia). These patients are frequently initiated on NPPV as outpatients in the sleep laboratory. This allows both the patient and the technologists, the entire night, to titrate the pressure, work on interface issues while minimizing unintentional mask leak, monitor ventilation with end tidal CO_2 or transcutaneous CO_2, and maximize patient comfort with the therapy as well as to determine whether treatment is optional for both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. These patients frequently have evidence of hypercapnic respiratory failure based on an awake arterial blood gas. Titration can be initiated during the daytime in the sleep laboratory, again working with the sleep technologist on making sure the pressure and interface work well with the patient. Patients with neuromuscular disease tend to do very well with NPPV because the etiology of their respiratory failure is due to progressive muscle weakness, and they have relatively normal lungs with normal respiratory system compliance. Improvements in quality of life and symptoms are readily achieved in this setting, which in turn encourages adherence to therapy.

For patients with acute respiratory insufficiency, initiation of noninvasive therapy is more troublesome. First, these patients present with acute onset of shortness of breath and impending respiratory failure possibly requiring intubation. They can have mental status changes associated with hypercapnic respiratory failure or may be hyperventilating from anxiety. The literature demonstrates that these patients do well with NPPV in the acute setting, preventing intubation and improving hospital length of stay [17]. Once the acute episode is resolved, some physicians will attempt to convert these patients to nocturnal NPPV in hospital in order to prevent further exacerbations of respiratory failure. This approach can be challenging for both the patient and the respiratory therapists responsible for treating the patient. First, in most instances there is no polysomnographic (PSG) evaluation of the sleep-related breathing disorder, if any, nor objective PSG-based titration of positive pressure to assess what patients can tolerate and is most effective for them; instead, they are typically started on an arbitrary IPAP and EPAP pressure. In addition, patients started on NPPV in the hospital frequently do not have access to all the different varieties of interfaces more commonly used in the sleep laboratory, and sometimes the prescribed NPPV may leave patients struggling with the interface they have been given. Finally, these patients are typically overcoming an acute respiratory illness, such as bronchitis, pneumonia, or viral upper respiratory infection (URI), and as a result may not be the optimal situation for starting and continuing on NPPV.

Despite efforts to provide the best therapy for the patient, there are limitations to NPPV, and some patients require more advanced therapy. Patients with obesity hypoventilation, for example, despite the use of high ventilatory support pressures, may continue to hypoventilate. Patients with neuromuscular disease whose disease advances, and/or who can no longer protect their airway and manage upper airway

secretions, may require tracheotomy-assisted ventilation. The benefits of tracheotomy and home ventilation compared with NPPV are: no air leak associated with the interface (if ventilated with the trache tube cuff inflated) and more efficient ventilation. Access to the airway for frequent and efficient suctioning of airway secretions is also of benefit in such a setting. The downside of such a therapy includes increased risk for infection, airway colonization, and the inability (in most cases) to speak. Additionally, patients with a tracheotomy typically require enteral nutrition through tube feeds via placement of a gastric feeding tube.

Tracking and Adherence

With the data management software available in many of the NPPV devices, we are fortunate to be able to objectively assess whether and how consistently the patient is using therapy, how well it is working, and to identify issues the patient may be having with therapy. This is a valuable tool to assist the clinician.

To date, there is no evidence in the literature that demonstrates monitoring patient adherence through data monitoring software actually improves acceptance of and adherence to therapy, or that it has any impact on long-term morbidity or mortality. However, clinical experience suggests that use of data management software can facilitate patient comfort, provide positive affirmation for those who use therapy well, and can help the clinician focus on specific issues that may be impeding progress with therapy. The following information is a clinical perspective of a best-practice approach that will hopefully lay the foundation for future work to verify and validate these management strategies.

Why Do We Track Compliance?

Patients are frequently initiated on nocturnal NPPV over the course of one night, having previously met criteria to qualify for therapy. Patients are first fitted with an interface that will work best and is most comfortable for them. Then positive pressure therapy is introduced by the technologist, following a previously planned titration algorithm. For those with chronic hypercapnic respiratory failure, there should be the ability to assess hypoventilation and/or apnea by measuring ventilatory effort, end tidal CO_2, or transcutaneous CO_2. The technologist will constantly monitor the patient and titrate the supportive pressure as needed. In some instances, an effective pressure prescription can be determined rather quickly. Other cases can be more of a challenge, and the technologist may spend the entire night titrating and attempting to get the patient comfortable with the therapy. The assessment of optimal nocturnal NPPV can be complicated by the duration of the sleep observed and the sleep architecture (e.g., achieving adequate REM sleep). Success can be negatively impacted by the environment, for example, a foreign location, and/or one

that is loud or disruptive (such as in a hospital). For all of the above reasons, it may be difficult to optimize nocturnal NPPV in one titration session. Barriers imposed by reimbursement and patient comfort frequently limit consecutive technologist-attended titration nights. It is for this reason that tracking acceptance and adherence to therapy is important for long-term management.

With the current data management software, the clinician can assess whether the device settings were sufficient after reviewing several days to weeks' worth of data under the patient's normal sleeping conditions. This helps the clinician determine whether there needs to be an adjustment in the delivered set pressure or volume, backup rate, or interface. These data allow the clinician to determine the degree of patient acceptance and adherence. Having longitudinal data to review allows the clinician and patient to work together to optimize treatment and address specific problems related to long-term therapy.

What Information Is Recorded?

When patients using NPPV present to clinic for follow-up, the tracking data can be obtained in multiple ways. Some machines are equipped with a modem or a cell phone chip, whereby the data can be uploaded remotely, without the patient bringing the machine to the clinic. In addition, all machines are equipped with a data card that resides in the back of the machine that can be removed and uploaded manually in the clinic using data management software. If the patient does not have a data card associated with the machine, selected devices allow data to be obtained from the machine itself. Virtually all positive pressure devices, including bi-level positive airway pressure, CPAP, adaptive servo-ventilation (ASV), AVAPS, and iVAPS offer the ability to review such data.

Usage

The initial data displayed on the report is usually the patient's usage. Tracking software can assess both how often and for how long the patient is using the therapy. The data report will show a breakdown of the patient's usage in days and hours, indicating usage patterns. Figure 8.8 provides an example of a patient's use of bi-level positive pressure ventilation over the course of several weeks. The *y*-axis displays hours of use while the *x*-axis displays dates in consecutive order. A minimum goal for patient usage of nocturnal NPPV that is extrapolated from the sleep apnea literature is typically considered to be 4 h a night. This concept is also applied to use of nocturnal NPPV for chronic hypoventilation. The bars in green represent individual nights/sessions that the patient achieved or exceeded the 4-h adherence threshold, while the red bars indicate that the 4-h threshold was not met. The total height of the bar represents the number of hours the therapy was used. Figure 8.9 displays

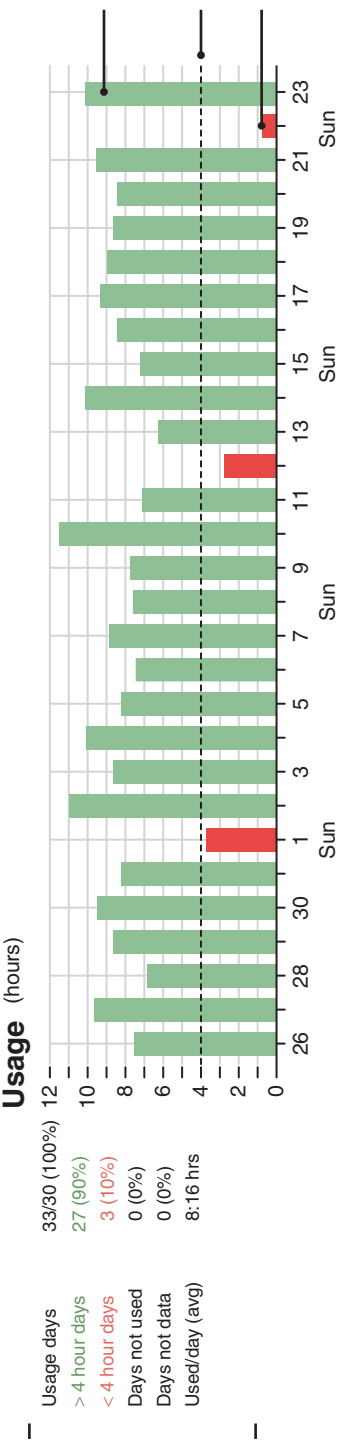

Fig. 8.8 Histogram analysis of patient's nightly usage of noninvasive ventilation. (Courtesy of ResMed)

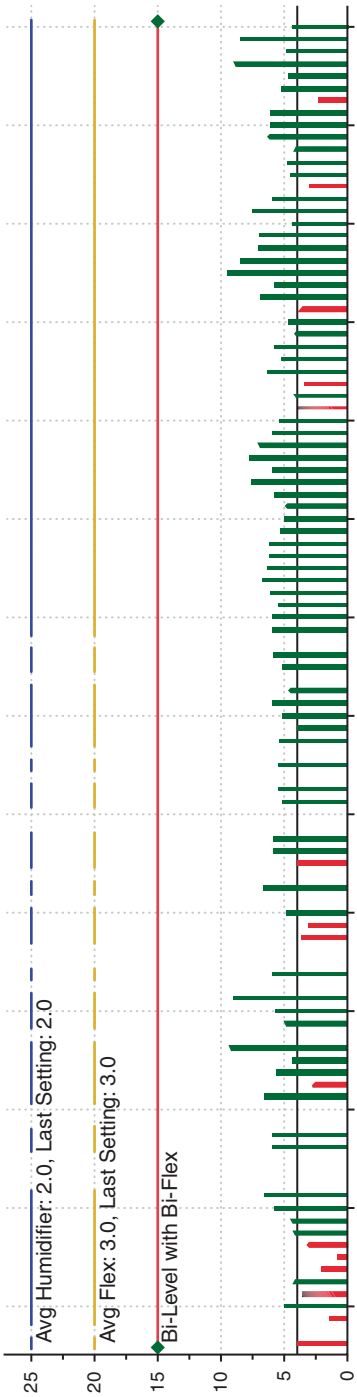

Fig. 8.9 Histogram analysis of nightly usage of noninvasive ventilation. *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure. (Courtesy of Respironics)

the same data in a different vender-specific format. In Fig. 8.10, a more granular breakdown of individual nights NPPV use over 6 weeks is displayed. The benefit of this view is that the clinician can see how long the patient has used the therapy overnight, if there was continuous or fragmented sleep, and for which days (or typically nights, if nocturnal NPPV has been prescribed) was the therapy not used at all.

Such objective data provide clinicians with the opportunity to validate and reassure those who have accepted therapy and are adherent on a regular basis.

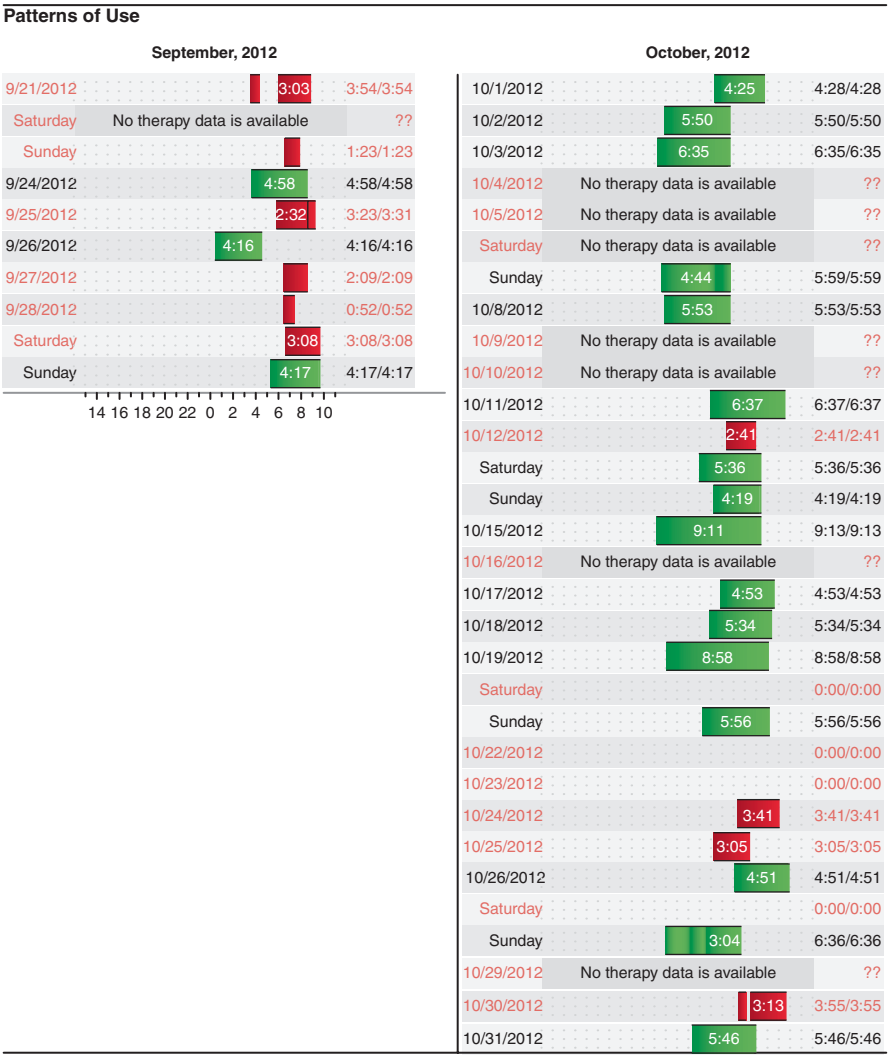

Fig. 8.10 Example of an individual's nightly usage of NPPV

Conversely, for those individuals with more variable usage, these data provide clinicians with the opportunity to discuss with the patient any issues they may be having with the therapy. Is the mask not fitting properly? Is the pressure difficult to tolerate? Is the patient's sinus congestion contributing to increased mask leak? Daily usage data is a key in improving treatment in patients.

Air Leak

When reviewing leak data, the unintentional leak is the key parameter. This is air escaping from the interface, either from a poor seal, or from an open mouth when using a nasal mask. When assessing the leak, the general rule is to observe the 95th percentile, which is the leak 95 % of the time the machine is in use. A general goal is that the 95th percentile air leak should be less than 24 L/min, which is a cutoff for both clinical and physiological efficacy. It is important to note, when interpreting data, that if a patient takes off the interface, for example, to use the washroom in the middle of the night but does not turn the machine off, it will indicate a leak, specifically a large leak (see Fig. 8.11).

Pressures/Tidal Volume/Respiratory Rate

Different modes of ventilation allow the clinician to either ventilate the patient in a pressure or volume control mode. With NPPV in pressure control mode, the clinician chooses both an inspiratory and expiratory pressure, and the difference between these pressures (i.e., the delta) determines the size of the delivered breath (Fig. 8.12). Some patients may be started on auto-bi-level, in which they are given a range for both the IPAP and EPAP and then a set pressure support, which is the difference between the IPAP and the EPAP. In general, for treatment of obstructive sleep apnea (OSA) the algorithm limits the delta between the IPAP and the EPAP to approximately 3 cm H_2O. This mode may also be sufficient to adequately ventilate a patient in chronic hypercapnic respiratory failure, particularly in the setting of comorbid OSA (Fig. 8.13).

With both bi-level and auto-bi-level positive airway pressure (PAP), the IPAP and EPAP pressures vary depending on the patient's airway anatomy, body position, and leak. Therefore, in pressure-controlled ventilation the tidal volume is variable (Fig. 8.14). In most patients, the patient's own respiratory drive sets the respiratory rate. Some conditions, however, require a set backup respiratory rate. NPPV allows the clinician to set this backup rate, and the data management software displays how often the patient exceeds the set rate and may insight into progression of disease (Fig. 8.15).

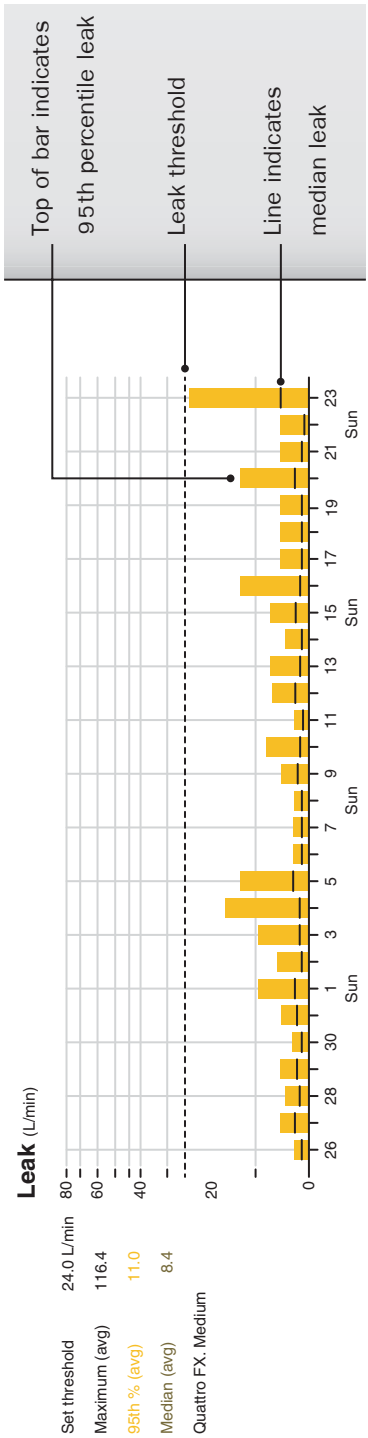

Fig. 8.11 Assessment of percentage of air leak during the use of NPPV. (Courtesy of ResMed)

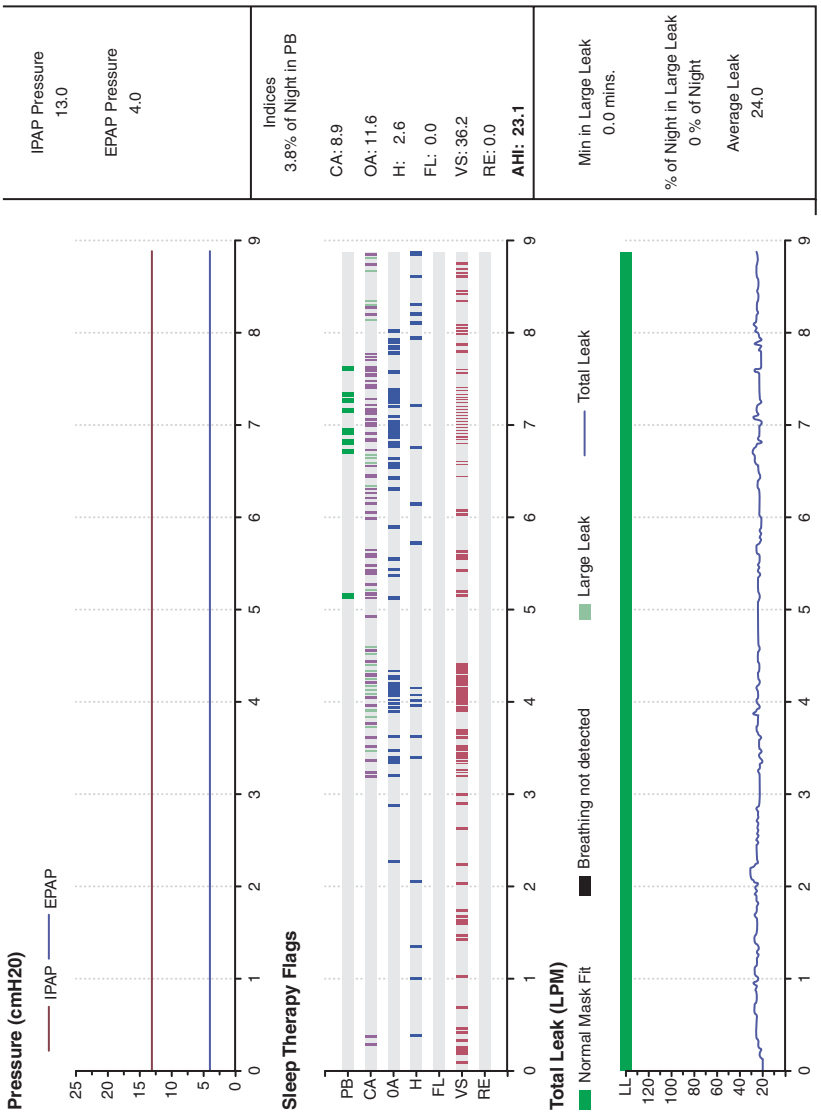

Fig. 8.12 Data analysis of individual events over the course of a 9-day trial of treatment with fixed inspiratory positive airway pressure (*IPAP*) and expiratory positive airway pressure (*EPAP*). *Top panel*: The IPAP is indicated by the *red bar* and the EPAP is indicated by the *blue bar. Middle panel*: number of events designated graphically (*center*) and in a tabular fashion (*right*). Displayed are periodic breathing (*PB*), central apnea (*CA*), obstructive apnea (*OA*), hypopnea (*H*), flow limitation (*FL*), vibratory snore (*VS*), and residual events (*RE*). *Bottom panel*: graphical and tabular leak data displayed. *AHI* Apnea hypopnea index

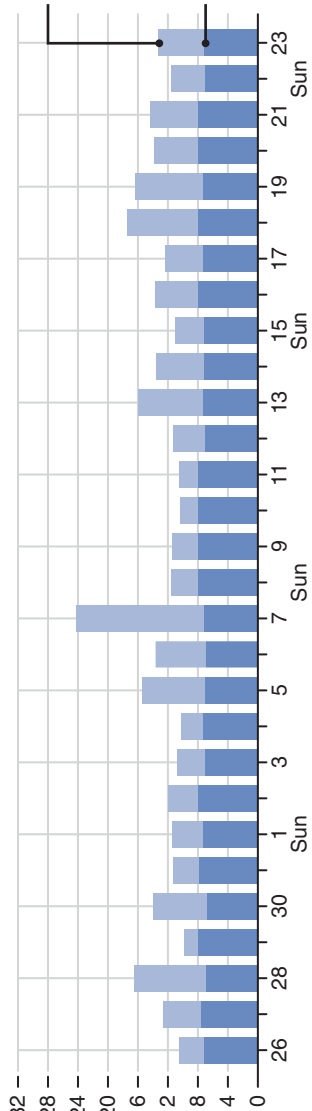

Fig. 8.13 Auto-bi-level positive airway pressure (*PAP*) assessment showing the range of pressure used by a patient and the variability between nights. The *top* of the *light blue bar* shows the 95th percentile of inspiratory positive airway pressure (*IPAP*) pressures and the *top* of the *blue bar* shows the 95th percentile of the expiratory positive airway pressure (*EPAP*)

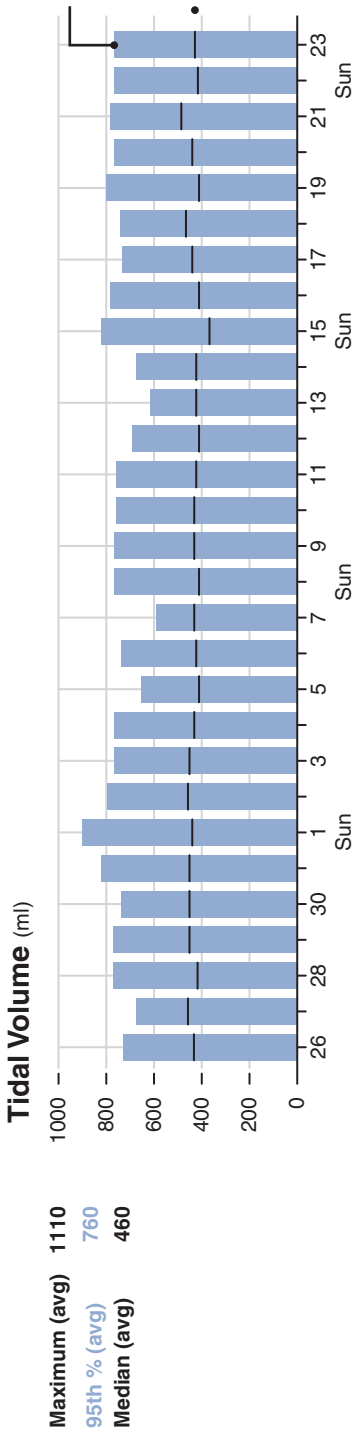

Fig. 8.14 Variability in tidal volume with auto-bi-level PAP

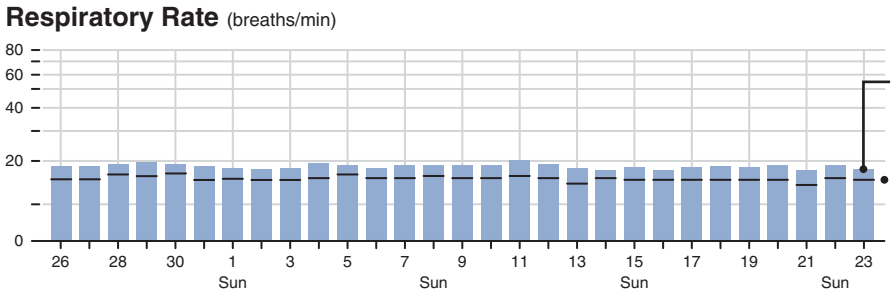

Fig. 8.15 Analysis of preset respiratory rate to treat hypoventilation due to either obesity hypoventilation or neuromuscular disease

Minute Ventilation

Minute ventilation is defined as the volume of air inhaled (inhaled minute volume) or exhaled (expired minute volume) within any 60-s period. Minute ventilation is an important target for assessing adequacy of therapy in hypercapnic respiratory failure. Based on the minute ventilation, the clinician can adjust either the IPAP, EPAP, volume-averaged pressure support and/or the respiratory rate to reach the goal minute ventilation that will be optimal for the patient (Fig. 8.16).

Apnea Hypopnea Index (AHI): The AHI is the number of apneas or hypopneas recorded per hour of sleep, or the number of events per hour of recording time if sleep is not specifically measured. Most reports include a reported AHI to assess how effective the therapy is. If the data download indicates an elevated AHI (typically considered >5) despite excellent adherence to therapy with nightly use, this suggests that the patient is not receiving enough pressure to adequately treat the sleep apnea. It could also be an indication that the patient has developed PAP-induced central apnea ("complex apnea" or "treatment-emergent central apnea"), and the patient may require another type of therapy (e.g., ASV and/or a backup rate) to treat the central apnea.

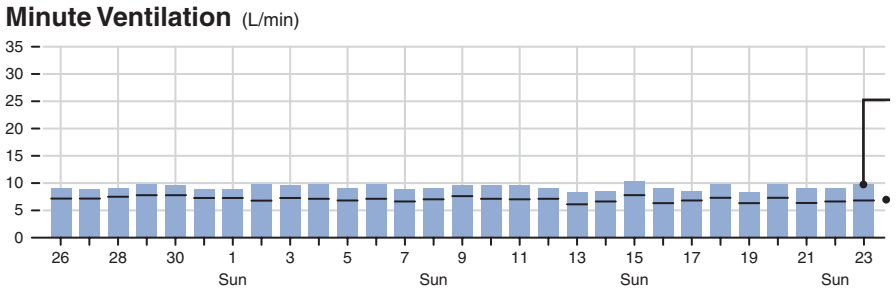

Fig. 8.16 Variability in minute ventilation based on changing both the inspiratory and expiratory pressure (IPAP and EPAP)

Trigger and Cycle Sensitivity

In more advanced NPPV, there is the ability to modify both the trigger and cycle sensitivity for patient comfort. Trigger sensitivity is how easily the patient can trigger the machine to deliver a breath or assist in a breath. In general, increased sensitivity is preferable to improve patient synchrony with therapy, especially in the neuromuscular patient population. However, in certain patient populations (COPD) excessively high sensitivity can lead to auto-triggering and potentially result in increased air trapping. Sensitivity can be pressure or flow triggered. Cycle sensitivity refers to the machine's adjustment of length of the respiratory cycle. Assessing NPPV efficacy data from one night is an efficient method of initiating treatment but is not ideal. Patients may sleep poorly or very well, may sleep in different positions (supine vs. lateral) or require hypnotic medications to initiate sleep, which they do not require in their homes. Health-care providers frequently determine therapy based on a snapshot of data, often under foreign (ecologically invalid for the patient) conditions. The degree/level/mode of necessary NPPV support may also vary on a nightly basis.

With the ability to objectively track data, health-care providers can assess if obstructive sleep apnea or hypoventilation is effectively treated. Leak data can provide insight relative to whether the interface is correctly worn and/or properly fit. Overall, data management software gives health-care professionals a more complete picture of the treatment in the patient's home conditions.

Adjusting Therapy Using Tracking Data

There are different approaches to adjusting NPPV for patients. First, patients can return to the sleep laboratory and undergo a repeat positive pressure titration. The benefit of this method is that the technologist will closely monitor the patient providing the clinician with the ability to assess the efficacy of the acute adjustments in therapy. Another option is to have the patient return to the sleep laboratory or durable medical equipment company for adjustment of the interface and education by the technologist. Using tracking data, the health-care provider may review the revised NPPV strategy and assess whether it is objectively effective as well as reassess patient comfort.

Limitations of Data Management Software

There are limitations related to the use of data management software that need to be addressed. First, standard data management software does not assess hypoxemia. A separate overnight pulse oximetry study may therefore be required while the patient is on nocturnal NPPV. Pulse oximetry allows for a more complete picture of whether hypoxemia was successfully treated with NPPV alone or if a prescription of entrained supplemental O_2 is necessary and/or adequate. Tracking software is also unable to directly assess the adequacy of treatment of nocturnal hypercapnia, as continuous end tidal CO_2 or transcutaneous CO_2 data are generally not collected in the home via this software. These data can be obtained in the sleep laboratory but not from NPPV tracking devices. Therefore, to assess whether gas exchange and alveolar hypoventilation is improved overall with nocturnal NPPV, patients are typically assessed with serial daytime arterial or venous blood gases. Providers can also monitor bicarbonate levels on routine labs to assess whether the patient may be retaining CO_2 to compensate for respiratory acidosis. Neither of these options allow for the ability to follow the efficacy of NPPV therapy addressing these critical parameters during sleep and specifically on a nightly basis.

While there appears to be clinical benefit for clinicians' use of adherence data in NPPV both to encourage adherence and assess problems in therapy, there is a deficit of literature to corroborate these clinical findings [20]. Considerable uncertainty exists regarding the accuracy of "advanced" data download reports that include measurements of leak, residual events (i.e., apnea/hypopnea/flow-limited events) and their characteristics (central vs. obstructive) [20]. Another barrier to efficiently using data download information is the variability in the nomenclature and presentation of the data that varies from vender to vender. At the present time, no peer-reviewed data have conclusively demonstrated that the use of data management software (i.e., data downloads) favorably impacts adherence or medical decision making in NPPV. The experience from the OSA population suggests, however, that using these data would be helpful.

There have been multiple studies looking at the role of acceptance of and adherence to continuous positive pressure in obstructive sleep apnea, and some insight can be gained from these reports. It has been well established that nasal CPAP is effective in correcting sleep-disordered breathing, but there continues to be significant resistance and intolerance to therapy, with reported failure rates as high as 25–50% of patients, many patients abandoning therapy in the first 12 weeks of therapy [21, 22]. The most common complaints leading to discontinuation of therapy include mask leak, nasal congestion, skin irritation, and difficulty tolerating the set pressure [23].

Adequate nasal CPAP compliance for obstructive sleep apnea has been operationally defined as >4.5 h of CPAP use on a nightly basis [24]. Early adherence studies were based on patient self-reported usage and have been demonstrated to overestimated usage. As technology has advanced, positive pressure machines have incorporated more sophisticated usage measures (e.g., time at set pressure) and additional physiological measures, giving a clearer picture of patient acceptance and adherence to therapy.

There are also data assessing the numerous techniques that have been used to improve patient acceptance and adherence to nasal CPAP for the treatment of obstructive sleep apnea (Table 8.3). First and foremost is patient education. When patients are given a clear and simple reason for therapy and how it works, compliance rates have been shown to increase [25]. There have also been studies evaluating the role of positive reinforcement over the telephone [26]. No difference was seen between the groups. There have, as well, been studies assessing efficacy of a patient's spouse or bed partner's involvement in the education process, with data showing

Table 8.3 Most common reasons for patient noncompliance with NPPV. (Adapted from Zozula [28])

Problem	Possible etiology	Available solutions
Mask issues		
Leak	Strap too loose or tight	Readjust headgear
Skin irritation	Incorrect mask size	Mask refitting
Pressure sores	Old/worn down interface	Inspect interface for breakdown or cracks
	Dirty equipment	Wash mask daily
		Replace equipment as needed
Nasal issues		
Nasal congestion	Dry air	Nasal saline spray
Epistaxis		Heated humidification
		Trial of nasal steroid
Oral care issues		
Dry mouth	Sleeping with mouth open	Use of Chinstrap
		Trial of full face mask
		Heated humidification
Eye issues		
Dry eyes	Mask too tight	Adjust headgear straps
Red eyes	Interface leaks	Eye patch
Swollen eyes		Inspect interface for breakdown or cracks
Conjunctivitis		
Sinus issues		
Rhinorrhea	Dry air	Nasal saline spray
Allergic rhinitis	Irritants in room air	Trial of inhaled nasal steroid
		Heated humidification
		Keep machine off the ground
		Use and change filters regularly
Machine issues		
Difficulty exhaling	Adjustment period	Trial of reduced pressure or longer ramp time
Noisy	Blocked air intake	Check air filters
Sinus discomfort	Too close to bed	Extra tubing
Bed partner issues		
Adjusting to therapy	Noise	PAP education for patient and spouse
	Anxiety	Support group
	Adjustment period	

PAP positive airway pressure

improvement in adherence [27]. Other techniques involve home-care interaction and education with the patient. It has been previously clinically demonstrated that when patients have a good interaction, it improves the patient's attitude regarding trying the therapy.

Overall, despite significant advances in technology for applying CPAP (better masks, auto-titrating machines, objective compliance monitoring), the keys to improving overall acceptance of and adherence to such therapy appear to be education and behavioral interventions. The use of recorded data is helpful in initiating a dialogue with patients to improve the understanding of therapy and the uses for it.

Ancillary Uses of Tracking Adherence: Cough Management

Many patients with chronic respiratory failure, especially those associated with neuromuscular disease, have difficulty mobilizing lower airway secretions due to their weak cough. It is extremely important in the long-term care for these patients to closely assess for the need for cough-assist techniques and machines, as the loss of a cough reflex puts the patient at increased risk for pneumonia and in some cases respiratory failure and acute respiratory distress syndrome (ARDS).

There have been numerous techniques used to manage and assist in patient cough, including breath stacking, oscillation, and chest vest vibration. The most effective has been the use of mechanical insufflation and exsufflation through a "cough-assist" machine. This is designed to give the patient a large breath at a set pressure, then hold the breath and quickly suck out the breath, simulating a cough and mobilizing secretions in the lower airway. This is very foreign to patients and requires some time to adjust to initiation of the therapy. It is extremely important to provide proper education about the use of such therapy, including how to use it, how often to use it, and techniques for tolerating the pressure. In most cases, it is essential for patient comfort to gradually build up the pressure until the patient and attendants get used to the new technique. Newer technology with the cough-assist machine offers tracking software to evaluate how often and effectively patients are using therapy. In addition, the upgraded technology called "cough trak" has an automatic sensitivity feature that allows the device to synchronize to the patients breathing pattern. It aids device titration and allows for more control of therapy in a comfortable and more natural treatment.

Conclusions and Future Directions

NPPV has made a significant impact on the treatment of acute and chronic respiratory failure over the past several decades. Despite its established use, there are little data addressing acceptance of and adherence to this critical therapy in outpatient

management. There have been multiple studies demonstrating different methods to improve acceptance and compliance in the obstructive sleep apnea population, specifically using CPAP, and some of these data may be extrapolated to patients using NPPV, although more trials demonstrating the validity and value of data management software directed at patients using NPPV are necessary. The current technology has the potential to provide substantial data including daily use, leak, and control of sleep-disordered breathing, and minute ventilation and tidal volume. Additional limitations of such tracking data include a lack of oximetry and continuous CO_2 monitoring, which are important in assessing the success of NPPV in the settings it is commonly used. Future research is necessary to better define the role of current and future tracking systems for improving NPPV efficacy and patient outcomes.

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Chapter 9
Use of nNIV in Obstructive Sleep Apnea: Modes, Flexes, and More

Jeremy A. Weingarten

The advent of positive airway pressure (PAP) for the treatment of obstructive sleep apnea (OSA) as a form of "nocturnal non-invasive ventilation" (nNIV) enabled clinicians to finally offer patients with this debilitating disease a viable and acceptable treatment modality. Previously, the only effective treatment for OSA was tracheostomy [1], a method of mechanically bypassing the upper airway, thereby avoiding the consequences of repetitive upper airway closure during sleep. Obviously, tracheostomy was not readily accepted by patients with OSA. With the seminal publication by Colin Sullivan and colleagues in 1981 [2], a new era of treatment for OSA with PAP therapy was begun. During the next three decades, technological advances resulted in the development of a plethora of PAP delivery modes (Fig. 9.1), which have complicated and may potentially improve the treatment of OSA.

Continuous Positive Airway Pressure

The first publication demonstrating the effective use of continuous positive airway pressure (CPAP) therapy in patients with OSA was in 1981 by Colin Sullivan and colleagues [2]. In their initial study, Sullivan et al. developed both a nasal interface, which was made from soft plastic tubes fit into each nostril and sealed by silicone rubber, and a "vacuum cleaner blower motor" connected by a wide-bore tube that could control the level of pressure delivered via mechanical narrowing of the free end of the tube. Five patients with generally severe OSA characterized by a mean apnea index of 62 events per hour during non-rapid eye movement (NREM) sleep and 64 events per hour during rapid eye movement (REM) sleep were fitted with a nasal interface and underwent polysomnography (PSG) with CPAP applied. The patients demonstrated complete cessation of obstructive events and marked improvement in sleep continuity, with CPAP pressures ranging from 4.5 to 10 cm H_2O. Each patient remained awake and alert for the entirety of the following day, in stark contrast to their daytime hypersomnolence prior to using CPAP.

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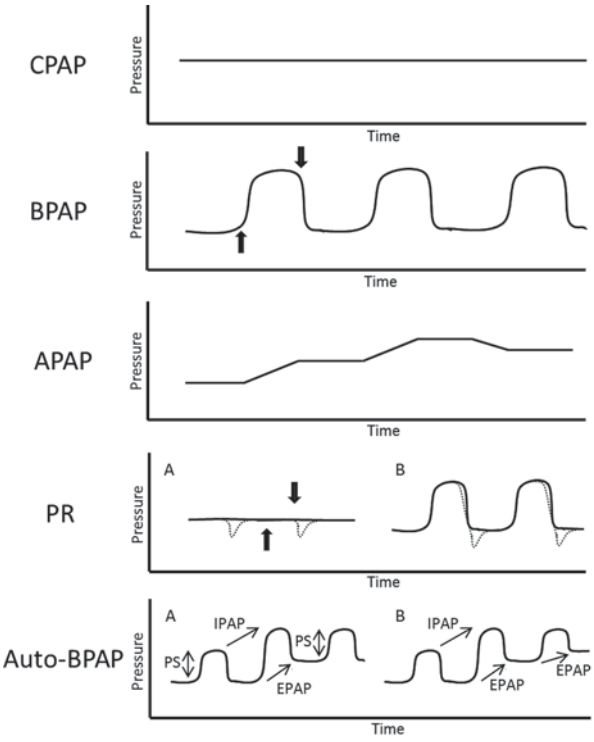

Fig. 9.1 Pressure versus time relationships among different types of positive airway pressure (PAP) devices. (*CPAP* continuous positive airway pressure, *BPAP* bi-level positive airway pressure, *APAP* autotitrating positive airway pressure, *PR* pressure relief (A—CPAP with PR; B—BPAP with PR); *Auto-BPAP*—Auto bi-level positive airway pressure (A—Auto-BPAP with fixed pressure support (*PS*); B—Auto-BPAP with independent inspiratory and expiratory PAP (IPAP and EPAP)). ↑—initiation of inspiratory phase; ↓—initiation of expiratory phase)

Despite early contradictory reports of the effectiveness of CPAP therapy [3, 4], it has become the standard of care for the management of OSA. CPAP consistently shows improvements in the apnea–hypopnea index, Epworth sleepiness scale (ESS), multiple sleep latency test (MSLT), maintenance of wakefulness test (MWT), and quality of life parameters as compared with placebo or conservative management in a recent systematic review [5]. CPAP is the standard of care therapy for moderate to severe OSA and should be considered in patients with mild OSA, particularly in those with daytime symptoms and/or other significant comorbidities [6]. The generally accepted mechanism by which CPAP resolves obstructive events is by acting as a pneumatic splint, maintaining patency of the upper airway in the setting of decreased intraluminal pressure during inspiration [7].

Nonadherence to CPAP therapy is a major challenge in the management of OSA. Adherence rates have been estimated to range from 46 to 83 % when adherence is defined as CPAP use of at least 4 h per night [8]. Current recommendations to improve compliance with PAP include close follow-up, the utilization of heated humidification, and CPAP educational programs [6]. Device manufacturers and the medical community have approached the problem of CPAP nonadherence by developing alternate modes of delivering PAP (bi-level PAP, autotitrating PAP) and pressure waveform modification (C-Flex, Bi-Flex, expiratory pressure relief (PR)). The remainder of this chapter discusses these differing modalities in an evidence-based manner in order to provide the practitioner a working knowledge of the current technology of PAP therapy.

Bi-level Positive Airway Pressure

The first description of bi-level PAP (BPAP) in 1990 [9] investigated the potential of providing differential pressures during inspiration and expiration with the hope of lowering positive pressure during the expiratory phase in order to improve comfort while still maintaining airway patency. Thirteen patients underwent a full night diagnostic PSG, a CPAP titration PSG, and BPAP titration PSG. BPAP was titrated based on the respiratory events: inspiratory PAP (IPAP) was increased for desaturation events while expiratory PAP (EPAP) was increased for apneic events. CPAP and BPAP were equally effective in resolving OSA. Final mean pressures were 14 cm H_2O for CPAP and 14/8.9 cm H_2O (IPAP/EPAP) for BPAP, confirming that despite a lower mean airway pressure, obstructive events were prevented. Some individuals required oxygen supplementation during the CPAP study, while the same individuals did not with BPAP study.

In randomized controlled trials evaluating CPAP versus BPAP in newly diagnosed patients with OSA, BPAP was not found to improve compliance with therapy. Reeves-Hoche and colleagues randomized patients with OSA (apnea-hypopnea index (AHI) $\geq$ 10 events/h) to 12 months of CPAP or BPAP therapy following in-laboratory PAP titration [10]. BPAP titration differed from the study by Sanders et al. in that CPAP was initially increased to resolve apneas followed by an independent increase in IPAP to eliminate hypopneas and snoring. There was no difference in the mean machine timer hours over the 12-month period. Of note, dropout was higher in the group randomized to CPAP. In a second study, 27 PAP naïve patients were randomized to CPAP or BPAP with Bi-Flex (Respironics) after separate titration nights with each device and followed for 1 month [11]. There were no observed differences in compliance, and the improvement in the ESS and the functional outcomes of sleep questionnaire (FOSQ) were similar between the groups. Because of these findings, BPAP is not recommended as a first-line PAP therapy for OSA, although it could be considered as an optional therapy in patients with CPAP intolerance due to high pressures [6]. The use of BPAP in patients with coexisting hypoventilation syndromes is not included in this review or in these recommendations.

Although PAP naïve OSA patients do not demonstrate improved usage patterns with BPAP when compared with CPAP use, failure of CPAP therapy, either during the titration study night or on follow-up after PAP has been used in the home, may be an indication to consider BPAP therapy. In a two-phase intervention trial of OSA patients with poor CPAP compliance, Ballard and colleagues demonstrated that compliance may be improved with BPAP therapy [12]. Of 204 patients with OSA, 24 % became compliant ($\geq$4 h of nightly CPAP use) after phase 1 of the trial, which consisted of educational measures, mask adjustment or replacement, therapy for nasal symptoms, and initiation of heated humidification. If these measures failed to increase CPAP adherence, patients underwent a "split-night" titration trial with 4 h of CPAP and 4 h of Bi-Flex (BPAP with pressure modification, to be discussed later). The patients were then randomized to home CPAP or Bi-Flex therapy for 3 months. The Bi-Flex group demonstrated greater compliance (49 % vs. 28 %; $p = 0.03$) and a higher increase in mean FOSQ scores from baseline compared with CPAP treatment.

Based on these findings, routine administration of BPAP after a diagnosis of OSA does not improve treatment adherence and hence, cannot be recommended. However, if a patient demonstrates treatment noncompliance with CPAP despite behavioral and medical optimization (education, humidification, mask fitting, nasal steroids for rhinitis, etc.), second-line therapy, of which BPAP is an option, should be considered. The choice of which second-line modality (BPAP, oral appliance, surgery) to pursue depends on the patient characteristics and preferences. If BPAP therapy is pursued, a formal in-laboratory titration should be performed to ensure pressure optimization and improved patient comfort. Of note, differences in BPAP titration techniques and pressure modifications (Bi-Flex vs. BPAP without pressure modification) may result in variable outcomes and different rates of improvement in adherence.

Autotitrating Positive Airway Pressure

The purported utility of BPAP therapy for OSA was to decrease expiratory pressure, and therefore mean airway pressure, against which an individual must breathe, thereby increasing comfort with the device and subsequent improvement in compliance. Another strategy for improved compliance that was and is still being explored relies on varying the delivered pressure throughout sleep via device-specific algorithms, which fluctuates between higher and lower pressures to relieve flow limitation and obstruction, as changes in position and sleep stage may require. The characterization of flow limitation was a crucial first step in this process [13]. Condos and colleagues demonstrated that upper airways resistance is increased when the contour of the flow-time curve is flattened. Automated analysis of the flow-time curves could then be used to guide computer-generated adjustment of pressure in the setting of obstructive respiratory events. Current autotitrating positive airway pressure (APAP) technology relies on the determination of obstructive events characterized by flow limitation (flattening of the flow-time curve), apneas (no or markedly reduced flow over time), and snore (measured via vibration sensors). In addition, current devices use the forced oscillation technique (FOT) [14] to help determine whether reduction in flow is obstructive (i.e., non-patent airway) or nonobstructive. If events are obstructive, delivered pressure will be increased, while raising pressures during non-obstructive events (central apneas or hypopneas) can be avoided. The FOT is a measure of mechanical impedance of the respiratory system that is determined by applying high frequency, low amplitude pressure waves via the mask interface; patterns of FOT help determine if the airway is open (patent) or closed (obstructed) [15].

APAP and CPAP demonstrate equal efficacy in relieving obstructive respiratory events and improving daytime functional parameters. In the first randomized controlled trial of APAP versus CPAP, 16 patients with OSA were randomized to fixed CPAP with pressure determined from full PSG (P_{eff}) or APAP (minimum pressure—(P_{eff} −2 cm H_2O), maximum pressure—(P_{eff} +4 cm H_2O)) [16]. Sleep and

respiratory parameters were similar with CPAP and APAP therapy (AHI, total sleep time, sleep architecture). Following 3 weeks of PAP therapy, patients in both groups demonstrated equal improvement in ESS, MWT, and the trail making test (a test of cognitive impairment) compared with baseline; no differences between the groups were detected. Subjects randomized to APAP spent 49 % of the time requiring pressure below P_{eff}, suggesting that APAP use at home may deliver pressures lower than that determined during a titration study for a significant portion of the night and thereby improve tolerance of PAP. Along these lines, another study of 15 patients with generally severe OSA demonstrated a positive correlation between the polysomnographically determined P_{eff} and the time spent below P_{eff} on APAP [17]; patients with more severe OSA may benefit to a greater extent with APAP due to spending a greater duration of the night at pressure levels below P_{eff}.

Although there is some evidence that APAP improves compliance compared with fixed pressure CPAP, the evidence depends on the study type and the improvement is of questionable clinical importance. A Cochrane Collaboration review demonstrated a statistical improvement of 0.21 h of machine usage time in crossover studies comparing APAP to fixed CPAP [18]. Although statistically significant, an overall increase of 13 min per night is not likely to result in improvements in clinically meaningful outcomes. Crossover trials generally show equivalent residual AHI between APAP and fixed CPAP [19–23], equal improvement in ESS scores from baseline [19–21, 24–26], and a reduction in delivered pressure with APAP treatment [20, 22, 23]. Although there was a general patient preference for APAP treatment [21, 22], this was not a universal finding with some patients preferring fixed CPAP [20]. Similarly, improvement in machine usage was not a universal finding; among parallel studies or the first arm of crossover studies, a statistically significant difference in machine usage was not seen (mean increase in machine usage with APAP—0.22 h (−0.05, 0.49; 95 % CI)) [18].

It is clear from the above discussion that APAP compared with CPAP therapy in an unselected patient population showed minimal to no improvement in treatment adherence and conflicting data on patient preference. However, several groups observed APAP treatment in patients with CPAP intolerance or those with high pressure variability to determine if these subgroups of OSA patients may benefit from APAP therapy. In one study, 27 patients with an AHI ≥ 20 and a high variability index, which was a calculated value based on the variability of pressures required during a 2-week run-in period on APAP, were randomized to 8 weeks of CPAP or APAP followed by crossover to the other treatment [27]. Machine usage time was not significantly different between the groups; however, mean pressure and ESS scores were lower in the APAP group and a greater number of participants chose APAP over CPAP when simply asked which device they preferred. Another study looked at a mixed population of patients in which CPAP was not the optimal treatment, as defined by patients with CPAP intolerance, CPAP requirements ≥ 12 cm H_2O, or central respiratory events accounting for ≥ 10 % of events [22]. Patients were randomized in a crossover fashion to either BPAP or APAP for 6 weeks each. Both modalities significantly improved respiratory parameters (although mean residual AHI while on PAP in each group was > 5) and sleep quality. Patients again preferred

APAP treatment as a long-term therapy for their sleep-disordered breathing. Although the heterogeneity of this study population prevents any firm conclusions, the search for subpopulations that may benefit from APAP therapy, as illustrated in these two studies, is an important strategy in improving patient's acceptance of PAP therapy, thereby improving overall outcomes.

APAP devices rely on brand-specific proprietary algorithms that use a variety of methods for detecting respiratory events and adjust pressure settings differentially. An early trial evaluated devices guided by "flow limitation ($APAP_{fl}$)" versus "FOT ($APAP_{fot}$)" for determining the presence of respiratory events [28]. In a group of 30 patients with moderate to severe OSA (AHI $\geq$20 events per hour) treated with each device in a "split-night" setting (4 h/device), there was a trend towards lower AHI in the $APAP_{fl}$ group, higher overall pressure in the $APAP_{fl}$ group, and greater pressure variability in the $APAP_{fot}$ group. Although based on this study it is unclear which detection system is more accurate in identifying obstructive respiratory events, most current devices use a combination of flow limitation and forced oscillation in order to identify both obstructive and non-obstructive events. Several studies have compared devices produced by competing manufacturers [29, 30]. It is apparent from these studies that there is variability in delivered pressure and respiratory parameters between the various devices but the clinical significance is unclear.

Although the concept of APAP was well conceived in attempting to lower average positive pressure and improving patient compliance with PAP devices, the evidence does not support this. Overall usage of APAP was slightly increased when all studies are taken into account, although these results were highly dependent on the type of study and the patient population studied. In an attempt to combine other technology with APAP, two recent studies looked at APAP with expiratory PR (which will be discussed in the next section) to further improve patient comfort [31, 32]. When compared with fixed CPAP, APAP with expiratory PR (see the following section) was essentially equivalent with respect to sleep/respiratory parameters and outcomes. Consistent with prior studies, the patients in one study were satisfied with both regimens but preferred APAP treatment [32], while in the other study, patients were less satisfied and felt they derived less benefit with APAP therapy [31]. Without clear and convincing evidence supporting the superiority of APAP over CPAP, this treatment modality cannot be recommended at this time except on an individual basis.

Pressure Relief

Many device manufacturers have developed technologies to decrease applied positive pressure during the expiratory phase in order to improve compliance with the device by encouraging more physiologic transitions between inspiration and expiration. Brand-specific algorithms differ in the degree and timing of such Pressure Relief (PR) [33, 34]. The pressure decrement is either flow based (pressure drop proportional to patient's flow amplitude) or prespecified (i.e., 1 cm H_2O, 2 cm H_2O

or 3 cm H_2O). Likewise, the pressure decrement is either in the early portion of the expiratory phase (returning to set pressure prior to inhalation) or throughout the entire expiratory phase. PR may be utilized in most modes of PAP, including CPAP, APAP, and BPAP. Although when in CPAP or APAP mode PR appears to be very similar to a bi-level mode of ventilation, the main difference is that the pressure differential between IPAP and EPAP is usually lower than 3 cm H_2O in PR mode and PR can be set in a stepwise manner (increase settings for more PR) as compared with the completely independently set IPAP and EPAP of BPAP therapy.

Similar to findings with APAP, there was no major difference in adherence when CPAP with PR was used compared with CPAP alone in clinical trials. This was confirmed in a systematic review [18] and meta-analysis [35]. Several randomized controlled trials comparing CPAP with PR versus standard CPAP demonstrated equal compliance between the two devices [36–41]. In one trial [41], low compliers, defined as those using standard CPAP for <4 h per night, demonstrated improved compliance using CPAP with PR compared with standard CPAP. Another trial demonstrated improved compliance with CPAP with PR [42]; however, this trial was limited by non-blinded patients. In patients with severe OSA defined as AHI > 30/h or AHI 20–30/h with ESS > 12, there was a trend towards improved compliance (4.7 vs. 3.0 h per night, $p = 0.15$) in one study [39]. Overall, it is apparent that PR does not improve compliance with PAP therapy based on the current literature, although certain patient populations (low compliance, severe OSA) may achieve better compliance from this modality. Further research into these patient populations is needed.

PR did not improve subjective sleepiness scores (ESS and Stanford sleepiness scale (SSS)) when compared with standard CPAP [36, 37, 42]. Conversely, one study demonstrated improved ESS in patients treated with standard CPAP when compared with CPAP with PR [39]. When objective measures were assessed, studies found no differences in psychomotor vigilance testing (PVT) and modified MWT results between those randomized to CPAP with PR or standard CPAP [36, 39]. Although vigilance measures and objective sleepiness would not be expected to change if compliance was similar between the groups, Marshall et al found a trend towards increased compliance in the CPAP with PR group (4.7 vs. 3 h, $p = 0.15$) without improvement in PVT or modified MWT measures [39]. Despite a lack of benefit seen with PR technologies, patients frequently preferred this modality over fixed CPAP [37, 38].

Auto-Bi-level Positive Airway Pressure

The most recent foray into technologies to improve compliance and comfort with PAP devices is auto-BPAP. Similar to the situation with APAP, algorithms and device settings are different among different manufacturers. One manufacturer's device analyzes the flow-time curve and adjusts pressure based on the presence of flow limitation, apnea events, and snoring events [43]. Clinical inputs include

EPAP minimum, IPAP maximum, and pressure support (PS). The device initiates PAP at the minimum EPAP setting, with IPAP delivered at EPAP + PS. IPAP is then increased when respiratory events (flow limitation, apnea, snore) are detected, delivering an appropriate pressure to resolve the events, with EPAP now delivered at IPAP—PS. For example, if $EPAP_{min}$ is set at 4 cm H_2O and $IPAP_{max}$ at 25 cm H_2O with a PS of 4 cm H_2O, the patient will initially receive an EPAP of 4 cm H_2O and IPAP of 8 cm H_2O. If obstructive respiratory events are detected and the device increases pressure to an IPAP of 18 cm H_2O, EPAP will now be 14 cm H_2O. Another manufacturer's technology differs in that the device adjusts EPAP and IPAP independently, with increases in EPAP based on detection of apnea and snore events and changes in IPAP based on detection of hypopnea and respiratory effort-related arousal events [44]. Clinical inputs for the device with independently adjusted IPAP and EPAP are as follows: $EPAP_{min}$, $IPAP_{max}$, PS_{min}, and PS_{max}. PR technology is also available with both devices described above.

In the only trial of auto-BPAP versus standard CPAP in patients with moderate to severe OSA requiring PAP for the first time, 35 patients were randomized and evaluated after using their respective device after 12 weeks [45]. Sleep parameters and AHI were not significantly different between the groups. ESS and the Pittsburgh Sleep Quality Index were improved in both groups but not significantly different between groups. Likewise, compliance with therapy was not significantly different between the groups. The final pressures in each group were 9.5 cm H_2O in the CPAP group and ~12/9 cm H_2O in the auto-BPAP group.

Although there was no benefit regarding AHI, subjective sleepiness levels, or compliance in using auto-BPAP in PAP naïve patients with OSA, several investigators have observed the utility of this modality in patients noncompliant with CPAP, intolerant of CPAP, or failed CPAP titration. In an observational cohort study, patients noncompliant with CPAP (CPAP use <4 h for $\geq 70\%$ of nights over the preceding 3 months) were initiated on auto-BPAP with PR and followed at 10 weeks [46]. Although the residual AHI was lower with auto-BPAP, both modalities (CPAP and auto-BPAP) resulted in AHI below five events per hour. Sleep parameters were not significantly different among devices. ESS and some domains of the FOSQ were improved with auto-BPAP. Most interesting, compliance was improved as compared with baseline and even more so in the subgroup of patients who initially required CPAP$\geq$10 cm H2O. In patients who failed CPAP use due to pressure intolerance, single night comparisons of standard BPAP versus auto-BPAP showed no significant differences in AHI or sleep parameters [47]. Finally, in a randomized controlled trial of 47 patients who initially failed CPAP titration (defined as sleep efficiency $\leq 70\%$, ≥ 20 arousals per hour, aborted titration, or "persistent sleep disruption despite therapeutic CPAP therapy and low probability of CPAP compliance in the judgment of the reviewing physician"), patients were prescribed either CPAP or auto-BPAP with PR [48]. At 30 and 90 day follow-up, there were no significant differences in compliance, Epworth Sleepiness Scale (ESS) scores, Functional Outcomes of Sleep Questionnaire (FOSQ) scores. Although there may be a role for auto-BPAP, particularly in patients who are CPAP intolerant and require higher pressures, further studies are indicated.

Summary

The development of PAP as a therapy for OSA has provided patients with this disorder a noninvasive, effective treatment modality. CPAP remains the gold standard treatment among nocturnal PAP modalities. Due to poor compliance with standard CPAP therapy, technological innovation has resulted in the development of multiple devices that alter pressure delivery designed to improve patient comfort and subsequently patient compliance. This has not been demonstrated in clinical studies. BPAP did not show improved compliance in PAP naïve patients, although it may be beneficial in patients with CPAP noncompliance. APAP demonstrated a slight improvement in compliance, although the improvement was not clinically meaningful. PR technologies did not improve PAP compliance. Similarly, auto-BPAP did not improve compliance rates in PAP naïve patients, although this technology is in its infancy.

Interestingly, specific subgroups of patients may actually benefit from these new technologies, such as those intolerant to CPAP, patients with high pressure requirements, and patients who did not achieve satisfactory results on the initial titration studies. The identification of patient populations that will require these technologies will be a fruitful line of inquiry as we strive towards an effective therapy for all patients with OSA. Regardless of the deficiencies in the current literature, a logical stepwise approach to management of poorly compliant patients actively on CPAP therapy should be undertaken: (1) education, mask adjustment, treatment of nasal symptoms, and initiation of heated humidification, (2) initiation of PR (most standard CPAP devices have this capability), (3) trial of APAP therapy, (4) in-laboratory bi-level titration with initiation of BPAP if study results are adequate or initiation of auto-BPAP if titration is not optimal. Although not formally studied, this stepwise approach utilizes the spectrum of current technologies in a practical way to assist patients in their pursuit of an effective therapy.

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Chapter 10
Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure

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Introduction

"Invasive" positive pressure mechanical ventilation (IppV) has become, with the development of endotracheal intubation and novel generations of ventilators, the gold standard for treating acute respiratory failure (ARF) [1]. As such, IppV has revolutionized the management of patients with ARF and has changed the prognosis of many otherwise fatal disorders. However, because of the necessity to apply positive pressure directly below the glottis through an endotracheal tube, thus bypassing the upper airways, IppV carries its own associated morbidity and mortality [2–8]. This limits the use and benefit of IppV in specific populations, for example elderly patients [9], chronic obstructive pulmonary disease (COPD), [10] idiopathic pulmonary fibrosis (IPF) [11], and cystic fibrosis [12]). For Patients with acute lung diseases traditionally regarded as an "ideal" indication for IppV (acute respiratory distress syndrome (ARDS), severe hypercapnic respiratory failure), the risk of hospital acquired infection, prolonged hospital stay, difficult weaning or reintubation [13] have now led to the development of strategies aimed at using noninvasive positive pressure ventilation (NIV) [10, 14]. Alternative solutions to IppV can also now be offered to patients chronically ventilated (e.g., neuromuscular deficit) or for whom intubation carries a poor prognosis (e.g., lung resection) when presenting with ARF [15]. A similar approach can be applied to the populations of patients with do-not-resuscitate (DNR) orders who can still benefit from an effective treatment of an acute and reversible episode of respiratory failure [16–18].

The recent development of noninvasive methods of ventilation for sleep related disordered breathing has made it possible to use new interfaces, ventilators and procedures, in treating various types of ARF [19–23]. NIV can be applied in most medical centers and critical care units or even, for very specific populations of patients

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[24, 25], at home [26]. The utilization of NIV for ARF has been accompanied by an important research effort to rationalize and define the proper indications, contraindications, and modality of administration to be used by the health care community to successfully implement NIV in an acute setting.

Since the 1980s, the number of publications on this topic has increased dramatically. Recommendations from the British Thoracic Society [27], based on available data and current practices have been published and the use of NIV has been evaluated in several clinical trials summarized in many excellent reviews [20, 23, 28–37] and clinical practice guidelines [21, 38]. NIV is also currently used in various forms of acute respiratory exacerbation for which clinical trials are lacking, such as neuromuscular deficit [26]. Nevertheless, (1) the evidence gained on the use of NIV for treating chronic respiratory failure, such as in patients with *chronic* hypoventilation [20], (2) the clear success of NIV in certain populations of patients based on retrospective or noncontrolled prospective studies, and (3) our understanding of the pathophysiology of the mechanisms of respiratory failure has led many to consider NIV as a valid option to treat different types of ARF in the absence of definitive evidence. Finally, even in populations of patients wherein evidence is against the use of NIV as a group, well selected patients can still benefit from NIV. More physiological studies are needed to improve the interfaces, develop additional strategies of respiratory therapy (e.g., assisting cough and nutritional support), and better understand patient–ventilator interaction during NIV in ARF [39, 40].

In this chapter, we will discuss the main indications, limitations, and modalities of NIV use in the context of acute or acute-on-chronic respiratory failure in a critical care setting. We will also present the current evidence linking sleep disturbances and the prognosis of NIV and attempts to apply domiciliary NIV in selected patients with acute respiratory distress.

NIV: Physiologic Rationale and Benefits

NIV combines a continuous end-expiratory pressure (CPAP) with an intermittent inspiratory pressure support (or assist), and thus exerts its effects on the respiratory system via both of these two components. Briefly, while the CPAP component allows the maintenance of the functional residual capacity (FRC) above the position of relaxation of the respiratory system in patients with reduced lung compliance, continuous positive pressure can, at low levels, diminish the intrinsic positive end-expiratory pressure (PEEP) in COPD patients [41]. The intermittent inspiratory pressure component is aimed at improving alveolar ventilation. Indeed, the positive intermittent pressure applied to the respiratory system (Prs) via a face mask is expected to overcome (1) the elastic properties of the respiratory system delivering sufficient tidal volume [42] to keep minute and thus alveolar ventilation at a "reasonable" level, (2) the resistive properties of respiratory system and, as such, to generate flow during inspiration and (3) to a lesser extent the inertia properties of the lungs and chest wall. Any patient unable to produce a level of transthoracopulmonary pressure capable of mobilizing a sufficient level of alveolar ventilation could in theory benefit from NIV.

The interactions between the end expiratory and intermittent positive pressure components are, however, more complex than the simple addition of the primary effects described above. For instance, in addition to its direct effect on alveolar ventilation, intermittent positive pressure, by recruiting lung volumes and preventing microatelectasis, also plays a significant role in restoring FRC [20]. The intermittent component may therefore improve blood oxygenation in patients with decreased lung compliance (e.g., pulmonary edema) regardless of the increase in alveolar partial pressure of oxygen (PAO_2). Similarly, the beneficial effect of the intermittent pressure component on muscle mechanics along with the reduction in the respiratory muscle activity contributes to the decrease in intrinsic PEEP [20]. The combination of inspiratory pressure support and CPAP has other advantages: (1) by reducing the work of breathing, this combination may reduce dyspnea [43] and (2) in patients with decreased ejection fraction, improvement of the left ventricular function can be obtained through a decrease in afterload [44]. This effect is, however, balanced by the potential reduction in cardiac preload and the resulting decrease in cardiac output produced by the increase in intrathoracic pressure. Any beneficial hemodynamic effect can therefore only be obtained if the decrease in afterload reduces the cardiac work more than the drop in venous return.

Clinical Applications of NIV During ARF

The role of NIV continues to expand with evidence of increasing usage in numerous acute disease states [45, 46]. The benefits of NIV include fewer patients referred to intensive care units for intubation, shorter stays in intensive care units, and fewer deaths (see [20] for review). Current level 1 evidence (randomized control trials) exists for favorable outcomes of NIV in patients with acute exacerbation of COPD (AECOPD), cardiogenic pulmonary edema, and immunosuppressed patients, as well as to facilitate weaning from mechanical ventilation in patients with COPD [47]. Level 2 evidence (cohort studies) exists for use in patients with a "do-not-intubate (DNI)" status, postoperative respiratory failure, and in COPD patients with community acquired pneumonia [47]. However, there appears to be increasing evidence suggesting poorer outcomes in the use of NIV in patients with ARDS, severe community acquired pneumonia, and prevention of extubation failure [47].

We will now address the specific use of NIV in patients presenting with different variations and underlying etiologies of ARF, including the supporting evidence and current clinical considerations.

NIV in COPD with Acute Exacerbation

AECOPD remains poorly defined but is characterized in a COPD patient by a "… change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability to warrant a change in management [48]." Severity has been defined by

three treatment settings (level 1-home, level 2-hospital, level 3-respiratory failure), with recommendations that all patients requiring inpatient treatment of their AECOPD undergo arterial blood gas analysis.

In the late 1980s and early 1990s studies were published touting the benefits of NIV for patients presenting with ARF related to COPD exacerbations. The main impetus for this paradigm change in ventilator support appears related to the known risks, complications, and poor outcomes associated with the need for mechanical ventilation in these patients [49–52]. In one of the earlier studies utilizing NIV, a case-control design demonstrated significant improvement in the avoidance of endotracheal intubation in patients presenting with AECOPD (1/13 patients requiring intubation versus 11/13 patients requiring intubation) [53]. Since that time, data continue to accrue on the successful use of NIV in patients with ARF related to AECOPD. The literature (including numerous randomized controlled trials) continues to support improved outcomes with the use of NIV in AECOPD including mortality [10, 36, 47], need for intubation [10, 36, 47], complications [10, 36], and length of hospital stay [10]. Other objective demonstrable improvements identified include a reduction in partial pressures of carbon dioxide [54, 55], respiratory rate [19, 54], as well as dyspnea score measurements [55]. These improvements appear related to an increase in alveolar ventilation, reduction in inspiratory muscle workload, and the resultant respiratory muscle fatigue [41, 53, 54, 56]. This had led to a significant increase in the utilization of NIV in COPD exacerbations throughout intensive care unit (ICU)'s in the USA [46]. Many authors defend the current opinion that patients presenting with AECOPD, evidence of respiratory failure, and in the absence of contraindications, a trial of NIV is now the standard of care [10, 36, 47, 52, 57].

The presence of AECOPD and respiratory failure (or potential thereof) appears to be the appropriate target population for NIV use. However, two studies have demonstrated no significant benefit for NIV use in hospitalized patients with AECOPD [58, 59]. Both these studies have been criticized for enrolling patients with mildly abnormal blood gas abnormalities and therefore many of their patients may not have been at risk for respiratory failure and subsequent endotracheal intubation, highlighting proper patient selection to be crucial in the decision to utilize NIV in patients with AECOPD.

The proper selection of patients for NIV initiation remains a subject of some controversy. A large systematic review of patients undergoing NIV for AECOPD concluded that patients with severe exacerbations of AECOPD benefited by reducing the need for intubation, length of hospital stay, and inhospital mortality. However, this benefit was not present in patients with mild AECOPD exacerbations [60], suggesting that patients with more severe exacerbations (hypercapnia, academia, etc.) benefit the most from NIV. The benefit is most likely limited to the more severe exacerbations, as those with mild exacerbations would most likely improve on standard medical therapy of bronchodilators and corticosteroids.

The initiation of NIV therapy will often occur within the emergency department or the medical ward, and controversy currently exists as to the proper location for NIV to be initiated [52]. The safe and effective application of NIV will most likely vary within each institution (emergency room, intensive care unit, medical floor,

etc.). The successful use of NIV has been linked to patient–ventilator coordination, decreased air leak from the mask appliance, and cooperation [52], all of which may be affected by the ongoing presence of medical personnel. The use of NIV has been associated with increased time commitments from nursing and respiratory therapy [54, 61], especially during the initiation of NIV.

NIV in Hypercapnic Respiratory Failure in Patients Without COPD

Patients with status asthmaticus and CO_2 retention have been offered NIV [62]. Some studies show a reduction in hospital admission and decrease in airway resistance, including improvements in forced expiratory volume in 1 second (FEV1), [63]. Some authors have supported the view that a short-term trial may be started in patients who do not respond to initial bronchodilator and anti-inflammatory treatment [64]. This approach remains controversial as intubation in the case of acute hypercapnic respiratory failure is still considered first-line therapy in such asthmatic patients when assisted ventilation is indicated. In their guidelines for the use of NIV in the acute setting, Kennan et al. [21] made no recommendation about the use of NIV in patients who have an exacerbation of asthma because of insufficient evidence, whereas the recommendations of the British Thoracic Society [27] are clearly against the use of NIV in acute asthma due to the lack of data.

NIV has also been attempted in cystic fibrosis patients as a “bridge to transplantation” [65, 66]. Few case series are available, but the severity of the respiratory insufficiency and spontaneous high mortality in this group of patients when presenting with ARF makes it difficult to definitively evaluate the beneficial effects of this approach [66]. Although the effect is more on the level of intrapulmonary shunting and ventilation-perfusion (V/Q) mismatch rather than on the level of alveolar ventilation—suggesting that the end expiratory pressure is very likely to play an effective role in the changes occurring during NIV in patients with cystic fibrosis—the indication remains hypoventilation.

Patients presenting with an acute exacerbation of obesity hypoventilation syndrome also appear to benefit from NIV [67]. The major decrease in the compliance of the respiratory system along with the increase in its inertial properties, however, typically requires the use of high levels of positive pressure to overcome the reduction in alveolar ventilation in morbidly obese patients. This represents a major limitation in the use of NIV which otherwise does represent a good indication to treat acute hypercapnic respiratory failure in these patients. Finally, as part of the management of post-extubation failure, El-Solh et al. [68] reported in obese patients with various causes of ARF—and not only primarily obesity hypoventilation syndrome—a reduced hospital mortality in the NIV group compared with the control group in hypercapnic patients at the time of extubation. Most patients treated with NIV following extubation did have a reduction of hospital stay.

NIV in Cardiogenic Pulmonary Edema

Current recommendations regarding the management of ARF in the setting of cardiogenic pulmonary edema often include the use of NIV [27, 69], along with the use of oxygen therapy, in hypoxemic patients [69, 70]. The European Society of Cardiology currently recommends that NIV "…should be considered as early as possible in every patient with acute cardiogenic pulmonary edema and hypertensive acute heart failure…" [69]. These recommendations have been supported by numerous studies suggesting improved outcomes, including decreased need for endotracheal intubation, in patients receiving NIV in the setting of respiratory failure secondary to cardiogenic pulmonary edema [71–73]. NIV offers a number of potential benefits to patients presenting with cardiogenic pulmonary edema. As hypoxemia is often related to V/Q mismatch and intrapulmonary shunt effects, NIV (CPAP, more specifically) is potentially beneficial via its ability to increase intrathoracic pressure and decrease shunting, thereby increasing arterial oxygenation and decreased work of breathing/dyspnea. As mentioned in the previous paragraph, CPAP decreases left ventricular afterload. Caution is needed during the initiation of CPAP in patients that are preload dependent as they may experience a decrease in cardiac output due to a decrease in venous return [74]. In contrast to meta-analyses supporting a reduction in mortality and decreased need for endotracheal intubation [33, 75], the most recent randomized, multicenter trial demonstrated no significant difference in survival or need for intubation in patients with cardiogenic pulmonary edema [76]. It also appears that NIV can be utilized safely and successfully in patients developing acute cardiogenic pulmonary edema on the medical ward. Combined with optimal medical therapy, a success (avoiding the need for endotracheal intubation or death) rate of 85 % (38/45) was obtained through the use of NIV by a medical emergency team [77].

After the initial introduction of NIV in the acute cardiogenic pulmonary edema population, two studies surfaced identifying a potential increase in the rate of myocardial infarction in patients receiving fixed bi-level positive airway pressure (bi-level PAP), for acute cardiogenic pulmonary edema versus CPAP. In the first study, Mehta et al. [78] identified patients with acute cardiogenic pulmonary edema who were randomized to receive CPAP versus bi-level PAP within the emergency room. The study was terminated at the first interim analysis after an increase in the rate of myocardial infarction in the bi-level PAP arm was discovered. Even though patients were enrolled in a randomized fashion, at the time of enrollment more patients in the bi-level PAP arm had chest or jaw pain (n= 10) compared with the CPAP arm (n = 4), with half of these patients experiencing a subsequent myocardial infarction. At enrollment, two patients (both in the bi-level PAP group) had abnormally high creatine kinase concentrations, with seven additional patients experiencing a rise in creatine kinase concentration within 12 h of admission. The authors offered a number of potential explanations for the increased rate of myocardial infarction, including increased severity of illness at enrollment and higher incidence of myocardial ischemia at presentation. They also discussed potential causative effects of bi-level PAP in leading to ischemic extension of cardiac infarction, which includes

a reduction in cardiac preload leading to a decreased cardiac output, potentially worsening an already ischemic heart. In a second study by Sharon et al. [79], a higher incidence of myocardial infarction was again identified in the bi-level PAP versus CPAP group (55% vs. 10%), along with a significantly higher incidence of endotracheal intubation in the NIV group (80% vs. 20%). This study also remains one of the outliers in regard to its exceedingly high intubation rate in the NIV arm.

A recent meta-analysis has also demonstrated a small increase in the incidence of myocardial infarction rate in patients receiving bi-level PAP when compared with CPAP. However this difference was not apparent when comparing bi-level PAP versus conventional therapy. Overall, the question still remains as to the "reality" and "meaning" of the increased myocardial infarction rate with the use of bi-level PAP in patients who are not otherwise at risk of acute coronary syndrome. Peter et al. [80] have suggested that bi-level PAP devices may increase the effort of breathing due to their complexity, with more potential for ventilator–patient asynchrony (and physiologic/hemodynamic disturbances), and also offer potential coronary vasoconstriction in the setting of rapid correction of respiratory acidosis—thereby increasing the risk of cardiac infarct. Current recommendations regarding this controversy appear within the British Thoracic Society guidelines [27]. They suggest the use of CPAP in patients presenting with acute pulmonary edema, and reserving the use of bi-level PAP in patients "…in whom CPAP is unsuccessful." However, definition of the unsuccessful CPAP patient is not clearly identified according to our review of the guidelines. These guidelines are unable to identify all clinical presentations in which the use of NIV could be beneficial, and particular methods and modes of ventilation need to be tailored to each situation.

NIV in Immunosuppressed Patients

Current data remain questionable for the use of NIV in patients without rapidly reversible etiologies of respiratory failure (e.g., pneumonia). However, NIV does appear to offer potential benefit in immunocompromised patients presenting with ARF (hypoxemic and hypercapnic). Although many patients may present with an acute pneumonic processes or ARDS, the use of NIV appears to decrease the need for endotracheal intubation and mortality in different classes of immunocompromised patients, including hematologic malignancies and solid organ transplants. Antonelli et al. [81] randomized patients developing ARF after solid organ transplantation to receive NIV versus standard oxygen therapy. Liver, lung, and kidney transplant patients were included with common diagnoses being cardiogenic pulmonary edema and ARDS. Significant improvement was identified in the NIV group wherein PaO_2 increased and the need for endotracheal intubation decreased; however, only trends towards improvement were noticed in length of ICU stay and mortality. Rocco et al. [82] specifically looked at the use of NIV in 21 lung transplant patients developing ARF in the immediate postoperative period. They identified significant improvements in gas exchange abnormalities as well as the avoidance of endotracheal intubation in 86% of their cohort with the use of NIV.

Patients with hematologic malignancies are also at increased risk for the development of pulmonary complications, respiratory failure, and subsequent death [83–85]. In a randomized trial of 52 immunosuppressed patients developing ARF, the use of NIV decreased the requirement for endotracheal intubation, serious complications (sepsis and ventilator associated pneumonia), ICU mortality, and hospital mortality when compared with standard treatment of supplemental oxygen via venturi facemask delivery [86].

A large multicenter observational study of over 150 ICUs and 1300 patients with hematologic malignancy (although hematopoietic stem cell transplant patients were excluded) found that upon the development of ARF 21 % were initially treated with NIV, of which 46 % subsequently required endotracheal intubation. The need for invasive mechanical ventilation was associated with higher mortality, and propensity-score adjustment identified that NIV was associated with lower mortality. The authors concluded that ARF in the hematologic malignancy patient should probably be managed initially with NIV [87]. In contrast, Depuydt et al. [85] identified 27 hematologic malignancy patients receiving NIV and compared them to a 1:2 matched cohort (based on the simplified acute physiology score II) receiving endotracheal intubation. They reported that in-hospital mortality was equivalent (65 %). NIV was associated with the ability to avert endotracheal intubation in 31 % of the patients, although in those requiring subsequent endotracheal intubation the mortality rate was 92 %. An increased mortality after failure of NIV has also been identified in a cohort of patients by Adda et al. [88]. They identified 99 hematologic malignancy patients developing ARF in which the hospital mortality in patients failing NIV was 79 %, compared to 41 % in those where NIV avoided endotracheal intubation. The largest limitation to the above studies remains their observational and mostly retrospective nature, and as such questions still remain regarding appropriate patient selection and timing for endotracheal intubation within this population. The increased mortality related to NIV failure may be attributed simply to the presence of worsening respiratory disease and/or improper patient selection and/or timing for NIV. However many still agree, including these authors, that NIV can be used successfully in this patient population in the appropriate settings and with a proper understanding of when endotracheal intubation is indicated [20, 85, 87, 88].

NIV in Patients with Neuromuscular Disease and ARF

As patients with neuromuscular diseases represent a very small sample of the general population admitted for acute, or more frequently acute-on-chronic, respiratory failure, no clinical trial is currently available to evaluate the benefit of NIV in this specific population. This population is nevertheless regarded as a favorable candidate population for NIV. Reviews on this question quote the very interesting retrospective study of Bach et al. [89] who offered an original view on the benefit of NIV during acute exacerbation in patients with neuromuscular disease. The approach consisted in using home NIV and assisted coughing to treat or prevent

episodes of acute O_2 desaturation. Although episodes of O_2 desaturation may not be specific markers of acute ventilatory failure, and these authors' approach included aggressive assisted coughing, the group of 24 patients treated with this protocol at home had a dramatically decreased rate of hospital admission (6 vs. 72 for a control group).

Weaning from Invasive Positive Pressure Ventilation

a) Can We Reduce the Duration of Mechanical Ventilation Using NIV?

In an attempt to reduce the length of intubation along with all its associated side effects [90], the possible benefit of early extubation aided by NIV has been investigated since the early 1990s [32]. The use of NIV for this indication carries the rationale of being able to both speed recovery during the weaning period from mechanical ventilation, and/or to prevent reintubation. Indeed, early studies suggested that there was a benefit in using NIV to facilitate weaning in various populations of patients, including tracheostomized, difficult to wean, and trauma patients.

In a randomized, controlled trial, Nava et al. [91] investigated the benefit of two strategies using NIV in COPD patients in whom a weaning protocol was implemented. These two strategies consisted in programed extubation and immediate application of NIV or weaning with NIV with early extubation. After 2 months of mechanical ventilation, about 30% of the patients who were intubated remained ventilated versus 20% for the NIV protocol, with a shorter period of mechanical ventilation and less complications in the latter. This benefit of weaning using NIV on the duration of mechanical ventilation, hospital stay, and mortality was not confirmed by Girault et al. [92]. This study found that although NIV allowed an earlier removal of the endotracheal tube and reduction in the duration of daily mechanical ventilatory support, without increasing the risk for weaning failure, the total duration of ventilatory support for weaning was about four times longer than in their group receiving mechanical ventilatory support. One of the most convincing trials supporting the use of NIV in facilitating weaning is the study of Ferrer et al. [93] who found that that the use of NIV in a population largely composed of intubated and mechanically ventilated COPD patients was associated with shorter ICU and hospital stay, less tracheotomy procedures, and lower incidence of nosocomial pneumonia. The conventional weaning approach (i.e., without the use of NIV) was an independent risk factor for worse ICU survival. These positive results should be understood in the light of the study of Jiang et al. [94], who evaluated the effect of NIV on outcomes following extubation in 93 patients among whom there were 56 elective extubations and 37 unplanned extubations so NIV used was post extubation in all. No significant difference in reintubation rate between the two groups was found. Therefore, not all randomized trials (see for review [95]) confirm the benefit of "premature" extubation, earlier than typically based on their usual practice, while using NIV.

b) Can Reintubation Be Prevented by NIV?

Some trials have looked carefully at patients who failed planned extubation. For instance, in the study of Jiang et al. [94], NIV was initiated as soon as the patient was extubated but no clear benefit of using NIV in terms of reintubation was identified. In these data the use of NIV did not take into account the presence of risk factors (factors as noted below) as it was applied in all patients after extubation without distinction between patients. When specific populations, regarding specific risks of reintubation, are considered, such as hypercapnia, hypoxia, or tachypnea, outcomes appear to be different. For example, in a study published in 2006, Ferrer et al. [96] reported that the early use of noninvasive ventilation averted respiratory failure after extubation and decreased ICU mortality among patients at increased risk of reintubation. Similar results were found by Nava et al. [91]. In all these studies the benefit is clearly observed in hypercapnic patients for whom noninvasive ventilation improved ICU mortality. The vast majority of these patients (98 %) had chronic respiratory disorders. On the other hand, a longer delay in reintubating patients treated with NIV could be a cause of higher mortality in the NIV group. El-Solh et al. [68] looked at the incidence of respiratory failure in the first 48 h post-extubation in 62 consecutive severely obese patients who were assigned to NIV via nasal mask immediately post-extubation. There was a significant difference in the ICU and hospital lengths of stay between this specific population of patients versus 62 historically matched controls. A subgroup analysis of hypercapnic patients showed reduced hospital mortality in the NIV group compared with the control group. The question remains whether other specific types of patients at risk of reintubation may also benefit from NIV.

A different, although related, question is certainly that of the efficacy of initiation of NIV after extubation only once signs of respiratory distress occur. Hilbert et al. [97] studied patients who, within 72 h post-extubation, presented with persistent tachypnea and/or an increase in $PaCO_2$ of at least 20 % above post-extubation values. They found that 6 of the 30 patients (20 %) treated with NIV were reintubated versus 20 of the 30 patients in the control group. The mean duration of ventilatory assistance and the length of ICU stay were also shortened by the use of NIV. A study of Keenan et al. [98], however, revealed a more nuanced picture, since they found a similar rate of reintubation whether NIV was initiated or not when signs of respiratory failure occurred.

Meta-analyses performed by Burns et al. [32] and Ferrer et al. [95], regarding use of NIV for weaning found that it is predominantly patients with COPD who consistently show positive effects on NIV weaning on mortality and ventilator associated pneumonia. In these patients, NIV is consistently effective in earlier extubation and decreasing complications associated with prolonged invasive ventilation in intubated patients with chronic respiratory disorders and difficult or prolonged weaning from mechanical ventilation. More studies are needed to describe in other pulmonary diseases the potential beneficial and deleterious effects of initiating NIV immediately following extubation versus waiting for signs of respiratory distress. Benefits of NIV for rapidly reversible complications following extubation, such as

glottic edema, also remain to be established. In their extensive review on "withdrawal from mechanical ventilation," Ferrer et al. [95] defend the view that NIV is not effective in preventing reintubation and may be even harmful in a mixed population who develop extubation failure, whereas NIV does prevent extubation failure and improve outcome in patients with predominant hypercapnic respiratory failure. In conclusion, while there is no clear evidence supporting the use of systematic NIV in patients after extubation, there appears to be a benefit in specific groups of patients such as hypercapnic COPD patients.

NIV in "DNR/DNI" Patients

Patients and/or families at the end stages of disease may consider the declaration of a DNI or DNR order, which has been accepted by many physicians as a treatment option providing patients and families the ability to manage death [20]. Interestingly, in these DNI patients, treatment of respiratory failure may involve the use of NIV [99–102]. A recent questionnaire has also revealed that many physicians believe NIV can play a significant role in palliative treatment measures, specifically aiming at the relief of dyspnea or allowing for more time related to family members coping with the impending death of their loved one [16].

A number of studies have attempted to look at the phenomenon of treating this patient population (patients refusing endotracheal intubation) and the outcomes associated with this approach. Bulow and Thorsager [96] published a 2-year follow-up study on Danish patients admitted to their ICU with a DNI order who received treatment with NIV for ARF. Of their 38 identified patients, 11 survived to discharge, although 5 of these patients died within the subsequent 6 months. They concluded that NIV may be a reasonable option in those with DNI orders, but also emphasized that of the few long-term (>6 months) survivors they had within their cohort, all had evidence of COPD or heart failure as the etiology of their respiratory failure. Cuomo et al. [103] identified 23 patients with solid malignancies currently receiving palliative treatment only, presenting with respiratory failure. These patients underwent NIV, and over half (56%) responded well to treatment with subsequent discharge to home. The authors concluded that the use of NIV may be appropriate in this patient population if they have a reversible cause of respiratory failure.

Levy et al. [101] identified a cohort of DNI patients receiving NIV in the setting of ARF in which 43% survived to discharge. Factors predicting survival included the presence of congestive heart failure, strong cough, and being awake at presentation. Azoulay et al. [102] published a large multicenter European cohort of patients receiving NIV for ARF. They identified approximately 700 patients over a 2-month period receiving NIV, of which 19% had standing DNI orders present. The DNI patients had significantly higher hospital mortality, 44% compared with 12% in those without care limitations (i.e., they would have undergone endotracheal intubation if required). However, the authors did note that at 90-day follow-up, there was no significant decline in quality of life questionnaires, nor significant increase in anxiety or depression scores when compared with those undergoing full management.

Management of NIV During Acute Respiratory Failure: When to Attempt NIV and What to Watch for

The decision to initiate NIV in a patient with ARF should not only take into account the expected benefits of this mode of ventilation on alveolar ventilation, FRC, intrinsic PEEP, VQ mismatch, and hemodynamics, but must also consider the anticipated magnitude of the mechanical alterations which will limit the applicability of NIV. Indeed, the maximum level of positive intermittent pressure support and end expiratory pressure applied during NIV, much lower than during IppV, is the main limiting factor for efficacy. Clear contraindications to the use of NIV must first be identified [21] Absolute contraindications [27] comprise cardiac or respiratory arrest; conditions wherein respiratory failure is part of hemodynamic or neurological conditions including septic, hemorrhagic, cardiogenic shock, or coma; recent facial surgery or trauma; fixed upper-airway obstruction, and conditions associated with an increased risk of aspiration. The experience of the team and the physician taking care of the initiation as well as the follow up of the patient care is also an important parameter to consider.

Nava and Ceriana [104] have proposed different steps to determine if a patient with ARF is a good candidate for NIV versus intubation. The first step is to determine the need for ventilatory assistance itself. This decision is typically based on the association of clinical signs of respiratory failure such as paradoxical abdominal motion, and accessory respiratory muscle activation, along with a respiratory acidosis (pH <7.35). For the patient presenting with significant hypoxemia due to pulmonary edema, criteria are not as clear. As a general rule, NIV failure in hypercapnic respiratory failure can be as low at 5% but as high as 40%. Therefore whenever NIV is initiated, even if patients belong to a population wherein NIV has been shown to be effective, the possibility of subsequent need for intubation must always be considered and discussed.

Aside from the contraindications discussed above, specific predictors of NIV failure do not exist when it comes to a given patient. Some factors which have been identified as associated with NIV failure in this setting include edentulous patients with pneumonia, higher Acute or Chronic Health Evaluation II score, lower level of consciousness, lower pH, more air leak around the interface, greater quantity of secretions, and the presence of pneumonia overall [27]. Pursed-lip breathing, and inadequate mask-mouth seal have also been associated with NIV failure. Among NIV failure patients, Plant et al. [105] found a lower pH and higher $PaCO_2$ at the initiation of therapy. In other words, NIV is less likely to be successful in the most acutely ill/medically compromised patients. The nature of the underlying respiratory compromise is also a very important factor to take into account, since the highest intubation rate is found among patients with ARDS (51%) or community-acquired pneumonia (50%), whereas the lowest intubation rate was among patients suffering cardiogenic pulmonary edema (10%) and pulmonary contusion (18%). The presence of any of these respiratory conditions should not, however, be understood as an absolute contraindication for NIV, but should provide a lower threshold for intubation due to the likelihood of NIV failure.

The question remains as to whether one can reliably predict or anticipate the response to NIV in a given patient. The lack of improvement after 1 h of NIV, as evidenced by a reduction in $PaCO_2$, correction of pH, and/or reduction in respiratory rate, is probably the best predictor of failure. Per its recommendation, the British Thoracic Society [27] proposes that in addition to a regular clinical evaluation, arterial blood gas analysis will be used to follow by the patient's clinical progress after 1–2 h of NIV and after 4–6 h if the earlier sample showed "little improvement". If there is no improvement in $PaCO_2$ and pH after this period, despite optimal ventilator settings, NIV should be discontinued and invasive ventilation initiated. This recommendation fits with data from the study of Anton et al. [106], who reported that NIV success, may be predicted by decreases in $PaCO_2$, and improvement in pH, and level of consciousness, after 1 h of NIV. Similarly, Mehta et al. [52] have identified a number of predictors associated with the successful use of NIV in ARF: objective predictors include younger age, lower severity of illness, moderately severe hypercarbia ($PaCO_2$ greater than 45 mm Hg but less than 92 mm Hg), moderately severe acidemia (pH greater than 7.1 but less than 7.35), improvements of gas exchange parameters, and decreased pulse and respiratory rates within the first 2 h of initiation [52].

The role of patient–ventilator asynchrony in failure of NIV should be briefly discussed. Criteria for asynchrony have been proposed based on the incidence of asynchrony or asynchrony index [107]. The mechanisms of asynchrony can be quite complex. Hess [40] has presented a rational approach to understand the potential mechanisms involved in asynchrony. Some are clearly related to the severity of the disease and the production of air hunger by the patients [108]. Other mechanisms are produced by the magnitude of the leak, use of inadequate interface with a given type of ventilator [109], as well as the mode which is utilized [37]. Viguaux et al. [107] found that the mechanism of asynchrony relates, in about similar proportions, to autotriggering, double triggering, ineffective breath or premature, and late cycling. The precise identification of the potential cause of asynchrony is an essential step when applying NIV in a given patient, as reducing such asynchrony improves patient comfort, although without a clear causal link with the outcome. Patients with ARF who have been chronically ventilated may respond very differently from ventilator naïve patients. Identifying the reasons and possible mechanisms for asynchrony requires a good understanding of the ventilators and interfaces, which are used, the identification of the magnitude of the leak, the presence of intrinsic PEEP, and ineffective triggering. Perhaps more importantly, asynchrony may reflect a failure in NIV, in a patient tiring due to ineffective ventilation or increased work of breathing, now requiring endotracheal intubation.

For all these reasons NIV should be used in patients with ARF only if there is a specific trained consultant committed to follow up. An ICU ideally must be accessible to provide back up for patients who do not improve on NIV. A successful determinant of NIV remains clinician education and experience [52, 110], which will also be affected by supporting staff such as a respiratory therapist and nursing staff [36]. The location of the initiation and monitoring of therapy is probably less important than the available resources and staff support during the initial usage.

Studies clearly demonstrate an increased utilization of respiratory support staff during the initial phases of NIV [54, 61] and therefore this support should be made available.

Sleep and Nocturnal NIV

As presented in details in other chapters of this textbook, one of the main reasons for the exponential development of noninvasive ventilation has certainly been its beneficial effect on the quality of sleep and the reduction in daytime sleepiness in patients with sleep disordered breathing or presenting with chronic respiratory failure. However, sleep disturbances during ARF cannot be regarded as an exacerbation of the sleep disordered breathing related to the background chronic respiratory failure (obesity, COPD, and muscle deficiency). Factors contributing to sleep disruption in patients with ARF includes anxiety, pain, discomfort, dyspnea, the mode of ventilation, and patient–ventilator asynchrony [111]. For instance, it seems that patients on pressure support have more sleep fragmentation than during control ventilation [112]. As pointed out by Cabello et al. [113], ineffective patient effort and inappropriate settings in keeping with the patient's effort are the major factors affecting sleep regardless of the mode of mechanical ventilation.

Understanding the specificity of the conditions created by ARF on sleep structures is essential, since more than 60 % of patients in mechanical ventilation appear to complain of disturbed sleep. NIV is however not deprived from negative effects on sleep: the discomfort of the mask can prevent the patient from falling asleep, air leak through the mouth is common when asleep and may decrease the benefit of NIV [114]. In some neuromuscular diseases, respiratory efforts may be insufficient to trigger a breath during sleep and thus NIV may not readily improved their sleep quality [115], not to mention the effects of iterative blood gas sampling.

In addition, it should be pointed out sleep alterations are present in almost all critically ill patients and should be regarded as one of the hallmarks of patients treated in an ICU [116, 117]. The mechanisms of sleep disturbances are intricate and complex, comprising in addition to the potential disrupting effects of the mechanical ventilation presented above, the medical intensive care unit (MICU) environment itself with its noise, excessive light and the patient's care activity, circadian rhythm disruption [118], the inherent effect of critical illness and the use of sedation [111, 117]. Watson et al. [119] have recently reported that 85 % of all electroencephalogram (EEG) recorded data in mechanically ventilated patients in ARF, corresponds to a form of atypical sleep, and that only 5 % normal sleep and 10 % wake can be clearly identified. This atypical sleep pattern consisted in lack of stage N2 markers, the presence of polymorphic delta and burst suppression making sleep difficult to characterize using standard polysomnographic staging criteria. Cooper et al. [120] or Druot et al. [121, 122] have previously reported similar results. A large proportion of conscious non-sedated ICU patients receiving invasive ventilation during

weaning or noninvasive ventilation for ARF did not display any stage-2 sleep [121]. Even when awake, abnormal features, including decreased reactivity to eye opening, were observed. The intriguing question is therefore about the nature of relationship between these sleep abnormalities and success/failure of NIV. In other words, could sleep be used as a clinical marker predicting the outcome of NIV in patients presenting with hypoxemic or hypercanic respiratory failure? Sleep disturbances in the ICU have long been proposed to lead to development of delirium, which is associated with prolonged ICU stay, and increased mortality [123] as recently reviewed by Boyko et al. [116]. Fanfulla et al. [118] have suggested that the sleep abnormalities observed in patients who were studied after ICU discharge are mainly associated with a high severity score, rather than being a direct consequence of mechanical ventilation. Regardless of the mechanisms leading to abnormal sleep in patients in ARF, this issue is crucial since criteria for success or failure of NIV have a poor predictive power. In an interesting study, Roche Campo et al. [124] have tried to clarify whether the severity of sleep disturbances after initiation of NIV in the ICU was associated with late NIV failure in patients with acute hypercapnic respiratory failure. Roche Campo et al. [124] used an important exclusion criterion, which was the administration of sedative within the last 48 h; sleep studies were performed between the 2nd and 4th night following the initiation of NIV. They found a mean fragmentation index was 33/hr with only 3/hr due to respiratory events. There were marked differences in sleep characteristics between the successful and failed NIV groups in terms of the rate of abnormal EEG patterns, circadian sleep cycle disruption and rapid eye movement (REM) sleep duration [124]. Late NIV failures were associated with longer ICU stay and higher ICU and hospital mortality rates. All patients with delirium failed NIV and 64 % of patients in the failed NIV group had delirium compared with 0 % in the NIV success group. The hypothesis developed in this chapter was that abnormal EEG patterns in NIV treated patients might well reflect subclinical acute brain dysfunction, even without clinical encephalopathy. The question asked by these authors was whether sleep disruption in ICU patients could be independently associated with adverse outcomes and merely constitutes a marker for cerebral dysfunction.

The exact mechanism(s) as well as the nature of the relationship between the prognosis of an ARF and sleep disturbances, a putative marker of brain dysfunction, in patients with acute respiratory distress will need to be investigated in larger populations of patients. Nevertheless, a link, which causality is yet to be established, between the late failure of NIV and poor sleep or abnormal sleep patterns seemed to emerge in the literature, making sleep analysis in the ICU a promising clinical tool to predict the outcomes of NIV.

Finally, a small subgroup of patients with severe COPD with recurrent admissions due to respiratory acidosis who have tolerated NIV have been offered the possibility to use NIV at home, mostly at night, during new episodes of acute exacerbations [24, 25]. Interestingly enough, these “atypical” experimental approaches have proved to be very effective in reducing the number of admissions and seem to have an impact of the quality of life and mortality rate [24, 25]. These studies,

although limited, suggest that the use of NIV in ARF in patients with chronic hypercapnia could be applied with a cost several fold lower than in an ICU [25]. The current literature supports a standardized approach which parallel the strategy used with invasive ventilation, but clearly patients with severe chronic respiratory failure from muscle origins or with COPD who present numerous episodes of acute exacerbation could benefit from a "lighter" strategy wherein domiciliary NIV could be applied, for instance, only at night or during few hours a day even in a context of ARF. The choice may be offered between increasing O_2 supply, initiate domiciliary NIV (or more aggressive NIV) and admission to these populations of patients for whom the outcome of the invasive mode of ventilation is very poor, typically leading to tracheostomy.

Conclusions

NIV, typically delivered in the form of assisted ventilation wherein breaths are supported by a ventilator via a mask, is now routinely used in the treatment of ARF. In COPD patients, patients with pulmonary edema, and to a less extent immunocompromised patients who do not initially require mechanical ventilation, NIV may prevent endotracheal intubation, with a reduction in the rate of complication and hospital stay. Other patient populations in hom the benefit of NIV has not been established due to the lack of available clinical trials, can still be considered for NIV during ARF on a case-by-case basis. The best overall indication remains the presence of alveolar hypoventilation with chronic expiratory airlow obstruction (i.e., COPD patients). The most reliable predictor of success is a positive response to the NIV during the first hour of treatment based on an improvement in $PaCO_2$ and a reduction in the clinical symptoms of respiratory distress. Patients with pneumonia, ARDS or asthma have much more higher chance of failing NIV. There is no clear indication for consistently using NIV following extubation in an attempt to reduce the duration of intubation. In specific populations of patients, in particular, COPD patients with a high risk of being reintubated, a weaning strategy including NIV deserves consideration. Simple and effective clinical tools to evaluate the interactions between the patient, the interface and the ventilator when using NIV remain to be developed and implemented. The strategy to be used in patients with numerous recurrent episodes of ARF is a challenging question, and the benefit of alternating domiciliary NIV, used intermittently at night, versus admission should be explored. This issue is particularly pertinent to the population of patients with severe COPD or neuromuscular disease for whom the number of episodes of hypercapnic exacerbations throughout the year makes it difficult to be treated according to the standard presented in this chapter and who would be traditionally regarded as candidates for tracheostomy and chronic invasive mechanical ventilation.

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Index

A
Acute respiratory failure (ARF), 19, 92, 99, 209, 247
  hospitalization with, 211
  management of, 252
  NIV during, clinical applications of, 249, 258, 262
  patients with, 53, 62, 250, 254, 255, 260
  types of, 247
  ventilation for, 261
Adaptive servo-ventilation (ASV), 74, 125, 139, 172, 219
  features of, 75
  meta-analyses of, 77
Adherence, 1, 17, 94, 209
  acceptance of, 218, 232
  CPAP, 237
  definition of, 145
  nNIV, 153, 154
  NPPV, 210
Apnea, 2, 3, 13, 83, 116, 166, 228
  patients with, 172
  with CPAP, 78
Assisted ventilation, 218
  form of, 262
  history of, 28–32
Automatically titrated positive airway pressure (APAP), 138, 238, 241
  concepts of, 240
  technology with, 240

B
Bi-level positive airway pressure (BPAP)
  implementation of, 149
Bilevel positive airway pressure (BPAP), 9, 10, 237, 241

C
Central complex apnea adaptive rebreathing, 167, 171, 228
Central hypoventilation, 119, 135
Central sleep apnea (CSA), 1, 3, 10, 113, 167, 181
  etiology, 153
  treatment of, 194
  types of, 119
Chronic respiratory failure, 49, 53, 59, 62, 232
  for COPD, 209
  NPPV
    impact of, 215
    role of, 213
  patients with, 210
Continuous positive airway pressure (CPAP), 11, 18, 51, 91, 138, 179, 233, 235
  effects of, 183
CPAP *See* Continuous positive airway pressure, 9

D
Data tracking, 219, 229, 233
Diaphragm, 2, 4, 14, 123
Disorder, 1–3, 6, 11, 14, 62, 103, 247
  definition of, 4
  effects of, 117
  NIV, 5
  treatment of, 146

H
Heart failure (HF), 1, 51, 55, 73, 84, 173, 192
  COPD with, 61
History
  of progression, 4
  of SRBDs, 117

R. C. Basner, S. Parthasarathy (eds.), *Nocturnal Non-Invasive Ventilation,*
DOI 10.1007/978-1-4899-7624-6

Hypercapnia, 2, 12, 13, 15, 84, 85, 140, 217, 250
development of, 93
induction of, 179
Hypercapnic respiratory failure, 2, 10, 20, 51, 60, 83, 85, 94, 99, 217, 223, 247, 261
NIV in, 251, 258
non-invasive ventilation for, 196, 198
Hypoventilation, 3, 6, 11, 12, 113, 116
definition of, 19, 146
development of, 88, 93
pathogenesis of, 147
treatment of, 209

N
Negative pressure noninvasive ventilation (NPNIV), 28, 33, 48, 49, 59, 61, 63
application of, 55
Neuromuscular, 2, 4, 8, 60, 116, 118
children with, 147, 151
patients with, 217
Nocturnal, 1, 2, 5–7, 14
management of, 151
NPNIV, 54
NPPV, 102, 217–219, 230
Nocturnal hypoventilation, 10, 120, 122, 123
treatment of, 146
Non-invasive positive pressure ventilation (NPPV), 91, 125, 209, 210, 232
benefits of, 101
goals of, 95
indications of, 212
titration of, 126
Noninvasive positive pressure ventilation (NPPV), 49, 65
Nocturnal noninvasive ventilation (nNIV), 1, 135, 256

O
Obesity hypoventilation, 103, 217
Obstructive lung disease, 9, 213, 215
Obstructive sleep apnea (OSA), 1, 9, 11, 153
Outcomes, 2, 5
of PAP therapy in, 99–102
with PVD, 18

P
Pediatric neuromuscular disorders, 149, 151
Pediatric sleep disordered breathing, 15
Periodic breathing (PB), 19, 75, 163, 171, 172, 192, 225
in CSA, 74
Physiology, 2, 122, 248
Poliomyelitis, 41, 43, 120, 135, 147
Pressure relief (PR), 176, 236, 240, 241

R
Restrictive thoracic/lung disease, 213

S
Sleep, 2, 14, 18
challenges of, 4
definition of, 20
forms of, 165
Sleep-disordered breathing, 3, 5, 84, 240
nosology of, 13, 14
prevalence of, 12, 13
types of, 88
use of PAP, 76
Sleep related breathing disorders, 8, 75

V
Ventilation, 2, 3, 6, 15, 18, 55, 57, 75
definition of, 228
non-invasive, 177
Ventilatory failure, 6, 19
history of, 28