Breathing easier during sleep: Case Study

Obstructive sleep apnea (OSA) is a chronic respiratory disorder that leads to disturbed sleep and causes sickness in at least 200 million people globally.[1] In 2018-19, over 39,000 Australians were hospitalised with a principal diagnosis of OSA.[2] NHMRC-funded researchers at The University of Sydney and Royal Prince Alfred Hospital developed what is now the standard treatment for this disorder and their work provided the foundation for a major global medical device company, ResMed.

Origin

Sleep is an essential biological activity so, when sleep disorders occur, they can cause a wide range of serious health consequences. OSA is the most common type of sleep disorder in the general population worldwide.[2]

While a key symptom of sleep apnea, snoring, was documented by the ancient Greeks and Romans,[3] sleep apnea itself was first described in 1965. In that year, two independent groups of researchers showed – by recording respiratory airflow, electroencephalogram (EEG) and other measurements – that airway obstruction when sleeping prevented patients with OSA from ever falling deeply asleep.[4]

Life with obstructive sleep apnea

Let me tell you what my life was like …. I d get up in the morning. I d sit down to breakfast, and I d fall asleep. I d go out in the car and on my way to work I would nod off at the first set of traffic lights …. When I d get to work, I couldn t sit down because I d go into spontaneous rapid eye movement sleep … so I just couldn t sit down. I wandered around just trying to keep awake …. I d go home, the same way I came in, couldn t go out to a movie, couldn t go out to dinner, couldn t go to an opera or anything like that. Forget it. I d fall asleep at dinner every night. Then I d go to bed for ten hours and not sleep and that was my routine.[5]

At this time, treatment for OSA primarily consisted of surgery, where those portions of the patient's upper respiratory system that appeared to be causing the obstruction were removed. If this did not work, a surgeon could install a breathing tube through the front of the patient's neck directly into their airway.

Such surgical interventions were a dramatic solution to the problem and could themselves have serious negative consequences for the patient. A better solution was needed.

Grants and Investment

NHMRC provided grant funding to a team of researchers at The University of Sydney and Royal Prince Alfred Hospital who were integral to developing a solution for OSA. Key members of this team were Colin Sullivan, Ron Grunstein, Jim Bruderer, Michael Berthon-Jones and Faiq Issa. Another NHMRC-funded researcher, Peter Farrell, played an important role in research translation and commercialisation.

During the period 1979-1992, Sullivan and his colleagues were supported by NHMRC grants to undertake research on a range of respiration-related topics including:

- regulation and control of breathing in sleep and the role of the upper airway
- respiratory muscle function and respiratory failure in sleep
- falls of blood oxygen during sleep
- sleep apnea, including neuropsychological profiles and the role of androgens and opiates in treatment
- treatments to improve breathing in chronic lung and chest wall disease
- the interaction of alcohol and sleep apnea on cognitive function.

During the period 1974-1986, Farrell was a chief investigator (alone, or jointly) on grants that supported research on a range of biomedical engineering challenges including:

- portable artificial kidneys, blood filtration and dialysis
- intravascular cannulae (tubes inserted into veins and arteries).

The Australian Government supported the commercialisation of Sullivan's research through an Industry R&D Board grant, an International Business Development Grant and a National Procurement Development Grant.

Research

During the late 1970s, Colin Sullivan was working as a clinician at Royal Prince Alfred Hospital, mostly looking after patients with respiratory failure.[6]

Within a hospital context, there was a long history of pushing air into the lungs through both the mouth and nose to assist the respiration of seriously ill patients and newborn infants.[7] This technique was known as positive airway pressure (or PAP) and Sullivan had been developing the experimental use of PAP – delivered solely through the nose – to understand the influence of sleep on the tone of muscles in the airway.

In 1981, Sullivan and his team discovered that providing a non-invasive continuous positive airway pressure of air (CPAP) into an OSA patient's nostrils during sleep would keep the patient's airway open. The effect was life-changing. Patients who were barely able to function while awake due to a lack of quality sleep and whose only treatment option was major surgery now had their sleep apnea completely removed each night. Their debilitating symptoms rapidly disappeared.

However, the CPAP machine that Sullivan's team had developed for experimental use was far from ideal for everyday use in the home. Notably:

- the airflow generator first used was originally designed for a spa bath: it weighed 6.75 kg and was too noisy to be placed near the patient
- the early face masks were based on plaster casts of each patient's nose, with a fibre-glass version being 'glued' to the patient's face each night using silicon rubber (an uncomfortable procedure!)
- the machine operated at full strength all the time rather than increasing or decreasing pressure according to the individual's needs at that time in the sleep cycle.[8]

Significant improvements were needed before CPAP could be made widely available.

Commercialisaton

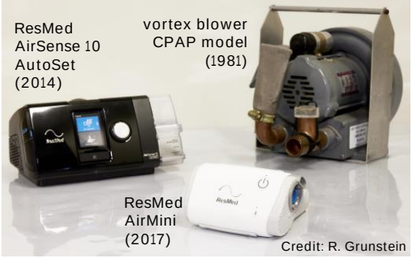
In 1984, Peter Farrell was appointed a Vice President of Research and Development at Baxter Healthcare Corporation, after some years providing consulting services to Baxter on kidney dialysis.[5]

In 1986, Farrell established the Baxter Centre for Medical Research (BCMR) at the University of New South Wales, whose purpose was to commercialise research projects. One of these projects arose when Sullivan approached Farrell about commercialising the CPAP machine.

After extensive research and development efforts, the first version of the new CPAP machine was marketed by Baxter in 1988 and 1989 as the *Sullivan Nasal CPAP System*. However, by 1989 Baxter Healthcare had sold its respiratory therapy division and was no longer interested in developing the CPAP system. Farrell raised funding from investors and formed ResCare Holdings to further develop and sell CPAP.[5]

While the process to commercialise and develop CPAP experienced many obstacles, sales of CPAP machines started doubling every month.[8]

Innovation and progress with CPAP machines



Credit: R. Grunstein

Health Outcomes and Impact

The impact of CPAP machines on clinical practice was rapid and significant. In 1991, NHMRC released a public statement on sleep disorders that noted "The mainstay of management of moderate to severe sleep apnea is nasal continuous positive airway pressure (nCPAP) treatment. A small number of patients would require a ventilator at home".[9]

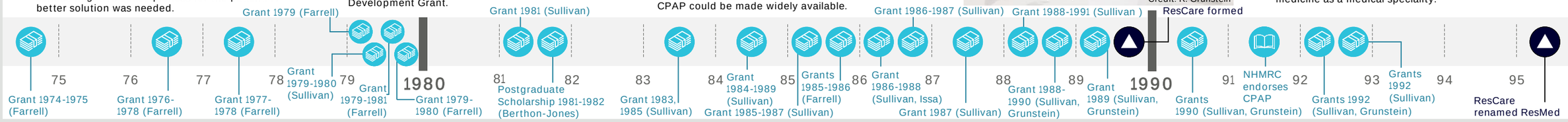
This prediction was a significant underestimate of patient demand based in part upon limitations of the early CPAP machines, which provided limited patient comfort and convenience.

Over time, continuous innovation by a variety of medical device companies led to CPAP machines that were much more comfortable to use, were extremely quiet (about 25 decibels, the sound of a whisper), could automatically determine the correct air pressure to apply to each individual user throughout the night and could send sleep apnea data directly to healthcare providers.

As a consequence of such innovations, the number of CPAP units used in private homes expanded into the millions worldwide. In 2019, the global market for CPAP devices was valued at over AUD3.5 billion and was expected to reach AUD6 billion by 2025.[10]

ResCare became ResMed in 1995. By 2007, ResMed was marketing its products in over 80 countries.[8] By 2021, this number had reached 140 and the company was employing 8,000 people worldwide, including about 1,500 in Australia.[11]

CPAP's introduction marked an entirely new phase in the history of sleep medicine. Soon after its introduction it became the treatment of choice for OSA. Its dramatic effectiveness compared with previous treatment options aided the expansion of the diagnosis and treatment of OSA and other sleep disorders and helped establish sleep disorder medicine as a medical speciality.[12]



Note: NHMRC grants are dated by their start year

Prof Colin Sullivan AO

Colin Edward Sullivan studied medicine at The University of Sydney and completed a PhD while a Resident Medical Officer at the Royal Prince Alfred Hospital in Sydney.

Supported by a John Read Memorial Fellowship of the Asthma Foundation of New South Wales, Sullivan undertook research on respiration at The University of Toronto (1976 1978) then returned to The University of Sydney as a Senior Lecturer. Sullivan was appointed professor in 1991. Following its establishment, Sullivan was Chair of ResMed's Scientific Advisory Board. Sullivan was made an Officer of the Order of Australia in 2009.

Dr Peter Farrell AM

Peter Craig Farrell received a bachelor's degree in chemical engineering with honours from The University of Sydney, a Master's degree from the Massachusetts Institute of Technology (MIT), a PhD in chemical engineering and bioengineering from the University of Washington and a science doctorate from the University of New South Wales (UNSW).

In 1978, he established UNSW's Graduate School of Biomedical Engineering. Farrell founded ResMed in 1989 and has been a board chair and director since that time. He was CEO of ResMed from 1990 2007 and 2011 2013. Farrell was made a Member of the Order of Australia in 2004.

Prof Ron Grunstein AM

Ron Grunstein is Professor of Sleep Medicine at the Woolcock Institute, The University of Sydney and Royal Prince Alfred Hospital. He was President of the World Sleep Federation (2007 2011) and in 2016 was awarded the Thoracic Society of Australia and New Zealand Medal. Grunstein was made a Member of the Order of Australia in 2019.

James Bruderer

James (Jim) W Bruderer was an instrument maker who trained in Switzerland and was a technician in The University of Sydney Biomedical Engineering Department.

Dr Michael Berthon Jones

Michael Berthon Jones studied medicine at The University of Sydney, worked in the area of respiratory medicine at Royal North Shore Hospital in Sydney then became Chief Scientific Officer at ResMed.

Dr Faiq Issa

Faiq G Issa studied medicine at Bashar University in Iraq and received his PhD from The University of Sydney in 1984. He became Associate Professor of Medicine at the University of Calgary in Canada and then at The University of Sydney.

Obstructive Sleep Apnea

A person's upper airway has no rigid support and is held open by the active contraction of upper airway muscles. Normally, during sleep, upper airway muscles relax and the airway narrows. Individuals who already have narrow upper airways or poor muscle tone are prone to temporary collapses of the upper airway during sleep, called apneas, and to near closures of the upper airway called hypopneas. These breathing events result in a lowering of blood oxygen concentration, causing the central nervous system to react to the lack of oxygen and/or increased carbon dioxide and signal the body to respond.

Typically, individuals experiencing sleep apnea subconsciously arouse from sleep. This causes their throat muscles to contract, opening their airway. After a few gasping breaths, blood oxygen levels increase and the individual can resume a deeper sleep until the cycle repeats itself. The severity of sleep apnea is determined by symptoms and the number of apnea and hypopnea events per hour: 5 14 is mild sleep apnea; 15 29 constitutes moderate sleep apnea; 30+ is considered severe sleep apnea. Some sufferers can have over 100 events per hour: 1 2 every minute. While these awakenings greatly impair the quality of sleep, the individual is not normally aware of them.[4]

Australian Government
National Health and Medical Research Council

NHMRC

References

This case study was developed with input from Professor Ron Grunstein and ResMed Ltd and in partnership with The University of Sydney.

The information and images from which impact case studies are produced may be obtained from a number of sources including our case study partner, NHMRC's internal records and publicly available materials.

The following sources were consulted for this case study:

1. R Grunstein 2022, pers. comm. 18 May. Figure extrapolated from data found in: Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. The Lancet Respiratory Medicine. 2015 Apr 1;3(4):310-8
2. Australian Institute of Health and Welfare 2021. Sleep–related breathing disorders with a focus on obstructive sleep apnoea. Cat. no. PHE 294. Canberra
3. Pirsig W. Snoring in the ancient world. Sleep and Breathing. 2002 Jan;6(1):29-39
4. Van Houwelingen KG, Van Uffelen R, Van Vliet AC. The sleep apnoea syndromes. European Heart Journal. 1999 Jun 1;20(12):858-66
5. Caruso D. Peter Farrell Interview – June 12, 2014 [Internet]. Library.ucsd.edu. 2014 [cited 15 March 2022]. Available from: https://library.ucsd.edu/sdta/transcripts/farrell-peter_20140612.html
6. How the CPAP machine beats deadly sleep apnoea [Internet]. The University of Sydney News. 2018 [cited 15 March 2022]. Available from: https://www.sydney.edu.au/news-opinion/news/2018/03/16/how-the-cpap-machine-beats-deadly-sleep-apnoea.html
7. Antonescu-Turcu A, Parthasarathy S. CPAP and bi-level PAP therapy: new and established roles. Respiratory Care. 2010 Sep 1;55(9):1216-29
8. Barnes CS. ResMed origins : a brief history of the establishment of a company manufacturing devices for the diagnosis and treatment of sleep disorder breathing. Bella Vista, N.S.W. ResMed, 2007
9. National Health and Medical Research Council. 112th Session, October 1991. Volume 3. Health Care Committee Report to 112th Session of Council, Item 13, Statement on Sleep Disorders Centres. p126
10. Industry Research. Global CPAP devices market insights, forecast to 2025. SKU ID: QYR-13916656 | 04-Mar-2019
11. ResMed Inc. United States Securities and Exchange Commission. Form 10-K. Annual report pursuant to section 13 or 15(d) of the Securities Exchange Act of 1934. For the fiscal year ended June 30, 2021. Commission file number : 001-15317. ResMed Inc.
12. Dement WC. The study of human sleep: a historical perspective. Thorax. 1998 Oct 1;53(suppl 3):S2-7.

Partner/s

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