Sleep disordered breathing in neurologic diseases

Claudio L. Bassetti[a], Matthias Gugger[b]

[a] Neurologische Universitätsklinik, USZ, Zürich
[b] Pneumologie, DIM, Inselspital, Bern

Wakefulness, NREM sleep, and REM sleep are accompanied by specific changes in breathing control, which arise from the interaction of automatic (metabolic, involuntary) and behavioural (voluntary and involuntary) control systems. Considering the complexity in the neuroanatomy and neurophysiology of breathing control, it is not suprising that neurologic disorders are frequently accompanied by sleep disordered breathing.

An introduction on pathophysiology, clinical features, diagnosis, and treatment of sleep disordered breathing in such diseases as stroke, epilepsy, dementia, spinal cord disease, polyneuropathies, and myopathies is presented.

Key words: sleep; breathing; apnea; neurologic disorders; stroke; epilepsy; myopathy

The control of breathing during wakefulness and sleep

A complex homoeostatic control system of sensors (afferent input), a central controlling mechanism and an effector system maintain arterial blood gases (PaO_2, $PaCO_2$) and pH within narrow limits (fig. 1). The respiratory control system output is system-dependent and is regulated by two anatomically distinct but functionally integrated elements, referred to as automatic (metabolic, involuntary) and behavioural (voluntary and involuntary) respiratory control systems [1–3] (fig. 2). The *automatic control system* depends upon respiratory neurons in the medulla, as already recognised by Legallois in the 19th century and by Lumsden at the beginning of the 20th century. The normal inspiratory-expiratory cycle is generated by the interaction between a primary respiratory pacemaker (pre-Bötzinger complex) in the ventrolateral medulla [4] and other medullary respiratory centres in the nucleus tractus solitarius (dorsomedial medulla, mainly inspiratory) and in the nuclei ambiguus and retroambiguus (ventrolateral medulla, inspiratory and expiratory). Effector neurons of respiration include bulbospinal motoneurons of the nuclei ambiguus and hypoglossus. The activity of these medullary breathing centers is modulated by vagal (O_2 receptors of aortic paraganglia, mechanoreceptors from respiratory tract and lungs) and glossopharyngeal afferents (O_2 receptors of glomus caroticus), afferences and influences from pons and other supratentorial areas. Pontine respiratory neurons are located in the lateral tegmentum of the upper (Kolliker-Fuse nucleus or pneumotaxic centre) and lower pons (apneustic centre). The *behavioural control system*, whose neural elements originate from supratentorial and supramedullary structures and descending (pyramidal and extrapyramidal) pathways, modulates ventilation mainly for non-respiratory functions such as phonation and eating.

Breathing during *wakefulness* is controlled by both automatic and behavioural mechanisms. The wakefulness stimulus (waking neural drive) represents a further stimulus for ventilation. At *sleep onset* ventilation decreases as behavioural control system output, metabolic rate and chemosensitivity decrease and upper airway resistance increases (sleep-related hypotonia). Hypopnoeas, apnoeas and periodic breathing may occur. In non-rapid eye movement *(NREM) sleep* breathing is regular as it is driven only by metabolic demands. During rapid eye movements *(REM) sleep* breathing becomes irregular as expression of a control system that is probably similar to that of wakefulness. Hypopnoeas and apnoeas may occur particularly during phasic REM activities, where ventilation is at its lowest level.

Figure 1

Scheme of breathing control (physiology). (From: Martin TJ, Sanders MH. Chronic alveolar hypoventilation: a review for the clinician. Sleep 1995;18:617–34, with kind permission.)
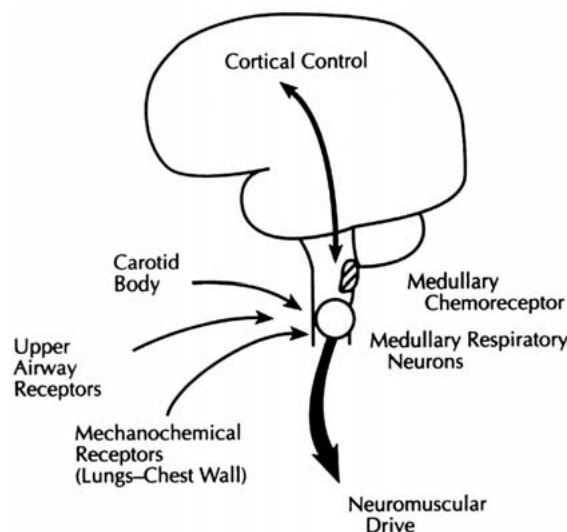
Figure 2

Scheme of brainstem breathing control (anatomy). Voluntary (shaded) and automatic (hatched) controls of respiration at upper pons (a), medulla (b), and spinal level (c).
PNC: pneumotaxic centre, PBm: nucleus parabrachialis medialis, KF: Kölliker-Fuse nucleus, PCS: pedunculus cerebellaris superior, TS: tractus solitarius, DRG: dorsal respiratory group, VRG: ventral respiratory group, NA: nucleus ambiguus, NRA: nucleus retroambiguus, Insp: to inspiratory motoneurons, Exp: to expiratory neurons (From: Vingerhoets F, Bogousslavsky J. Respiratory dysfunction. In Bogousslavsky J, Caplan L, eds. Stroke Syndromes. Cambridge: Cambridge University Press; 2001, with kind permission.)
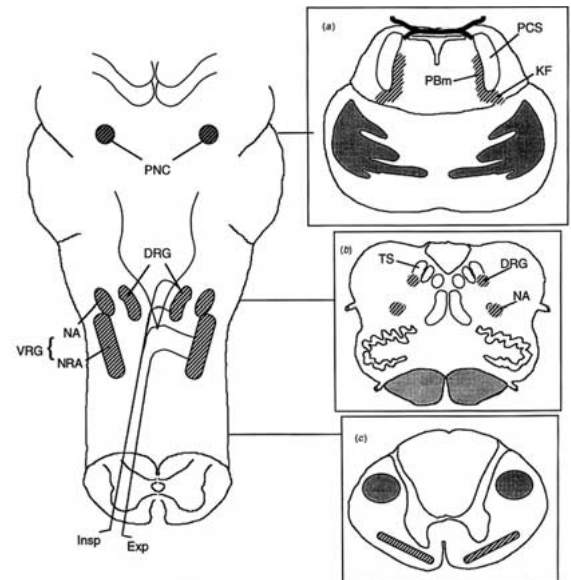
Segmental neurology of disordered breathing during wakefulness and sleep[1]

Considering the complexity in anatomy and physiology of breathing control, neurological disorders are expected to impair breathing during wakefulness and/or sleep in different ways according to type, extension, and topography of the lesion [5, 6]. Because of the convergence/overlap in the brainstem of mechanisms controlling respiration and other somatic and vegetative functions, disorders of breathing in neurological patients are often associated with a variety of sleep-wake and autonomous deficits.

The *mechanisms* involved in patients with disordered breathing and neurological disorders can be separated on the basis of topographic criteria:

1. Involvement of *afferent inputs* to the medullary respiratory neurons (e.g. polyneuropathies, spinal cord lesions). This may lead to obstructive or non-obstructive reduction or cessation of airflow *(central and obstructive hypopnoea and apnoea)*.

2. Direct dysfunction of *medullary respiratory neurons* (e.g. medullary stroke, multiple sclerosis, multisystem atrophy, encephalitis, poliomyelitis). This can be manifested by central apnoea, alveolar hypoventilation, irregular breathing *(Biot's or ataxic breathing)*, failure of automatic breathing *(Ondine's curse)*, or decreased CO_2 sensitivity during both wakefulness and sleep [7]. In these conditions insufficient alveolar ventilation has been called "Won't breathe" type of hypoventilation [7a]. Ondine's curse may voluntarily be overcome during wakefulness and decompensate during sleep. These patients often also present dysphagia or dysphonia, indicating involvement of the nucleus ambiguus in the ventrolateral medulla. Ondine's curse is usually due to bilateral medullary lesions, though there are a few exceptions in the literature [8, 9].

3. Involvement of the *efferent respiratory control* at the level of respiratory neurons (e.g. poliomyelitis) or muscles (e.g. myasthenia gravis, postmyelitis syndrome) may be accompanied by central or obstructive hypopnoea/apnoea and alveolar hypoventilation. In these circumstances insufficient alveolar ventilation has been called "Can't breath" type of hypoventilation [7a]. Bilateral *diaphragmatic weakness* is a feature of several neuromuscular disorders which present with prolonged central apnoea and mainly hypoventilation during REM sleep (particularly during phasic events), paradoxical abdominal movements, a restrictive pattern on spirometric testing (especially when assessed in the supine position), and blood gas analysis showing hypoxia and hypercapnia. Patients with isolated diaphragmatic weakness typically remain eucapnic and oligosymptomatic during wakefulness because intercostal and accessory muscles (which are paralysed, in contrast to the diaphragm, during REM sleep) are often sufficient to maintain alveolar ventilation.

4. Dysfunction of *supramedullary breathing control mechanisms* may present a variety of forms of disordered breathing (see also 4.). Cortical, corticobulbar and corticospinal lesions may affect volitional breathing partially *(respiratory apraxia)* or completely *(failure of voluntary breathing)* [10]. The lesion may be as high as the frontal cortex and as low as the cervicomedullary junction [11]. These patients cannot hold their breath or voluntarily change their respiratory rate. Bilateral lesions in the ventro-tegmental pons (e.g. following stroke, tumours or multisystem atrophy) have been reported to cause inspiratory breath holding *(apneustic breathing)* or metronomically regular and rapid breathing *(central neurogenic hyper-*

1 For definition/ classification and nomenclature of sleep disordered breathing see Littner and Shepard, Sleep 1999;22: 665–89

Figure 3

Sleep disordered breathing in acute stroke. 50-year-old patient with mild, unilateral middle cerebral artery stroke (National Institute of Health Stroke Score = NIH = 8) and severe, mainly obstructive sleep apnoea syndrome (Apnoea-Hypopnoea-Index = AHI = 47). Sleep study 3 days after stroke: prolonged obstructive respiratory event during NREM sleep with oxygen desaturation to 54% is shown (from conventional polysomnography).
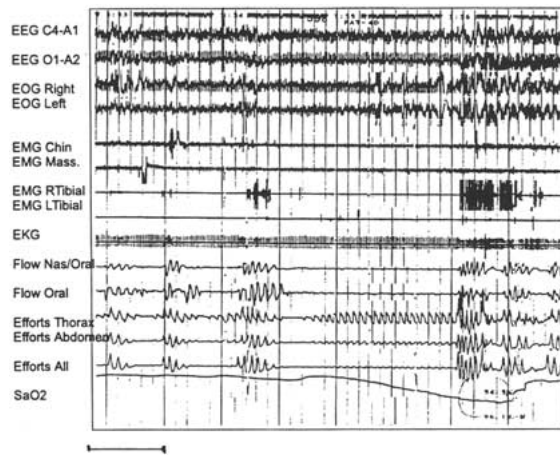
Figure 4

Sleep disordered breathing in acute stroke. 68-year-old patient with moderately severe, unilateral thalamo-mesencephalic stroke (NIH = 12) and severe, mainly central sleep apnoea syndrome (AHI = 45). Sleep studies 2 days after stroke (from conventional polysomnography) demonstrating the presence of central periodic apnoea.
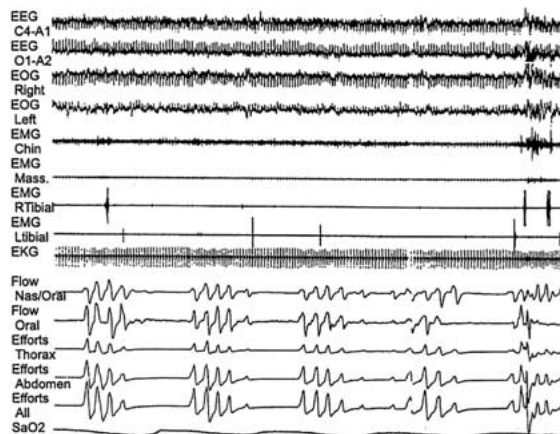
ventilation) [12–15]. In patients with pontomedullary lesions (e.g. in association with stroke, multisystem atrophy, multiple sclerosis or tumours), complex abnormalities of voluntary and automatic breathing can be observed. Patients exhibit disorders during wakefulness and sleep including irregular breathing *(cluster breathing)*, central apnoeas during wakefulness and sleep, hiccup, inspiratory breath holding and stridor during sleep (see also 4.).

The contribution of neurogenic factors to the pathophysiology of the two most common forms of sleep disordered breathing (SDB), *Cheyne-Stokes breathing* (CSB) and *obstructive sleep apnoa* (OSA), remains poorly understood, as is also proven by their high prevalence in such disorders as stroke and neurodegenerative diseases (fig. 3 and 4). The cyclic fluctuation in breathing amplitude with periods of central apnoea/hypopnoea alternating with periods of hyperpnoea called CSB (fig. 4) may be related to CO_2 hypersensitivity induced by bilateral supratentorial lesions [16]. This abnormality is also reflected by the presence in these patients of *posthyperventilation apnoea* during wakefulness. The presence of bilateral supratentorial or pontine lesions may be crucial for the appearance of CSB already during wakefulness [16–18]. In these patients a decreased level of consciousness and especially heart failure are additional predisposing factors. Conversely, CSB only during sleep can also be seen in patients with unilateral lesions of variable topography and without a disturbed level of consciousness or heart failure [19, 20]. Disturbed coordination of upper airway, intercostal and diaphragmatic muscles due to brainstem or hemispheric lesions may favour the appearance of OSA. Finally, CSB and OSA potentiate each other [21].

In patients with neurological disorders, breathing disturbances are often of *multifactorial origin*. This is the case for example of SDB and neurogenic hyperventilation observed in stroke patients. In addition to the neurological disorder per se, pre-existing cardiorespiratory conditions (e.g. OSA and heart failure) and indirect complications of brain damage (e.g. aspiration, lung oedema, immobility, respiratory infection in stroke patients) may favour the appearance of OSA.

Clinical features

Several studies have suggested that in patients with brain damage the *frequency* of breathing disturbances may be higher during sleep than during wakefulness [20, 22]. For example, CSB is highly prevalent in acute stroke patients during sleep [19], but only in a minority are also present during wakefulness. The severity and type of SDB may vary during sleep according to sleep stages and body position [23]. For example, OSA tends to be more accentuated in REM sleep whereas CSB is chiefly present in light NREM sleep and usually disappears in REM sleep.

Sleep disordered breathing may present a variety of symptoms and signs that are sometimes misinterpreted and attributed to the underlying neurological disorder. *Night-time symptoms* of SDB include difficulty in falling asleep (sleep-onset insomnia); respiratory noises (snoring, stridor); irregular or periodic respiration; apnoea; agitated sleep with increased motor activity and frequent awakenings (sleep-maintenance insomnia), sudden awakenings with choking sensations, shortness of breath, palpitations, "panic attacks", orthopnoea and increased sweating. Finally, in patients with severe hypoventilation arousal responses can be suppressed by the increasing sleep debt and lead to death during sleep. *Day-time symptoms* of SDB may be headache, excessive daytime sleepiness, altered mentation with concentration and memory difficulties, irritability and depression. Some patients may also exhibit breathing abnormalities during wakefulness including dyspnoea, apnoea, inspira-

tory breath holding, irregular breathing, rapid-shallow breathing, CSB, hiccup, and much more. Disturbances of sleep-wake, bulbar (phonation, deglutition, coughing), and cardiovascular functions can also be observed.

Consequences of SDB include recurrent nocturnal hypoxia, cardiovascular morbidity with systemic and pulmonary hypertension, and brady-tachyarrhythmias, hypercoagulability [21a]; sleep fragmentation with decrease in amounts of slow wave sleep and REM sleep; excessive daytime sleepiness; neuropsychological deficits; and aspiration/infections. The impact of breathing disturbances on the course and outcome of neurological disorders has been only rarely investigated. In patients with acute stroke the presence of breathing disturbances during wakefulness represents a bad prognostic sign [22, 24]. In patients with stroke and multisystem atrophy the presence of SDB has been shown to herald a poor outcome [25–27].

Specific neurological disorders associated with sleep disordered breathing

Stroke

Several prospective studies on hundreds of patients have documented a 50–60% prevalence of SDB in patients with acute stroke [21, 28–30]. The most common form of SDB is OSA, some patients having CSB or a combination of both OSA and CSB (fig. 3, [20]). Other breathing disturbances (see also 2.) are less common. The presence of OSA should be suspected particularly in male and elderly patients with diabetes and night-time onset of TIA/stroke [21, 31]. A similar SDB prevalence in patients with TIA and stroke suggests that SDB more often precedes than follows the onset of cerebrovascular events [28, 30]. Nevertheless, acute stroke may aggravate pre-existing SDB or even cause it "de novo". In line with this assumption, improvement of SDB often occurs in the recovery phase after stroke [30]. The presence of SDB in stroke patients seems to herald a worse longterm outcome [25, 32]. This may be related to OSA complications such as hypertension, cardiac arrhythmias, decreased cerebral blood flow, and hypoxia-induced accelerated atherosclerosis, or to comorbidity. Two key questions about the link between SDB and cerebrovascular diseases are still unanswered: (1) is OSA an independent risk factor for stroke, as is the case for habitual snoring [33]? (2) does CPAP treatment reduce cerebrovascular morbidity in patients with and without a history of cerebrovascular events?

Epilepsy

Sleep disorders in patients with epilepsy have rarely been investigated. A recent prospective study found a 33% prevalence of SDB (defined by an AHI $\geq$5) in 39 patients with medically refractory epilepsy [34]. Obese males with sleep-associated seizures and excessive daytime sleepiness should particularly be suspected [35, 36]. Sleep deprivation, hypoxaemia, and an increased number of arousals are the possible mechanisms by which OSA may aggravate epilepsy. About one third of patients with both epilepy and OSA may enjoy improved seizure control with CPAP treatment alone [37, 38]. Less commonly, epilepsy may aggravate OSA as a consequence of uncontrolled (nocturnal) seizures or weight gain due to antiepileptics (e.g. valproic acid). Occasionally, apnoea may be directly due to epileptic seizures in the absence of SDB [39]. Vagal stimulation for refractory epilepsy may affect sleep breathing control, with a reduction in airflow and effort, which may aggravate a pre-existing OSA [39a].

Neurodegenerative disorders

Patients with *Alzheimer's disease* have a 33–53% prevalence of SDB, which may not be much higher than in the elderly healthy population. Involvement of upper airway muscles and increased prevalence of SDB (of unknown clinical relevance) were also reported in *idiopathic Parkinson's disease* (PD) [40, 41]. Patients with PD may also exhibit respiratory apraxia or irregular/rapid breathing during wakefulness and REM sleep [42]. Patients with *multisystem atrophy* (MSA) may present a variety of breathing abnormalities during both wakefulness and sleep. Stridor (in inspiration or expiration), snoring, obstructive and central apnoea and hypopnoea, irregular breathing, CSB, apneustic breathing and Ondine's curse may be present in the absence of major subjective complaints. Typically, no pulse rate or blood pressure changes are seen in the course of respiratory events and arousals, and hypercapnic and hypoxic ventilatory responses are abnormal. Breathing abnormalities may vary according to sleep-wake state, body position (more in the supine or erect position), or stage of the disease and represent a risk factor for sudden death in sleep. Neuronal loss in the tegmentum of pons and medulla is the usual autoptic correlate of breathing disturbances.

Spinal cord diseases

In a recent study of 30 patients SDB was found to be present in 1 of 13 patients with *syringomyelia* and 13 of 17 patients with *syringobulbia* [43]. Prolonged central, mixed, and obstructive apnoea, severe oxygen desaturation, and apneoa and irregular breathing during wakefulness were observed despite the absence in most cases of subjective symptoms. Dysphagia and dysphonia, but not the size of cavity on MRI, were predictive of SDB. *Arnold-Chiari malformation* may be complicated by OSA, central hypoventilation, and other forms of SDB including respiratory arrest occurring during sleep or postoperatively [44]. After *antero-lateral*

cordotomy for cancer-pain SDB can be observed, thus confirming the importance of this afferent input for normal breathing [45]. *Poliomyelitis* and *post-polio syndrome* may be associated with complex breathing disturbances during wakefulness and sleep, reflecting the variable involvement of brainstem, spinal cord, peripheral nerves, and chest wall in these disorders.

Polyradiculopathies and -neuropathies

Significant SDB may occasionally be observed in patients with Guillain-Barré syndrome and polyneuropathies affecting the autonomic nervous system or the phrenic, vagal, or pharnygeal nerves.

Neuromuscular disorders. SDB often precedes the onset of respiratory insufficiency in patients with neuromuscular disorders. In a consecutive series of 60 patients attending a neuromuscular clinic, 80% of patients had an AHI >5 and 42% an AHI >15. Clinical characteristics (muscle functions) and spirometry are not always predictive of the presence of SDB. Fatigue and excessive daytime sleepiness maybe the first symptoms of SDB, whereas rapid-shallow breathing may signal the onset of respiratory failure. The first signs of SDB in neuromuscular disorders are often prolonged hypopnoea or hypoventilation during phasic REM sleep (*REM sleep hypoventilation*) in the supine position, indicating significant diaphragmatic weakness. Diaphragmatic weakness is the major cause of SDB and respiratory failure in *acid maltase deficiency* [46]. In patients with *myotonic dystrophy* SDB a combination of central and obstructive components is often found [47, 48]. Patients may become symptomatic with excessive daytime sleepiness in the first decade of life. Sleepiness and SDB are due in these patients to neuromuscular weakness but also to neuronal degeneration in the reticular formation of the medulla [49]. In *amyotrophic lateral sclerosis* hypoventilation is the dominant feature. SDB is usually a late complication of the disease, although acute respiratory failure may in rare cases be among the presenting manifestations [50]. In *generalised myasthenia gravis* SDB and diaphragmatic weakness may be found (in 11 of 20 cases in one study), even in clinically well-controlled patients [51].

Others. Treatment of OSA in patients with *migraine and cluster headache* can result in significant improvement of headache control [52]. A few studies have suggested increased frequency of central and obstructive events in patients with *narcolepsy*.

Diagnosis and treatment

Diagnosis

Diagnosis of SDB in neurological patients requires a high degree of suspicion, particularly in disorders known to have a strong association with SDB (e.g. stroke) or with a chronic-progressive course (e.g. Shy-Drager syndrome, syringobulbia), since in such patients subjective symptoms may be minimal. In the setting of acute brain damage (e.g. stroke) the use of *intelligent CPAP* machines (that is CPAP devices with diagnostic and treatment mode) or *respiratory polysomnography* may represent an alternative to *conventional polysomnography* [30]. Detailed *pulmonary function testing* in awake subjects, including quantitative positionally dependent changes in vital capacity, various respiratory tests and *blood gas analysis* should be obtained [53]. A reduction in inspiratory vital capacity of 20% or more in the supine posture suggests diaphragmatic weakness and is predictive of SDB in patients with maltase deficiency [46]. Respiratory failure can be anticipated by a ventilatory capacity reduction of 50% or more [3].

Treatment

Treatment of SDB in neurological patients may represent a major clinical, technical, and logistical challenge. Treatment programmes should always include management of the underlying illness, prevention of secondary complications (e.g. aspiration, respiratory infections), and general measures such as cautious use or avoidance of alcohol, sedative-hypnotic drugs and perioperative anaesthetics. Continuous positive airway pressure *(CPAP)* is the treatment of choice for OSA. Bi-level positive airway pressure *(BiPAP)* applied through a nasal or full face mask, or more sophisticated forms of noninvasive ventilation, are preferred in neuromuscular patients with hypoventilation [53]. A detailed discussion of ventilatory options and strategies in patients with sleep disordered breathing is beyond the scope of this review. Compliance to CPAP is reduced by such neurological problems as dementia, aphasia, anosognosia, pseudobulbar/bulbar palsy, hemiparesis or hypo-/akinesia. Improvement of CSB can be obtained with *oxygen*, occasionally with BiPAP and in the near future probably with more sophisticated devices. Adaptive servo-ventilation, a novel method of ventilatory support, has been shown to suppress central apnoea and/or CSB in patients with heart failure and to improve sleep quality more than CPAP or oxygen [53a]. *Theophylline*, *sedatives* and *opiates* have anecdotally been reported to improve CSB and neurogenic hyperventilation, but should be used with caution [54]. In a study of 5 conscious patients with acute ischaemic stroke, theophylline (250 mg i.v. over 1 hour) and oxygen inhalation by face mask (2 l/min over 1 hour) resulted in normalisation of breathing pattern and oxygen saturation (for the short time of treatment) [19]. In a recent 5-day trial theophylline reduced the number of episodes of apnoea and hypopnoea and the duration of oxygen desaturation during sleep in patients with CSB and stable heart failure [54a]. Theophylline may

induce seizures in patients with CSB related to neurological disorders [3]. *Tracheostomy* and mechanical ventilation may improve survival in some patients with central hypoventilation [27]. *Diaphragmatic pacing* is reserved for a few highly specialised centres in the world [55].

Correspondence:
Prof. Claudio Bassetti
Neurologische Poliklinik
Universitätsspital Zürich
Frauenklinikstrasse 36
CH-8006 Zürich
E-Mail: claudio.bassetti@nos.usz.ch

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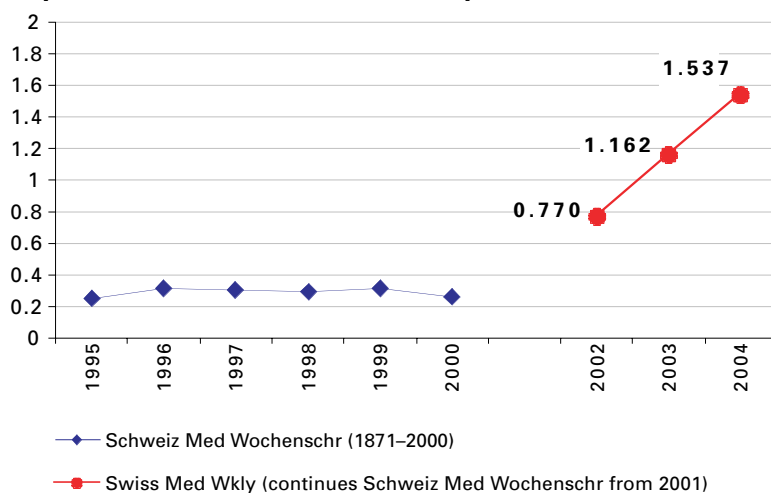- No page charges and attractive colour offprints at no extra cost

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