



An interview with Dr Peter Gay



Peter C Gay is an Associate Professor of Medicine at the Mayo College of Medicine in Rochester, MN. He has been a consultant in the Division of Pulmonary, Critical Care and Sleep Medicine since 1988 and after receiving all of his training at Mayo, he obtained board

certification in all of these subspecialties. He is now president of NAMDRC, Vice-Chair of the ACCP Home Care Network, and a delegate to the ACCP Sleep Institute. Dr Gay has been a major force in changing CMS coverage criteria for patients with sleep-disordered breathing.

How would you describe Complex Sleep Apnea (CompSA)?

Complex Sleep Apnea is defined as a condition occurring in patients who primarily have obstructive sleep apnea or mixed sleep apneas observed during their diagnostic sleep study but when exposed to continuous positive airway pressure (CPAP), then develop profound or increased levels of central sleep apnea (CSA) that does not respond to raising or lowering CPAP pressure.

Research has indicated that it is more prevalent in males than females. What are your thoughts on this?

My colleague Tim Morgenthaler has published data that looks at the results from over 200 patients referred to the Mayo Clinic Sleep Disorders Centre over one month. This revealed that about 15% had CompSA, and that 81% of them were males, with a higher AHI at 32.¹ However, maleness is not a good discriminator for CompSA. We note that maleness (usually greater than 90%) is a factor in Cheyne-Stokes respiration (CSR), and perhaps CompSA is a transitional disease between OSA and CSR, although we haven't documented any such transition between the two disease states.

Does the severity of OSA predispose the patient to a higher risk of developing CSA and CompSA?

Actually, it's probably the opposite. The more severe a patient's

OSA, the more likely they'll respond to CPAP treatment. CompSA is unique in that it is, by definition, only diagnosed as a result of what happens during CPAP treatment.

With what comorbidities might you expect to find CSA and CompSA?

The classic patient with CSA has Cheyne-Stokes respiration associated with congestive heart failure (CHF). There is what I call a pentad for CSR in CHF patients:

- New York Heart Association classification ≥ 2
- Atrial fibrillation
- Ejection fraction 25% or less
- Mitral Regurgitation
- Maleness.

CompSA has no truly distinctive comorbidities. Our study did show that just over 50% of patients also have cardiovascular problems such as hypertension, atrial fibrillation, or reduced left ventricular function but this is far less than patients with CSR.²

CompSA appears to be predominantly seen during CPAP therapy in OSA sufferers. Could you describe the physiology behind this?

By definition, CompSA occurs when a patient is on CPAP therapy with suspected OSA—the CPAP eliminates the OSA, exposing the fact that the patient is experiencing CSAs. CPAP delivers airway pressure to stent open the upper airway and eliminate apneas caused by obstruction, but it may further exaggerate the rapid breathing phase or hyperpneas that characterize recovery from CSAs. CSAs are caused by problems with the respiratory control system. We don't know whether the effect that CPAP has on the upper airway reflex responses or changing lung volumes, bears any relation to the development of CSAs—this is the subject of future investigation.

How prevalent is CompSA in diagnostic studies or is it more a 'side effect' disorder of CPAP therapy intervention?

There's a lot of speculation about this. Some people think there's a behavioral component—that CPAP is a challenging

Continued from page 1

initial experience that induces breath-holding, drifting in and out of sleep. However, when these patients are initially put onto adaptive servo-ventilation (ASV), the CompSA may rapidly disappear, so that seems to negate the idea of it being a response to the experience of the mask and positive airway pressure PAP therapy of all kinds.

Does CompSA reduce or diminish on some patients who continue with CPAP over time?

Clearly this is the case with some patients—it can even diminish during a CPAP titration night. Interestingly, some patients who have their OSA component removed with CPAP and are left with the CSA component are worse on their backs—when they're turned onto their sides you can treat them with lower pressure and the CSA may diminish or disappear as well because the higher CPAP pressure may have been triggering the CSA.

Could you describe what treatment methodologies have been used to treat CSA?

There's a variety of treatment options for CSA. The largest number of patients are heart failure patients so the important thing there is to optimize the treatment for their underlying CHF, and this can potentially eliminate CSR. We've also seen that OSA can be reduced when people are given pacemakers—speeding up the heart reduces both CSA and OSA. CSA can also develop at high altitude, and people on high levels of pain medications that affect the function of the respiratory controller can also develop CSA. In both of these cases, removing the trigger will reduce or eliminate the CSA.

A number of pharmacological treatments have been tried, but no reliably effective medication treatment has been found—if there was one we'd be using it. Oxygen has been tried, but it only appears to have an effect on the oximeter results—it does nothing to improve the patient's frequent arousals and sleep quality.

CPAP has not been found to improve heart function enough to change mortality or transplantation rate³—it only reduced nocturnal breathing events to about 50% of the baseline level. Alternative airway pressure devices have been shown to be more effective in treating CSA and CompSA. We found that bilevel devices with a backup rate could work in these patients, and now we have the ASV devices which seem to be even more effective and are probably the device of choice now for CSR. One study by RJ Thomas bled CO₂ into a PAP device in the sleep lab to balance apneic spells and showed significant improvements⁴—this was somewhat effective but the need for a cumbersome CO₂ tank would not be easily managed in the home.

The development of algorithms to address CSA has opened new therapy paradigms of PAP in adaptive servo-ventilation. What has been your experience?

In OSA the patient wakes with a gasp during the end of an apnea; in CSA the apnea is followed by a gradual increase in rapid breathing and the patient wakes up panting. The design of equipment for people with CompSA must be able to rapidly respond to both of these states—to the patient's increased pressure needs during an apneic spell and the decreased pressure needs during a hyperneic (rapid breathing) phase.

What percentage of cases fall into the traditional categories of Cheyne-Stokes respiration and idiopathic central sleep apnea (masked by upper airway involvement at time of diagnosis)?

It depends on the population of patients that you study. If you look at all comers to a sleep lab, idiopathic CSA is probably less than 5%. If you look at patients with heart failure, CSR may be seen in more than 30% of patients studied in a sleep lab.

To what extent is heart disease (or other comorbidity) a factor in CompSA development?

There is probably some connection but there is no clear evidence that heart disease provokes CompSA. There are definitely interrelationships between heart disease and all forms of sleep-disordered breathing so this is an area many will be looking into further.

What role do concomitant medications such as serotonin-reuptake-inhibitors and diuretics play in producing an under-damped ventilatory control?

There is some improvement in patients primarily with OSA who are given serotonin-reuptake-inhibitors as it has effects on the tongue muscle tone. It's such a small effect that it's not even considered as a secondary treatment for OSA. Diuretics can be dangerous if given in excess to patients with CSR but some have tried to do this cautiously with modest success. As I said earlier, we don't know of any pharmacological treatments that consistently work very effectively.

1. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex Sleep Apnea Syndrome: Is it a unique clinical syndrome? *Sleep* 2006; 29(9): 1203-1209.
2. Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus non-invasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. *Sleep* 2007; 30(4): 468-475.
3. Bradley TD et al. Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure. *N Engl J Med* 2005; 353: 2025-33.
4. Thomas RJ, Daly RW, Weiss JW. Low-Concentration Carbon Dioxide is an Effective Adjunct to Positive Airway Pressure in the Treatment of Refractory Mixed Central and Obstructive Sleep-Disordered Breathing. *Sleep* 2005; 28(1): 69-77.



From the editor



This is a very special edition of ResMedica, as we publish interviews with three leaders in the field of sleep medicine. Our interviews focus on the recently defined syndrome of 'complex sleep apnea', and how that fits into the range of sleep apnea types.

Our first interview is with Dr Peter Gay, Associate Professor of Medicine at the Mayo College of Medicine, Rochester, and co-author of an article published in *Sleep* in April this year on a clinical trial that assessed the effectiveness of adaptive servoventilation (ASV) versus non invasive positive pressure ventilation in treating central, mixed and complex sleep apnea. His interview with us explores complex sleep apnea, explaining the term and looking at its occurrence and treatments.

We also hear from Dr Ian Wilcox, who is in practice as a Cardiologist in a group Academic Cardiology practice, a Consultant in Cardiology at Royal Prince Alfred Hospital and is a Clinical Associate Professor at the Department of Medicine, Sydney University supervising a research program on sleep and cardiovascular disease. His work on sleep and cardiovascular disease made him an ideal person for us to interview to understand the connections between heart failure and sleep-disordered breathing. His insights into the pathophysiology of sleep-disordered breathing are particularly useful.

Finally, Dr Helmut Teschler draws on his overall depth of knowledge in this field to provide us with a succinct overview of complex sleep apnea. Dr Teschler was one of the first researchers to work with ASV, and published, with his colleagues, the first paper on ASV—there is a summary of it in the *Key Research Articles* section of this edition of ResMedica. Dr Teschler is Professor of Medicine and Head of the Department of Respiratory Medicine, High Dependency Unit, and Center of Sleep Medicine at the Ruhrlandklinik, Faculty of Medicine, University of Essen, Germany.

With this line-up of experts we thought we would have all our questions answered, but the frank responses and willingness to acknowledge where more work needs to be done show us that sleep-disordered breathing is an area where major discoveries are still being made.

We've also provided some background articles to place the current discussions of complex sleep apnea in context, and we have a fascinating interview with Phil Lovell, who shows us how patients can work with their clinicians to find the most effective treatment.

Thanks to all our interviewees for their generosity with their time and expertise.

If you would like to comment on any of the articles in ResMedica, please contact us at **clinicalnews@resmed.com.au**

You can also find more information about ResMed on our website **www.resmed.com.au**

Rhonda Russo, Editor.

*' Our interviews focus on the recently defined syndrome of **complex sleep apnea** and how that fits into a range of sleep apnea types.'*

An introduction to sleep apnea

In later years, portly Brahms frequently snoozed in the afternoon in the cafes of Vienna, and his motionless flowing beard comprised a familiar sight for gawking tourists. A subsequent nap on the occasion of Brahms' first hearing of a promising young conductor by the name of Gustav Mahler in 1890 was interrupted by a 'queer snort'. While one is reluctant to ascribe too much significance to a single such description, the episode is reminiscent of the 'resuscitative snort' that frequently terminates an obstructive event in sleep apnea.¹

Dr ML Margolis's article convincingly gathers evidence that the composer Johannes Brahms (1833–1897) suffered from obstructive sleep apnea (OSA), citing a friend's comments on his snoring, his propensity for falling asleep during the day, progressive obesity and a short, thick neck all exacerbated by a high alcohol intake.²

Brahms is not the only figure from the past to be diagnosed in the present with sleep apnea. John Sotos wrote on the possibility that President Taft (US president 1909–1913) had OSA,³ and Chouard et al presented evidence for the same diagnosis for Napoleon Bonaparte (1769–1821)⁴.

Literature also records sleep-disordered breathing (SDB): Charles Dickens' character 'Joe, the fat boy' in the *Pickwick Papers* (1836–37) spends his time eating and sleeping, has pathological sleepiness and is difficult to wake from sleep, while Samuel Pickwick himself may have exhibited sleep apnea when intoxicated. Dickens' description is so well-observed that, "It was almost 150 years before a clinical description of sleep apnea that surpassed the description of Dickens' was published."⁵

Examples from antiquity include descriptions of Dionysius of Heracleia (born approximately 360 BC) that are consistent with the occurrence of sleep apnea,⁶ and reports by the Greek philosopher and historian Athenaeos (170–230 BC) that indicate that several members of the Ptolemys, the royal family that ruled Egypt from 305 to 30 BC, "suffered from obesity and sleep-disordered breathing."⁷

' A person will present with complex sleep apnea when they experience both central and obstructive sleep apneas.'

SDB is a general term for a sleep disorder with apneas and hypopneas.

- Apnea: a cessation of airflow for ten seconds or longer
- Hypopnea: a 50% or greater decrease in airflow for ten seconds or longer

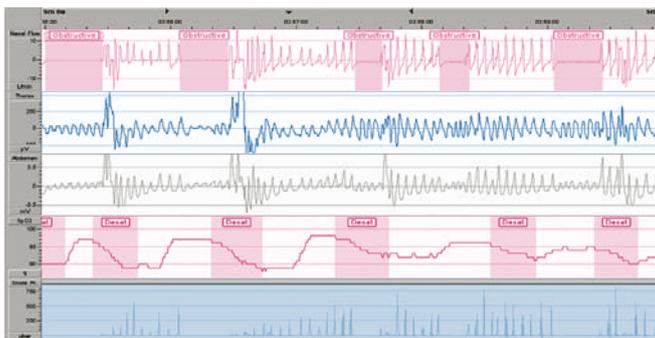
Both apneas and hypopneas frequently cause sleep arousals—moments when an individual wakes enough to resume breathing but not enough to remember any interruption of sleep. Some arousals simply cause the sleeper to shift into a lighter stage of sleep. In either case, the arousal lessens the quality of sleep. Apneas and hypopneas may cause blood oxygen levels to drop.

Hypertension and decreased blood oxygen levels are common symptoms for people with sleep apnea, but these are not easily detected. The symptoms that are easiest to identify without diagnostic testing are:

- Excessive sleepiness
- Snoring
- Witnessed apneas or irregular breathing during sleep (gasping, long pauses, etc—a spouse or partner may notice these)
- Impaired concentration
- Impaired memory
- Morning headaches
- Sexual dysfunction.

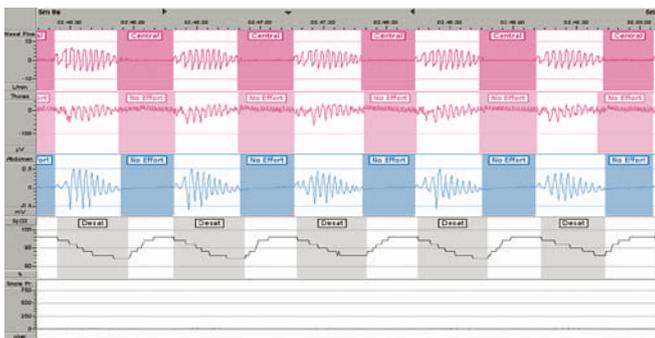


Apneas in Obstructive Sleep Apnea



People with obstructive sleep apnea experience apneas resulting from upper airway obstruction. This is the most common type of sleep apnea. It occurs when the upper airway closes but efforts to breathe continue. The primary causes of upper airway obstruction are lack of muscle tone during sleep, excess tissue in the upper airway, and anatomical abnormalities in the upper airway and jaw.

Apneas in Central Sleep Apnea



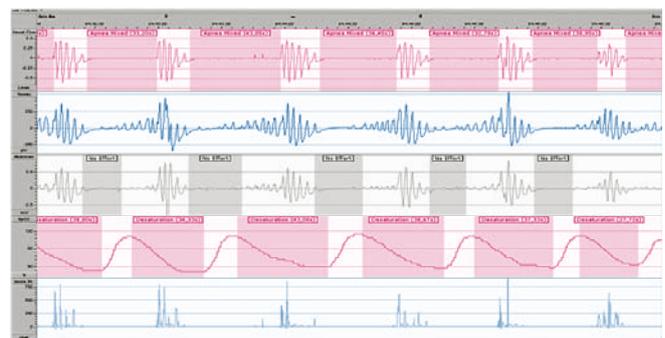
People with Central Sleep Apnea (CSA) experience apneas resulting from dysfunction of the body's automatic drive to breathe—the respiratory controller. This affects only 5-10% of the sleep apnea population. It occurs when breathing stops but the airway is open. This cessation of breathing results from the body's failure to breathe automatically. It's as if a short circuit prevented the brain from keeping the respiratory system functioning properly.

Apneas in Complex Sleep Apnea



A person will present with Complex Sleep Apnea (CompSA) when they experience both central and obstructive sleep apneas, with increased levels of central apneas during CPAP therapy.

Cheyne-Stokes respiration



Cheyne-Stokes respiration (CSR) is a cyclical breathing pattern, involving waxing and waning (crescendo and decrescendo) breathing amplitude with relatively stable respiratory rate. This may or may not be associated with central apneas, during which no respiratory effort occurs. CSR is due to instability in respiratory control.

1. Margolis ML. Brahms' Lullaby Revisited: Did the composer have obstructive sleep apnea? *Chest* 2000; 118:210-213.
2. *ibid.*
3. Sotos JG. Taft and Pickwick: sleep apnea in the White House. *Chest* 2003; 124: 1133-1142.
4. Chouard, C, Meyer, B, Chabolle, F Napoleon souffrait-il du syndrome d'apnee du sommeil. *Ann Otolaryngol Chir Cervicofac* 1988; 105: 299-303.
5. Kryger MH. Sleep Apnea: From the Needles of Dionysius to Continuous Positive Airway Pressure. *Arch Intern Med* 1983; 143: 2301-2303.
6. *ibid.*
7. Michalopoulos A, Tzelepis G, Geroulanos S. Morbid obesity and hypersomnolence in several members of an ancient royal family. *Thorax* 2003; 58: 281-282.

An interview with Phil Lovell

Phil Lovell lives in Sydney's Inner West and is an international Resource Manager for a banking software solution supplier. Phil has been receiving treatment from Dr Ian Wilcox since 2002. Over these five years Phil has worked with Dr Wilcox so that his treatment could reflect changes in his condition.



"When I first went to see Dr Wilcox, the pressure on my CPAP was very high. He said I needed a CPAP with variable pressure. He told me that he wanted me to be responsible for what's going on, so I monitored my therapy regularly." Phil would capture the results from his AutoSet Spirit™ and view them in ResMed's AutoScan™ software, sending them to Dr Wilcox at regular intervals.

Phil was treated successfully for a number of years and experienced the benefits of sleeping better, having more energy and being more active. This changed when an occasional arrhythmia became more permanent. "I was like a car that's not firing on all cylinders," he explains. "My mind was saying 'let's move on' but my body was saying 'no'. It came to a head one day—I felt so ill and dizzy I had to go and see my local doctor, even though I had a scheduled appointment with Dr Wilcox the day after!"

An angiogram showed that there was no blockage in the heart. He then underwent a cardioversion, and his heart rhythm normalized for a short time. After a second cardioversion Phil noticed on his Autoscan software that during the period when his heart rhythm was normal his apneas were improved, but on the night when the apneas returned, the arrhythmia also returned. He faxed his report off to Dr Wilcox.

Looking at his results for the month after the cardioversion showed his AutoSet Spirit settings were at min 4cm/20cm, and his average apnea-hypopnoea index (AHI) was 11.6 per hour. The following week the data changed dramatically, with his AHI jumping to 41.4.

Phil was told to increase his minimum pressure on his AutoSet Spirit to 6cm until he could undergo an Embletta study. His AHI improved slightly, to 37/hr. The Embletta study was performed using his AutoSet Spirit. These results showed central hypopnea with clear Cheyne-Stokes respirations. Phil commenced a trial with the AutoSet CS2™, starting with a two-hour monitoring session in the ResMed North Ryde clinic.

' They tell me I sound more relaxed now.'

"Since being on the AutoSet CS2 the apneas have gone—I haven't even had one," Phil notes with satisfaction.

He was sleeping better, but he was still experiencing arrhythmia. He had a cardiac ablation in March 2006, and since then his heartbeat has been regular.

The improvement in his condition means that Phil has been able to return to the exercise he likes best—cycling with his mates. Before his treatment was resolved he would cycle for an hour and spend the next few hours sleeping. Now he does a regular 30 km cycle every Saturday morning, and sometimes a further ride on Sunday. Phil has noticed that his better health gives him more energy, and his family say he's now much more fun to be with. His work involves a lot of telephone contact with clients, and they've noticed the difference too. "They tell me I sound more relaxed now," he says.

Phil purchased a VPAP Adapt™ SV in 2006. "I use it every night," he says. "I don't miss even one night—what would be the point? I travel a bit and always take it with me. I went to India last year for a conference. I arrived at my hotel at about 2 am to find the powerpoints in my room were too far away from the bed, but I was determined not to sleep without it. The staff raced around looking for extension cords so I could go to sleep."

Phil is enthusiastic about his therapy. "If I hadn't had the AutoSet CS2 the apneas would have put more pressure on my heart. Now I can sleep well, and my arrhythmia is also gone." Phil's willingness to take control of his own condition and to work with his clinicians has led to highly effective treatment. Now he just needs a solar-powered VPAP Adapt SV so he can go trekking.



An interview with Professor Ian Wilcox

Professor Wilcox is in practice as a Cardiologist, including appointments as Consultant in Cardiology at Royal Prince Alfred Hospital and Clinical Associate Professor at the Department of Medicine (Central Clinical School), Sydney University where he supervises a Research Program on Sleep and Cardiovascular Disease. He is also Head of the Department of Medicine at Strathfield Private Hospital, Sydney.



How prevalent is Cheyne-Stokes respiration/Central Sleep Apnea (CSR/CSA) compared to Obstructive Sleep Apnea (OSA)?

We know OSA is common, affecting about 20% of middle-aged men and 10% of middle-aged women. It is the predominant type of sleep apnea in patients without heart failure or stroke. Central sleep apnea occurs in four relatively common situations. Firstly, you may see a few central apneas during sleep studies in patients with predominant OSA. Secondly, traditional teaching has been that central sleep apnea occurs in people with stroke—in various patterns—but the overwhelming majority of people with stroke actually have OSA. Thirdly, and most commonly, it is the predominant breathing abnormality in heart failure, present in up to 70% of people with the more severe grades of heart failure. In this group it has traditionally been called Cheyne-Stokes breathing and you can have abnormal breathing during both sleep and wakefulness. It's interesting to note that the symptom of paroxysmal nocturnal dyspnea, or PND—well recognized to be associated with worsening congestive heart failure—was known to be central sleep apnea in the 1930s when it was first described. During PND the person describes being woken up with a sense of breathlessness and this arousal from sleep happens at the end of a central apnea, or the beginning of the hyperpnea which follows. We now know that PND and CSR/CSA are one and the same thing. Finally, central apneas occur commonly in otherwise healthy individuals at altitude, and may be associated with altitude sickness.

What causes CSA? What is the mechanism?

In its commonest form it occurs primarily as a consequence of developing heart failure. This is the result of various diseases causing loss of the contraction reserve of the heart and this may be acute or chronic and reversible or not. Sleep-disordered breathing appears to develop over time, because we can see people who have an acute heart attack who don't necessarily develop the clinical syndrome of sleep apnea at the time. People with acute heart failure and Cheyne-Stokes respiration/central apnea improve a lot when they have their heart failure treated. I think of it as a *changing snapshot* disease, as it can vary within the night—within the day—within the week—and due to changing medical therapy. The first approach in people with central apneas in the setting of heart failure is to search for reversible factors such as arrhythmias, valve disease or coronary artery disease and optimize their therapy, either with drugs or devices.

' SDB appears to develop over time.'

The pathophysiology is a combination of factors which involve the brain, the heart and lungs. A key factor is enhanced chemoreceptor responses—the degree to which you hyperventilate, in response to hypoxia and hypercapnia. A characteristic feature of CSA is hyperventilation, which is where it has its parallels with altitude sickness. The difference is that in altitude sickness it's hypoxia that is the primary factor driving hyperventilation and hypocapnia is a consequence of that. In heart failure there's increased ventilation due to a number of factors including the fact that the lungs are wet and receptors in the lungs are sending nerve signals to the respiratory control centers in the brainstem to cause hyperventilation. In healthy individuals carbon dioxide levels normally rise during sleep. If we go to sleep with a low CO₂ level below a certain value (the 'apnea threshold') breathing will be inhibited and reduce or even stop until the CO₂ rises when breathing resumes. It is common in patients with heart failure, and healthy individuals at altitude, for hyperventilation and the resultant hypocapnea to make breathing unstable during sleep. In patients with heart failure and sleep-disordered breathing, breathing is made more unstable as the prolongation of circulation time means that the effects of blood gas changes in the periphery take longer to reach the brainstem where control of breathing occurs.

Continued from page 7

Another factor influencing control of breathing in heart failure is the fact that brain bloodflow depends on CO₂ levels. Hypocapnia (low arterial CO₂) reduces bloodflow to the brain, delaying delivery of changes in blood gases to the brain and breathing control centers in the brainstem, worsening breathing instability during sleep. Hypoxia acts as an amplifier of breathing (ventilatory) drive but is not the primary factor in the central apnea of heart failure. Genetic and gender differences influence the occurrence of central sleep apnea in heart failure too although these have not been studied particularly extensively.

‘ Heart function is known to improve with successful PAP treatment. ’

Are there differences as to how the heart responds to OSA and CSA?

Absolutely. One of the key differences is that there are changing pressures in the chest. When you have a closed airway and you have respiratory efforts made against that, you get negative intrathoracic pressure and that is believed to actually increase the work that the heart has to do to eject blood into either the lungs or general circulation. The failing heart is very vulnerable to changes in afterload with an approximately inverse relationship between afterload and cardiac output. By definition, although not actually measured in most clinical settings, central apneas are not associated with breathing effort and therefore intrathoracic pressure changes.

In terms of the sort of blood pressure changes we see, particularly after termination of apnea by an arousal, they're much more marked in the patient with an obstructive component than the patient with a central component. However, while the blood pressure changes with a central apnea may be less, the failing heart is much more vulnerable to pressure overload, so the changes may still have an adverse impact.

When CSR/CSA is seen in OSA patients during initial PAP therapy, does it resolve or diminish with long term PAP therapy? Why does this occur?

In thinking about this you have to separate those without heart failure and those with it and the effects of PAP treatment on OSA and CSA. It's not unusual for normal individuals who don't have obstructive apnea to have a few central apneas, particularly changing between sleep stages, and so you may also see a few central events or a central element to what is otherwise predominantly OSA in patients without heart failure. You can also get occasional central apneas in untreated OSA and during PAP treatment possibly due to stimulation of upper airway afferents as there's a protective reflex that stops you from continuing to inhale when there is something in your upper airway. In general, therefore, we don't usually worry about the occasional apnea, central or obstructive, during PAP treatment. In the absence of heart failure you would not normally expect a change in the central component of OSA over time.

Using PAP to treat predominant OSA in heart failure you would expect to see a reduction in the (minority) central component over time as heart function is known to improve with successful PAP treatment.

However, if you find that a patient is initially successful on PAP therapy but that increasing sleep fragmentation develops due to central or predominantly central apneas, you should ask yourself whether the patient could have developed heart failure or whether pre-existing heart failure has worsened.

In other patients it would appear that a CSR/CSA component remains and CPAP treatment may in fact disrupt their sleep. Can you elaborate?

In thinking about the beneficial effects of PAP on sleep, you have to remember that those with predominantly OSA will have an increase in non-respiratory arousals during sleep due to the treatment itself—at least in the initial stages—but there is a net benefit which results from substantial elimination of arousals due to obstructive events. The major endpoint of using PAP to treat sleepy patients who have OSA but no heart failure is to eliminate breathing-related events, to restore normal sleep structure and to eliminate daytime symptoms of tiredness or sleepiness. If the patient has a substantial central component before or after initial PAP treatment—as is common in heart failure—this may well not improve over time and by adding to the non-respiratory arousals due to the treatment itself, make PAP therapy a further disruption to already poor quality sleep.



When we, and others, started to look at using PAP to treat predominantly central apnea in patients with heart failure we had mixed, and often poor, results. While some groups reported great success in using PAP in CSA/CSR, the experience in many other centers—like ours—with a lot of expertise in sleep-disordered breathing and PAP therapy, was that in heart failure patients with a significant burden of central apneas, PAP therapy was poorly tolerated and not effective in correcting the sleep-disordered breathing.

In the heart failure population, people are tired and lacking in energy because they've got significant heart disease. They're not necessarily sleepy as such, so they're harder to treat from the beginning, but that makes it all the more important that their sleep-disordered breathing is treated meticulously. The situation is further complicated by the fact that in heart failure, sleep can be disrupted by a number of non-respiratory events such as periodic limb movements and nocturia.

The rise of the term 'complex sleep apnea' reflects the observation that applying PAP can change the pattern of apnea to one where the obstructive elements are eliminated and a central pattern is more clearly present. I think it's a very logical concept which adds to the notion of how sleep apnea in heart failure is diagnosed and treated. However, sleep physicians and technologists already uses terms like 'complicated sleep-disordered disorders' to cover all sorts of things including elements of narcolepsy, periodic limb movements with arousals and so on, so the word 'complex' is in my view, a potential source of confusion. If it allows people to understand that polysomnography is not a 'gold standard' diagnostic modality in heart failure and sleep apnea then it's a good thing.

' It is extraordinary that ASV treatment was developed in advance of widespread recognition of the diagnosis.'

The use of adaptive servo-ventilation (ASV) has been shown to bring significant improvement to CHF patients with CSR. How is this form of PAP different to the more commonly used CPAP and what is its effect on the heart?

A whole series of studies that have been performed all over the world have looked at the value of positive airway pressure in heart failure, showing that it reduces afterload, functional mitral regurgitation, heart size and sympathetic nerve traffic. If patients can tolerate the therapy it does them good. The problems have been getting people to use it and also identifying which patients benefit from it.

Adaptive servo-ventilation is founded on essentially different principles to the use of PAP in OSA. Obstructive sleep apnea in the absence of heart failure is associated with normal or reduced average breathing during sleep. This may result in hypercapnic respiratory failure in some patients. When hypercapnia in OSA is mild it will often improve with PAP treatment but non-invasive ventilation may be needed in some patients at least initially.

In contrast, patients with heart failure and CSA/CSR are alternating between hyperventilation and apnea, but are hypocapnic because they are hyperventilating on average. Theoretically, by ventilating patients the cycle of apneas and hyperventilation with attendant sleep fragmentation could be eliminated, but it is very difficult using treatment protocols and devices designed to treat respiratory failure. While applying PAP to such patients will tend to eliminate predominantly obstructive apneas and reduce the work of breathing on inspiration, it increases the expiratory work of breathing. In addition, increased hyperventilation by the device itself would theoretically worsen the situation by, amongst other things, promoting glottic closure due to hypocapnia. Nonetheless, we and others had some success with fixed rate ventilation in heart failure and CSA/CSR.

Lessons from the failure of PAP to treat most patients with CSA/CSR and the limited value of simple approaches to controlling breathing patterns in heart failure led to the development of ASV. The concept of an intelligent breathing algorithm which anticipated what the breathing pattern would be, and responded to normalize it, is a remarkable innovation. When compared with CPAP, PAP with variable inspiratory and expiratory pressures or oxygen, it proved to be extremely successful in firstly reducing the burden of sleep-disordered breathing and secondly controlling total arousals during sleep and normalising sleep. It is extraordinary that ASV treatment was developed in

Continued from page 9

advance of widespread recognition of the diagnosis. Usually medical treatments follow recognition of the disease—they're normally linked together—but therapies normally lag behind.

' ASV proved to be extremely successful in firstly reducing the burden of SDB.'

And it has that positive effect on the heart?

We have seen beneficial effects, but the studies are modest in size at this time and I think in order to get cardiologists to adopt it in a widespread fashion we need reasonably large randomized studies to convince them that this is important therapy which they need to incorporate into their practice. It's important to understand where this treatment fits in to the plethora of other treatments for heart failure, which include drugs and devices.

Are some types of patients more prone to CSR/CSA than others?

I think that there are individual factors that affect this. At no point in heart disease is the incidence of CSA/CSR ever 100%—20–30% of patients don't develop SDB, no matter how bad the heart is. I personally think that there are aspects of respiratory control that are inherited or innate, and which determine the proneness of patients to central apnea. I think chemoreceptor sensitivity is critical and just like altitude sickness, which certainly is a bit commoner in the young and the male, I think that we have seen a preponderance of sleep-disordered breathing of the central kind in men rather than women with heart failure. I don't think that's an accident—I think that one of the key factors is genetic differences and gender differences in ventilatory control, prior to the onset of heart failure. The effect of pre-existing OSA on development of CSA in the setting of new heart failure remains to be evaluated but you would have to think it would influence it one way or another.

Abbreviations

- Central sleep apnea (CSA)
- Cheyne-Stokes respiration (CSR)
- Complex sleep apnea (CompSA)
- Congestive heart failure (CHF)
- Continuous positive airway pressure (CPAP)
- Ejection fraction (EF)
- Obstructive sleep apnea (OSA)
- Positive airway pressure (PAP)



An interview with Helmut Teschler

Dr Teschler is Professor of Medicine and Head of the Department of Respiratory Medicine, High Dependency



Unit, and Center of Sleep Medicine at the Ruhrlandklinik, Faculty of Medicine, University of Essen, Germany. He is a fellow of each of the following associations: German Pneumology Society, American Thoracic Society, European Respiratory Society and American Sleep Disorders

Association. He is also President-Elect of the German Pneumology Society.

How has the recognition of sleep-disordered breathing (SDB) patterns evolved over the last 20 years or so?

Since the invention of nasal cannulas for diagnosing sleep-disordered breathing we have been able to detect respiratory-related arousals (RERAs), and our diagnoses have become much more precise. This led to the new International Classification of Sleep Disorders, version 2 (ICSD 2) in 2005, which differentiates between obstructive and central sleep-disordered breathing as well as sleep-related hypoventilation. For the first time now central sleep-disordered breathing is divided into seven different sub-categories: primary CSA; CSA due to Cheyne-Stokes Respiration; CSA due to High-Altitude Periodic Breathing; CSA due to a Medical Condition other than Cheyne Stokes; CSA due to Drug or Substance; and Primary Sleep Apnea of Infancy.

What is Complex Sleep Apnea (CompSA) and how is it defined?

The term 'Complex Sleep Apnea' addresses the gaps in the ICSD 2 since there is a substantial fraction of patients with sleep-disordered breathing who show a combination of different forms of SDB. There is no official definition of CompSA yet. Three different publications have used the following definition of Comp SA:

- obstructive events are treated well by CPAP
- under CPAP: CAI \geq 5/hr or Cheyne-Stokes respiration

Does the severity of OSA predispose the patient to a higher risk of developing CSA and CompSA?

Through causing hypertension and systolic or diastolic heart failure more severe OSA could predispose to CSA or CompSA.

' For the first time now central SDB is divided into seven categories.'

Are there comorbidities associated with CSA and CompSA?

Looking at the only study that addressed characteristics of CompSA patients compared to OSA and CSR patients, there were no differences between the groups. However, patients with systolic dysfunction were excluded. There might be a link to diastolic dysfunction, and perhaps to atrial fibrillation or autonomic neuropathy, eg in patients with diabetes mellitus. Also, comorbidities or medications associated with abnormalities in ventilatory control could play an important role!

CompSA appears to be predominantly seen during CPAP therapy in OSA sufferers. Could you describe the physiology behind this?

There are three possibilities for the central events under CPAP therapy. Firstly, they may be caused by the pressurization of the upper airway (Hering-Breuer Reflex). Secondly, it is a coexisting form of central sleep apnea, which might have been partially or totally disguised by the obstructive sleep apnea. In this case, the PAP might splint the upper airways and treat obstructive events quite well but unmask underlying periodic breathing abnormalities, for example due to diastolic dysfunction or due to side effects of different medications. Thirdly, the pressurization of the upper airway is causing a change in ventilatory control through interactions with chemosensitivity and respiratory drive.

How prevalent is CompSA in diagnostic studies or is it more a 'side effect' disorder of CPAP therapy intervention?

There are no real data on it. Estimations are based on prescription rates (other than CPAP therapy for SDB without hypoventilation). The appraisal is 5-10% in a general sleep laboratory population and up to 60% in laboratories dealing with heart failure patients and patients suffering from less well controlled hypertension, from renal failure or diabetes mellitus with neuropathy.

' We know from many trials that ASV treats Cheyne-Stokes respiration extremely well.'

In your experience, what effect does CPAP have on CompSA over time?

There will be some patients who lose their central events over time. But neither the proportion nor the timeframes are clear yet. Long-term follow-up studies are urgently needed in order to answer this important question.

What treatment has been the most effective in treating CSA and CompSA?

We know from many trials that ASV treats Cheyne-Stokes respiration extremely well. In CompSA we have conducted a pilot study that also shows excellent results for controlling its complex breathing abnormalities during sleep.

What percentage of cases fall into the traditional categories of Cheyne-Stokes respiration and idiopathic central sleep apnea (masked by upper airway involvement at time of diagnosis)?

That depends on the patient's comorbidities. In heart failure and stroke patients primarily CSR is seen, while in other conditions (also due to the new classification) primarily central sleep apnea will be found. Overall pure CSA comprises only a small fraction of all SDB patients.

To what extent is heart disease (or other comorbidity) a factor in CompSA development?

Diastolic dysfunction could be a key to CompSA, but that needs to be investigated in the near future.

What major area of future research needs addressing in regard to CompSA?

First of all more data on prevalence and clinical relevance are needed. The impact of different comorbidities needs to be studied in detail. It is of interest to compare cycle length and other characteristics in patients with CompSA und CSR/ CSA due to heart failure. Also, abnormalities in respiratory drive and arousal response of individuals with CompSA and the impact of PAP on these abnormalities should be investigated. Lastly, trials focusing on therapy modalities and effects and long-term compliance are needed.



Adaptive servo-ventilators: AutoSet CS2 and VPAP Adapt

In 2001 Teschler et al¹ published the results of a study that compared the effectiveness of a new device—an adaptive servo-ventilator (ASV)—against existing treatments for patients with central sleep apnea and Cheyne-Stokes respiration (CSA/CSR) and heart failure. The ASV was designed to directly suppress CSA/CSR while providing hemodynamic benefits similar to CPAP.

Teschler's study compared the ASV's impact against nasal oxygen, nasal CPAP and bilevel spontaneous plus timed (ST) mode nasal ventilation. They found that during the one-night study, while all four forms of treatment reduced the central apnea index, it was lowest for those using the ASV. Sleep and breathing were better for the patients on the ASV than for those treated with oxygen or CPAP. The patients—who all had stable cardiac failure and CSA/CSR—preferred using the ASV to bilevel or CPAP.

Philippe et al followed up with a six-month study that compared ASV with CPAP treatment for patients with CSA/CSR and congestive heart failure (CHF), concluding that, "At six months, the improvement in quality of life was higher with ASV and only ASV induced a significant increase in LVEF."²

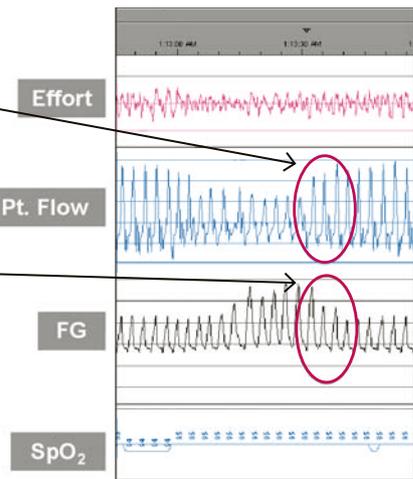
ResMed has developed two adaptive servo-ventilators (ASV), the AutoSet CS2™ and the VPAP Adapt™. Development of the ASV algorithm for the AutoSet CS2 began in the late 1990s to provide a device that could deliver a positive varying degree of support pressure. It starts with a target ventilation of 5 L/min then, over the following few minutes, updates this to be equal to 90% of the patient's recent average ventilation. This average ventilation is constantly updated while the patient is breathing on the device. Because the target is slightly less than the actual ventilation, the ASV algorithm cannot make the overventilation worse. This strategy of using an adaptive target would not work for respiratory insufficiency or hypoventilation, but does work for CSA/CSR, which is an overventilation syndrome.

The ASV algorithm automatically adjusts inspiratory pressure by varying the amount of pressure support. It synchronizes the level of support with the patient's breathing by using the patient's own recent average respiratory rate and monitoring the patient's airflow. It also has a back-up respiratory rate which is used during the first moments of therapy, or during a lengthy apnea. It provides minimal support during the over-breathing (hyperpnea) phase or during normal breathing, and increases support during under-breathing (hypopnea or apnea). While the pressure support varies as the patient's breathing demands it, a constant low level of pressure support helps decrease pulmonary congestion.

Example 1

Ventilation increases above target

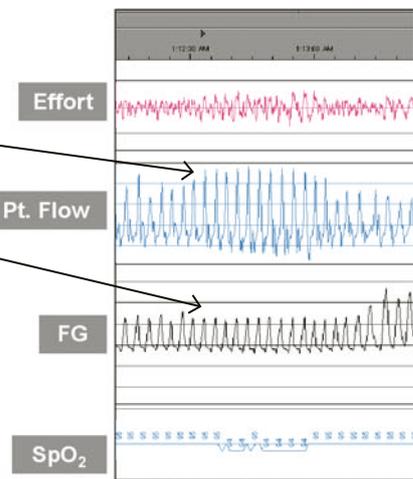
ASV responds by rapidly dropping back to minimum support ensuring the pt is not over-ventilated (causing hypocapnia or vocal cord closer)



Example 2

Ventilation is above the target during hyperpnea (also with normal breathing)

ASV provides minimum degree of support



ResMed has now used the ASV algorithm in the VPAP Adapt. This uses the same platform as other recent ResMed devices, giving it the advantage of interchangeable modules such as humidifiers and masks, and monitoring devices. Humidification for breathing comfort and good mask fit for leak minimization are both extremely important for a high therapy compliance rate.

1. Teschler H, Döhring J, Wang Y-M, Berthon-Jones M. Adaptive Pressure Support Servo-Ventilation: A Novel Treatment for Cheyne-Stokes Respiration in Heart Failure. *Am J Respir Crit Care Med* 2001; 164: 614-619.
2. Philippe C, Stoica-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L, Michel P-L, Rouault S, d'Ortho M-P. Compliance with and efficacy of adaptive servo-ventilation (ASV) versus continuous positive airway pressure (CPAP) in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006 Mar; 92(3): 337-42. *Epub* 2005 Jun 17.

Key research articles: complex sleep apnea

1 Adaptive Pressure Support Servo-Ventilation: A Novel Treatment for Cheyne-Stokes Respiration in Heart Failure.

Teschler H, Döhring J, Wang Y-M, Berthon-Jones M. *Am J Respir Crit Care Med* 2001; 164: 614-619.

Adaptive servo-ventilation (ASV) is a novel method of ventilatory support designed for Cheyne-Stokes respiration (CSR) in heart failure. The aim of our study was to compare the effect of one night of ASV on sleep and breathing with the effect of other treatments. Fourteen subjects with stable cardiac failure and receiving optimal medical treatment were tested untreated and on four treatment nights in random order: nasal oxygen (2 L/min), continuous positive airway pressure (CPAP) (mean 9.25 cm H₂O), bilevel (mean 13.5/5.2 cm H₂O), or ASV largely at the default settings (mean pressure 7 to 9 cm H₂O) during polysomnography. Thermistor apnea + hypopnea index (AHI) declined from 44.5 ± 3.4/h (SEM) untreated to 28.2 ± 3.4/h oxygen and 26.8 ± 4.6/h CPAP (both p < 0.001 versus control), 14.8 ± 2.3/h bilevel, and 6.3 ± 0.9/h ASV (p < 0.001 versus bilevel). Effort band AHI behaved similarly. Arousal index decreased from 65.1 ± 3.9/h untreated to 29.8 ± 2.8/h oxygen and 29.9 ± 3.2/h CPAP, to 16.0 ± 1.3/h bilevel and 14.7 ± 1.8/h ASV (p < 0.01 versus all except bilevel). There were large increases in slow-wave and rapid eye movement (REM) sleep with ASV but not with oxygen or CPAP. All subjects preferred ASV to CPAP. One night ASV suppresses central sleep apnea and/or CSR (CSA/CSR) in heart failure and improves sleep quality better than CPAP or 2 L/min oxygen.

2 Compliance with and efficacy of adaptive servo-ventilation (ASV) versus continuous positive airway pressure (CPAP) in the treatment of Cheyne-Stokes respiration in heart failure over a six month period.

Philippe C, Stoica-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L, Michel P-L, Rouault S, d'Ortho M-P. *Heart* 2006 Mar; 92(3): 337-42. Epub 2005 Jun 17.

Aim: Central sleep apnoea syndrome (CSA) with Cheyne-Stokes respiration (CSR) has an important influence on prognosis of congestive heart failure (CHF). Nocturnal Continuous Positive Airway Pressure (CPAP) has been found to improve transplant-free survival. Adaptive Servo-Ventilation (ASV) is a novel positive pressure mode that provides servo-controlled bi-level pressure support. The present study compared the compliance with and efficacy of ASV to CPAP, in patients with CSA-CSR and CHF, using Apnoea Hypopnoea Index (AHI), quality of

life and LVEF over 6 months. Methods and results: 25 patients (age: 28-80y, NYHA: II-IV) with stable CHF and CSA-CSR were randomised to either CPAP or ASV. At inclusion, both groups were comparable for NYHA class, LVEF, medical treatment, BMI and CSA-CSR. Both ASV and CPAP decreased the AHI, but noticeably, only ASV completely corrected the sleep apnoea syndrome (SAS), with AHI below 10/h. At 3 months, compliance was comparable between ASV and CPAP, however, at 6 months compliance with CPAP was significantly less than with ASV. At 6 months, the improvement in quality of life was higher with ASV and only ASV induced a significant increase in LVEF.

Conclusion: These results suggest that patients with CSA-CSR might receive greater benefit from treatment with ASV than with CPAP.

3 Complex Sleep Apnea: Is It a Unique Clinical Syndrome?

Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. *Sleep* 2006; 29(9): 1203-1209.

STUDY OBJECTIVES: Some patients with apparent obstructive sleep apnea hypopnea syndrome (OSAHS) have elimination of obstructive events but emergence of problematic central apneas or Cheyne-Stokes breathing pattern. Patients with this sleep-disordered breathing problem, which for the sake of study we call the "complex sleep apnea syndrome," are not well characterized. We sought to determine the prevalence of complex sleep apnea syndrome and hypothesized that the clinical characteristics of patients with complex sleep apnea syndrome would more nearly resemble those of patients with central sleep apnea syndrome (CSA) than with those of patients with OSAHS. DESIGN: Retrospective review SETTING: Sleep disorders center. PATIENTS OR PARTICIPANTS: Two hundred twenty-three adults consecutively referred over 1 month plus 20 consecutive patients diagnosed with CSA. INTERVENTIONS: NA. MEASUREMENTS AND RESULTS: Prevalence of complex sleep apnea syndrome, OSAHS, and CSA in the 1-month sample was 15%, 84%, and 0.4%, respectively. Patients with complex sleep apnea syndrome differed in gender from patients with OSAHS (81% vs 60% men, p < .05) but were otherwise similar in sleep and cardiovascular history. Patients with complex sleep apnea syndrome had fewer maintenance-insomnia complaints (32% vs 79%; p < .05) than patients with CSA but were otherwise not significantly different clinically. Diagnostic apnea-hypopnea index for patients with complex sleep apnea syndrome, OSAHS,



and CSA was 32.3 +/- 26.8, 20.6 +/- 23.7, and 38.3 +/- 36.2, respectively (p = .005). Continuous positive airway pressure suppressed obstructive breathing, but residual apnea-hypopnea index, mostly from central apneas, remained high in patients with complex sleep apnea syndrome and CSA (21.7 +/- 18.6 in complex sleep apnea syndrome, 32.9 +/- 30.8 in CSA vs 2.14 +/- 3.14 in OSAHS; p < .001).

CONCLUSIONS: Patients with complex sleep apnea syndrome are mostly similar to those with OSAHS until one applies continuous positive airway pressure. They are left with very disrupted breathing and sleep on continuous positive airway pressure. Clinical risk factors don't predict the emergence of complex sleep apnea syndrome, and best treatment is not known.

4 Treatment of complex sleep apnea syndrome: A retrospective comparative review.

Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI. *Sleep Medicine* 2006; 7: 474-479.

Background and purpose: Some patients with obstructive sleep apnea syndrome (OSAS) develop problematic central apneas or Cheyne-Stokes pattern with acute application of continuous positive airway pressure (CPAP), herein called complex sleep apnea syndrome (CompSAS). This response makes it difficult to be certain that CPAP will be a successful treatment strategy. We sought to compare treatments between patients with CompSAS vs. OSAS and hypothesized that CompSAS patients would find CPAP less effective and have more problems with adherence than patients with OSAS. **Patients and methods:** We performed a retrospective review of patients studied in our sleep disorders center over 1 month. **Results:** There were 133 patients with OSAS (mean age=57.6±12.2 years; males=63.9%) and 34 with CompSAS (mean age=54.4±16 years; males=82.35%). CPAP was prescribed in 93.7 and 87.9% of OSAS and CompSAS patients, respectively (P=0.284), with no significant difference in required CPAP pressures (P=0.112). There was no difference in prescription frequency of alternative therapies. Mean time to the first follow-up was shorter in CompSAS patients (46.2±47.3 vs. 53.8±36.8 days; P=0.022). CPAP compliance in OSAS and CompSAS patients (5.1±1.6 vs. 6.1±1.5 h, P=0.156) and improvement in Epworth Sleepiness Scale (ESS) (-4.6±4.8 vs. -5.9±6.9, P=0.483) was similar. However, interface problems were more common in CompSAS patients, especially air hunger/dyspnea (0.8 vs. 8.8%) and inadvertent mask removal (2.6 vs. 17.7%) (all P<0.050). **Conclusion:** CompSAS patients have more

CPAP interface problems and require more follow-up than OSAS patients but with intervention may have similar treatment results compared to patients with OSAS.

5 Central Sleep Apnea: Pathophysiology and Treatment.

Eckert DJ, Jordan AS, Merchia P, Malhotra A. *Chest* 2007; 131: 595-607.

Central sleep apnea (CSA) is characterized by a lack of drive to breathe during sleep, resulting in repetitive periods of insufficient ventilation and compromised gas exchange. These nighttime breathing disturbances can lead to important comorbidity and increased risk of adverse cardiovascular outcomes. There are several manifestations of CSA, including high altitude-induced periodic breathing, idiopathic CSA, narcotic-induced central apnea, obesity hypoventilation syndrome, and Cheyne-Stokes breathing. While unstable ventilatory control during sleep is the hallmark of CSA, the pathophysiology and the prevalence of the various forms of CSA vary greatly. This brief review summarizes the underlying physiology and modulating components influencing ventilatory control in CSA, describes the etiology of each of the various forms of CSA, and examines the key factors that may exacerbate apnea severity. The clinical implications of improved CSA pathophysiology knowledge and the potential for novel therapeutic treatment approaches are also discussed.

2007 Calendar of events

Global Offices

United States

ResMed Corp.
Poway CA USA
Tel: +1 858 746 2400
or 1800 424 0737
Fax: +1 858 746 2900
reception@resmed.com

Australia

ResMed Ltd
Bella Vista NSW
Tel: +61 2 8884 1000
or 1800 658 189
Fax: +61 2 8883 3114
reception@resmed.com.au

Austria

Tel: +43 803 4800

China

Tel: +86-10-68492133

Egypt

Tel: +20 3 546 8825

Finland

Tel: +358 0 9 8676 820

France

Tel: +33 4 26 100 200

Germany

Tel: +49 0 89/99 01-00

Hong Kong

Tel: +852 2366 0707

India

Tel: +91 11 4223 5348

Italy

Tel: +39 0586 503674

Japan

Tel: +81 3 5840 6781

Malaysia

Tel: +60 3 6201 7177

Netherlands

Tel: +31 0 70 79904 00

New Zealand

Tel: +64 274 737 633

Norway

Tel: +47 67 11 88 50

Singapore

Tel: +65 6284 7177

Spain

Tel: +34 916 393 579

Sweden

Tel: +46 520 420 110

Switzerland

Tel: +41 61 564 70 00

United Kingdom

Tel: +44 1235 862 997

9–12 June 2007	Hamburg, Germany	Heart Failure 2007 (European Society of Cardiology)
9–14 June 2007	Minneapolis, USA	APSS 21st Annual Meeting (Associated Professional Sleep Societies)
11–16 June 2007	San Diego, USA	ASBS Annual Meeting (American Society of Bariatric Surgery)
1–5 September 2007	Vienna, Austria	World Congress of Cardiology 2007
2–6 September 2007	Cairns, Australia	5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies
15–19 September 2007	Stockholm, Sweden	European Respiratory Society Congress
25–29 September 2007	Las Vegas, USA	Annual Obesity and Associated Conditions Symposium (American Society of Bariatric Physicians)
2–4 October 2007	Orlando, USA	Medtrade
20–25 October 2007	Chicago, USA	Chest 2007
4–7 November 2007	Orlando, USA	AHA Scientific Sessions (American Heart Association)
14–17 November 2007	Düsseldorf, Germany	Medica 2007
1–4 December 2007	Orlando, USA	AARC International Respiratory Congress (American Association for Respiratory Care)

AN IMPORTANT NOTE TO YOU, THE READER

ResMedica publication is the subject of copyright owned by ResMed Ltd 2006, all rights reserved.

Requests for permission to reproduce contributions from ResMedica should be addressed in writing to the editor.

ResMedica is a trademark and servicemark of ResMed Ltd.

ResMedica clinical newsletter is intended to serve as a forum for topics of interest to healthcare professionals. Contributions by the editor and authors may contain information or opinions that have not been verified for accuracy or completeness by their authors or the editor.

You should make your own independent inquiries before relying on ResMedica contributions and accordingly neither the ResMed Group of companies nor the editor offer to, nor will accept liability for, the consequences of any reliance you may place on ResMedica contributions. Opinions by authors in ResMedica contributions are not intended to be the opinions of, nor are they endorsed by, the ResMed Group of companies or the editor.

While the editor has striven to make correct attributions of authorship and to acknowledge ownership of copyright any omission or error is unintentional and the editor invites the notice of any suspected omission or error. ResMed publications adhere to the Chicago Manual of Style, 15th edition and the ResMed Writing Guide.