To sleep, perchance to breathe: how ResMed’s treatment of sleep-disordered breathing can improve cardiovascular health

Although it appears passive, sleep is an active, vital process. The brain and body undergo patterned physiological changes throughout the sleep cycle that are essential for physical and mental health. These changes, of course, are independent of conscious control. Likewise, breathing during sleep is also free of conscious control, automatically compensating for changes in physical position, activity and environment. However, for many people, breathing while asleep is not restful. Sleep-disordered breathing (SDB) may affect as many as 1 in 5 adults, not only disrupting the beneficial effects of undisturbed sleep, but also introducing its own detrimental effects on cardiovascular health and metabolic function. ResMed was founded in the late 1980s to help those suffering from SDB to get a good night’s sleep. As the broader impact of SDB has begun to emerge, ResMed has focused on five critical areas of public health: the impact of SDB on heart disease and the link between them; diabetes and metabolic syndrome; chronic obstructive pulmonary disease (COPD) and other forms of respiratory failure; occupational health and safety; and perioperative care.

A disturbed night

Sleep-disordered breathing (SDB) was first diagnosed in people who were not properly rested after a night’s sleep and exhibited “excessive daytime sleepiness” that impaired their ability to work and play. Most commonly, SDB is thought of as obstructive sleep apnoea (OSA), in which relaxation of the muscles around the upper airways causes a physical blockage to the passage of air from the nose or mouth to the lungs. Eventually, the resulting decrease in oxygen delivery and increase in carbon dioxide levels (hypercapnia) stimulates the sympathetic nervous system and arouses the sleeper enough to relieve the obstruction and resume normal breathing.

But SDB is not always caused by a narrowing or total obstruction of the upper airway. Central sleep apnoea (CSA) is characterized by a lack of drive to breathe during sleep, causing repetitive periods of insufficient ventilation and compromised oxygen supply, and inducing chemical, neural and haemodynamic changes similar to those seen in OSA. The resulting pattern of breathing often displays a periodic pattern referred to as Cheyne–Stokes respiration (CSR), which is frequently found in heart disease, following a stroke, and in renal insufficiency. Additional patterns of SDB are associated with chronic diseases of the airways and the neuromuscular system, as well as with obesity. These combine with the decrease in muscle tone characteristic of sleep to result in hypventilation.

Signs of disrupted breathing during the night can be seen in many daytime manifestations, ranging from depression, mood swings, insomnia and morning headaches to sleepiness during the day, coupled with ‘drowsy driving’ and therefore an increased risk of road traffic accidents. Women can show different patterns of symptoms to men, appearing less sleepy but fatigued, depressed and prone to insomnia. Definitive diagnosis of SDB can be made by home sleep testing (HST), using respiratory polygraphy, which monitors several parameters during sleep, including respiratory airflow and oximetry (measuring the oxygen level in the blood). It has become clear, however, that SDB also affects the cardiovascular and metabolic health of many people who do not exhibit obvious daytime sleepiness, so the true prevalence of the problem has probably been underestimated. Risk factors for developing SDB include obesity, although approximately one-third of SDB sufferers are of normal weight but have other risk factors, such as micrognathia (an undersized jaw) and tonsillar hypertrophy.
Breathe easy

ResMed’s goal is to alleviate sleep-disordered breathing. The company was initially founded on SDB technology developed in 1980 by Colin Sullivan and colleagues at the University of Sydney, Australia. The original technology for delivering continuous positive air pressure (CPAP) to the upper airway and lungs was literally based on the reversal of a vacuum cleaner motor. Even though these early devices were very noisy, and had cumbersome and primitive nasal masks, they had a startling ability to promote restful sleep by restoring the smooth cycle of uninterrupted breathing⁶. Sullivan’s technology was acquired by Peter Farrell while he was vice-president of research and development for Baxter International. When Baxter chose not to develop the CPAP technology, Farrell took the opportunity to set up what has become the leading global provider of health solutions for sleep-disordered breathing and respiratory failure, even though, faced with a highly skeptical medical community, the risks were far from insignificant.

Since its founding in 1989, ResMed has refined and considerably enhanced CPAP technology, culminating in the development of new and more efficient motor technologies and sophisticated algorithms, as well as small, silent patient interfaces (Figure 1). In 2001, with the introduction of Adaptive Servo-ventilation (ASV), which is responsive to the breathing patterns of individual patients with CSA and CSR as well as OSA, we completed a technology portfolio that addresses virtually every form of disturbed breathing during sleep⁷. More recently, in recognition of real-world motivations and barriers, we have driven the development of our devices to maximize comfort and convenience, making them easier for patients to use.

The heart of the problem

There is a complex reciprocal relationship between SDB and cardiovascular disease. The most convincing evidence comes from studies of patients with chronic heart disease, driven by the high prevalence rates of SDB in this area (Figure 2). In drug-resistant hypertension, for example, up to 80% of patients suffer from moderate to severe OSA, and treating it dramatically improves the management of the disease⁴,¹⁰. Similar findings have been published for arrhythmia and atherosclerotic disease⁴,¹⁰. It seems that SDB/OSA is a clear and independent risk factor for the development and progression of cardiovascular disease. As seen in observational studies, treatment of OSA can decrease the cardiovascular disease burden and improve outcomes for patients suffering from SDB⁷.

Given the cardiac risk attributed to SDB, there is increasing focus on SDB in the perioperative space, with the goal of improving the quality of care and reducing the risk of adverse events after surgical or interventional procedures¹². In recent years, ResMed has focused on the relationship between heart failure and SDB. Despite recent advances in pharmacological treatment, heart failure continues to cause debilitating symptoms, frequent hospital admissions and high mortality. Many heart-failure patients still suffer from persisting symptoms of the disease, poor quality of life, and high morbidity and mortality. More than half of heart-failure patients exhibit moderate to severe SDB, with half of those having CSA/CSR¹⁰. Several physiological and molecular mechanisms linking SDB with cardiovascular problems have been proposed (Figure 3). At the root of these mechanisms are chronic alterations in the activation of the sympathetic nervous system, as well as molecular and cellular responses to intermittent hypoxia.

While the correlative and pathophysiological evidence linking SDB and heart failure has mounted, what’s lacking is interventional evidence that correcting SDB results in improved cardiovascular health. With the help of ResMed’s ASV technology, the quality of life for heart-failure patients can be substantially improved¹³. A treatment that can control SDB has the potential to improve outcomes and quality of life in patients with chronic heart failure. Such an overall improvement in the symptom burden by targeting one co-morbidity is a compelling proposition (Figure 4).

Trials and tribulations

When ResMed’s CPAP machines were first developed, sleep-study pioneer William Dement of Stanford University, California, remarked: “Rarely in the history of medicine has an effective treatment for an illness been developed before the true magnitude of the problem was scientifically established.” With the technology in hand to treat SDB, ResMed is now in a position to test directly whether or not an SDB treatment can improve cardiovascular outcomes. We are running an international randomized

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**Figure 1.** Continuous Positive Airway Pressure (CPAP) therapy equipment through the years.

**Figure 2.** Prevalence of moderate to severe sleep-disordered breathing in cardiovascular disease.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Drug-Resistant Hypertension</td>
<td>80%</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>50%</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>50%</td>
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<tr>
<td>All Hypertension</td>
<td>35%</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>30%</td>
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<tr>
<td>Angina</td>
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clinical trial on the use of ASV in chronic heart-failure patients with SDB. The trial — SERVE-HF (www.servehf.com) — will have enrolled more than 1,300 patients throughout Europe and Australia by May 2013, with the goal of determining whether ASV treatment results in a decrease in morbidity and mortality. A previous meta-analysis of 11 studies of ASV treatment on heart failure (8 of which used ResMed technology) indicated an improvement in cardiac function, but SERVE-HF is the first randomized clinical trial in SDB specifically designed to reveal such a survival effect. The results are expected in late 2015.

Randomized clinical trials are the gold standard of clinical research, but they suffer from certain well-recognized limitations. By their very nature, these trials operate in controlled circumstances on a defined patient population, and clinicians understand that ultimately it is only over time in ‘real world’ populations that the true impact and applicability of a therapy can be understood. ResMed is also committed therefore to following the results of our therapies through patient registries. The ResMed-initiated SchlHaHF patient registry in Germany (NCT01500759) has enrolled more than 10,000 patients with the goal of investigating the prevalence and type of SDB in heart-failure patients and the associated clinical characteristics. A registry of ASV-treated patients has already enrolled more than 100 patients in France and will complement the data obtained by SchlHaHF.

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**Future health**
The treatment of SDB and OSA is now recognized as a holy grail of medical intervention. Treatment with PAP remarkably improves quality of life, slows down and sometimes improves co-morbid disease progression, and results in considerable cost savings. With cardiovascular and metabolic disease rising throughout the world, and the evidence mounting for an intimate relationship between these diseases and SDB, we believe that the need for proper monitoring and management of SDB will only increase. With this in mind, ResMed...
has developed online therapy monitoring systems that can be integrated with our SDB treatment devices. These systems will support the adherence of patients treated with PAP devices, ease the burden placed on healthcare providers, and further magnify the health and economic benefits of treating SDB with PAP.

ResMed’s suite of technologies reaches beyond the treatment of SDB to providing non-invasive ventilation therapies, for example in the management of COPD. The treatment of acute exacerbations of COPD has already become standard practice globally, and we expect within the next few years that the evidence will grow for a chronic treatment of these patients with home mechanical ventilation. Given the obesity epidemic in the Western world, these ventilation solutions will also help to manage respiratory challenges in the care of overweight patients. For ResMed, what began as a treatment to ameliorate the ravages of sleep deprivation has become a mission to return the body to physiological homeostasis and to restore the health benefits associated with normal sleep and breathing.

References