Cardiac or Other Implantable Electronic Devices and Sleep-disordered Breathing – Implications for Diagnosis and Therapy

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Abstract

Sleep-disordered breathing (SDB) is of growing interest in cardiology because SDB is a highly prevalent comorbidity in patients with a variety of cardiovascular diseases. The prevalence of SDB is particularly high in patients with cardiac dysrhythmias and/or heart failure. In this setting, many patients now have implantable cardiac devices, such as pacemakers, implantable cardioverter-defibrillators or implanted cardiac resynchronisation therapy devices (CRT). Treatment of SDB using implantable cardiac devices has been studied previously, with atrial pacing and CRT being shown not to bring about satisfactory results in SDB care. The latest generations of these devices have the capacity to determine transthoracic impedance, to detect and quantify breathing efforts and to identify SDB. The capability of implantable cardiac devices to detect SDB is of potential importance for patients with cardiovascular disease, allowing screening for SDB, monitoring of the course of SDB in relation to cardiac status, and documenting of the effects of treatment.

Keywords

Implantable cardiac devices, heart failure, Cheyne-Stokes respiration, sleep-disordered breathing; obstructive sleep apnoea, central sleep apnoea

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Implantable cardiac devices, such as pacemakers, are used to treat a number of heart conditions, especially those related to the electrical conduction system. Cardiac pacemakers are a well-established and effective therapy, and have been in use for more than 50 years.

The first pacemaker was implanted in a patient in October 1958 by Åke Senning in Stockholm, in cooperation with engineer Rune Elmqvist from Siemens. This pioneer work formed the basis of further developments in implantable cardiac device technology, resulting in the devices available today, including implantable cardioverter-defibrillators (ICDs) and biventricular stimulating implanted cardiac resynchronisation therapy (CRT). These newer devices have better effectiveness and a positive impact on patient quality of life (QoL), and are important cardiology treatment strategies.

The idea of treating sleep-disordered breathing (SDB) using implantable cardiac devices is not new. In 2002 Garrigue et al. investigated 15 patients with SDB and permanent atrial-synchronous ventricular pacemakers for symptomatic sinus bradycardia using polysomnographic evaluations on consecutive nights. On the basis of one night of treatment, given in a random order, dual-chamber atrial overdrive pacing reduced the apnoea–hypopnoea index (AHI) to 11 ± 14 , compared with 28 ± 22 in spontaneous rhythm ($p < 0.001$).¹ Initially it had been suggested that atrial pacing would improve SDB in patients with bradycardia, but this hypothesis has not been supported by the results of recent studies.^{2,3}

In addition to their treatment capability, there are a number of algorithms available for today's implantable cardiac devices that allow them to also be used as diagnostic tools. For example, detection of transthoracic impedance has been used to measure respiratory efforts for many years. In addition, for more than a decade many pacemakers have included integrated respiratory minute volume sensors as part of a basic algorithm to adapt the heart rate.⁴ Recently, this capability was enhanced to allow detection of cardiac decompensations by measuring changes in intrathoracic fluids.⁵ A growing number of implantable cardiac devices also now have the ability to detect SDB.^{6–8}

Sleep-disordered Breathing

Interest in SDB among cardiologists is increasing rapidly due to the high prevalence of SDB in patients with cardiovascular disease. The prevalence of SDB in cardiovascular patients is particularly high in those with cardiac dysrhythmias and heart failure (HF; see *Figure 1*).⁹

There are two main types of SDB: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). OSA is characterised by repetitive interruptions of ventilation during sleep caused by collapse of the pharyngeal airway. An obstructive apnoea is a 10-second pause in respiration associated with ongoing ventilatory effort, combined with a decrease in oxygen saturation and/or arousal. A diagnosis of OSA syndrome is made when the number of respiratory events (AHI per hour) is five or more per hour and the patient has symptoms of

excessive daytime sleepiness.^{10,11} CSA is characterised by repetitive cessation of ventilation during sleep resulting from a loss of ventilatory drive. A central apnoea is a 10-second pause in ventilation with no associated respiratory effort. CSA is present when a patient has five or more central apnoeas or hypopnoeas per hour.^{10,12}

Implantable Cardiac Electronic Devices and SDB Diagnosis

The ability of current implantable cardiac devices (pacemakers, ICDs and CRT) to determine transthoracic impedance, and therefore detect and quantify breathing efforts, makes them capable of detecting SDB. Multichannel polysomnography (PSG) is the gold standard tool for the detection and quantification of SDB.¹³ However, PSG is costly and needs to be undertaken at specialist clinics. As a result, alternative, less expensive and more convenient options that can offer good reliability are becoming increasingly attractive, particularly for the detection and monitoring of SDB in cardiac patients and for monitoring the effects of therapy.

Thoracic impedance is determined by the relation of air to fluids between the measurement locations. Implantable pacemakers measure transthoracic impedance between an endocardial implanted lead and the pectoral aggregate. Thoracic impedance rises with inspirational efforts and falls during expiration.⁴ Implantable cardiac devices have been used to detect SDB for at least a decade, and their ability to do so has been validated in comparisons with multichannel polysomnography (PSG) recordings, the gold standard for diagnosing SDB.^{7,8,14–20} Recently, the internal SDB detection algorithm of an implanted pacemaker device documented a high prevalence of SDB (up to 75 %) in a cohort of 32 unselected cardiac patients.²¹

SDB definition varies between different devices. The algorithm of a pacemaker by Sorin (Paris, France) records an apnoea when there is breathing cessation of >10 seconds, and a hypopnoea when the breathing amplitude is reduced by ≥50 % for >10 seconds; the number of events per hour is used to calculate the respiratory disturbance index (RDI).²² In devices from Boston Scientific (St. Paul, Minnesota, USA), the SDB detection algorithm also registers apnoeas as breathing cessation of >10 seconds, but hypopnoeas as a ≥26 % decrease in transthoracic impedance amplitude for >10 seconds and the AHI is calculated as a reflection of the RDI. The algorithms of devices from both companies have been validated against multichannel PSG, with the Sorin algorithm in Talent™-3 pacemakers (ELA Medical, Montrouge, France) identifying severe SDB with sensitivity of 75 % and specificity of 94 %.²² In another study utilising Boston Scientific (Guidant) pacemakers, there was a good correlation between the calculated RDI and the AHI measured using PSG ($r = 0.8$), with sensitivity of 82 % and specificity of 88 % for detecting severe SDB.²³

Newer generations of implantable devices include updated SDB detection algorithms. The novel sleep monitoring algorithm of Sorin pacemakers from the Reply™ 200 family (SleepApnoea Monitoring) was investigated in 31 patients and data compared with multichannel PSG 30–90 days after device implantation. Severe SDB was detected with sensitivity of 89 % and specificity of 85 %.²⁴ Boston Scientific has a new SDB detection algorithm in their ICD and CRT devices, called ApneaScan™, and a validation study of Boston's Incepta™ ICD family of devices compared with polygraphy in the outpatient setting is ongoing (NCT01979120).

To date there are no randomised controlled clinical trials of the new implantable device technologies, but the ability of this approach to

Figure 1: Prevalence of Sleep-disordered Breathing in Cardiovascular Patients with Cardiac Dysrhythmias and Heart Failure

Data derived from Fox H et al. [2014] showing the high prevalence and distribution of sleep-disordered breathing in a population of cardiovascular patients with cardiac dysrhythmias and heart failure⁵. CSA = central sleep apnoea; OSA = obstructive sleep apnoea; SDB = sleep-disordered breathing.

Figure 2: Improvements of Sleep-disordered Breathing after Cardiac Resynchronisation Therapy Implantation in Patients with Heart Failure and Central Sleep Apnoea

Data derived from Oldenburg et al [2007]; 77 patients with heart failure (19 females; 62.6 ± 10 years) eligible for CRT were screened for the presence, type and severity of sleep-disordered breathing (SDB) before and after CRT initiation (5.3 ± 3 months) using multichannel cardiorespiratory polygraphy. SDB parameters only improved in CSA patients [AHI decrease from $31.2 \pm 15.5/h$ to $17.3 \pm 13.7/h$, $p < 0.001$]²⁶; CSA = central sleep apnoea; AHI = apnoea hypopnea index; CRT = cardiac resynchronisation therapy.

overcome the limitations of PSG and polygraphy appears promising. In addition, ability to continuously monitor SDB means that patient monitoring can be improved, with the possibility of detecting deterioration early and therefore initiating appropriate changes in therapy.^{25–27}

Implantable Cardiac Electronic Devices and SDB Therapy

Patients with relevant SDB and symptomatic HF need to be treated with optimal medical therapy according to current local guidelines. When left ventricular function is severely impaired ($\leq 35\%$) and in the presence of left bundle branch block, CRT implantation is indicated.²⁸

In addition to beneficial cardiovascular effects, CRT implantation has been shown to also be associated with a significant improvement in

Figure 3: Two X-rays of an Implanted Phrenic Nerve Stimulator, With and Without Sensing Lead, into the Epicardiophrenic Vein (left) or Vena Brachiocephalica (right)

(A) The left X-ray shows an implanted phrenic nerve stimulator (Remedē®, Respicardia Inc., Minnesota, USA) in the right pectoral area. The system comes with a stimulation lead and a sensing lead and the aggregate itself. A guidance catheter was introduced into the left brachiocephalic vein (the site of epicardiophrenic vein discharge). This vein follows the left phrenic nerve, and use of this close anatomy allows phrenic nerve stimulation via the transvenous stimulation device. The arrow marks the stimulation lead placed into the epicardiophrenic vein. The stimulation lead is introduced by selective contrast dye exploration using an 'over-the-wire' technique. (B) As shown on the right X-ray, a stimulation lead can also be placed into the right vena brachiocephalica to stimulate the right phrenic nerve. Placement of the sensing electrode is similar; after selective exploration with a suitable catheter it is positioned into the azygos vein, as close to the diaphragm as possible. When the guidance catheters are removed, electrode fixation follows and the aggregate is placed into a prepared subfascial pouch. The arrow on the right marks the stimulation lead placed into the right vena brachiocephalica.

CSA.²⁶ Sinha et al. reported a beneficial effect of CRT on CSA and CSR in 24 patients with chronic HF. There was a significant decrease in AHI (from 19.2 ± 10.3 per hour to 4.6 ± 4.4 per hour, $p < 0.001$) and in subjective sleep quality assessed using the Pittsburgh Sleep Quality Index (from 10.4 ± 1.6 to 3.9 ± 2.4 , $p < 0.001$); no significant changes were documented in patients without CSA.²⁹ In a larger study, Oldenburg et al. investigated the influence of CRT on SDB in 77 patients with severe HF before and five months after device implantation. CRT improved clinical and haemodynamic parameters, but only had a significant effect on SDB parameters in patients with CSA (AHI decreased from 31.2 ± 15.5 per hour to 17.3 ± 13.7 per hour, $p < 0.001$). In addition, improvements in CSA were only documented in responders to CRT (see Figure 2).²⁶

Current first-line therapy for sleep apnoea consists of positive airway pressure. The specific treatment used depends on the underlying type of SDB – continuous positive airway pressure (CPAP) for OSA and adaptive servo-ventilation (ASV) for CSA/CSR. However, although there are a variety of devices and patient interfaces, not all patients are able to tolerate positive airway pressure therapy. Most current literature suggests that about 15 % of patients are unable or unwilling to tolerate masks and ventilation therapy, and another 15 % quit ventilation therapy within the first six months of treatment.^{30–33} These patients could potentially benefit from implantable devices to treat SDB.

A new implantable device (Remedē®, Respicardia Inc., Minnesota, USA) is currently undergoing clinical testing. Treatment of CSA is thought to be achieved by nocturnal unilateral phrenic nerve stimulation. The system comes with a stimulation lead and a sensing lead and the aggregate itself. Programming can be modified by an external programmer, which allows readouts of diagnostic parameters and programming of stimulation therapy. The device is implanted under local anaesthesia, preferably in the right pectoral area, similar to basic pacemaker implantation. After puncturing the subclavian vein, a guidance catheter is introduced into the left brachiocephalic vein (the site of epicardiophrenic vein discharge). This vein follows the left phrenic nerve, and use of this close anatomy allows phrenic nerve stimulation via the transvenous stimulation device (see Figure 3). The stimulation

lead is introduced by selective contrast dye exploration using an 'over-the-wire' technique. Alternatively a stimulation lead can also be placed into the right vena brachiocephalica to stimulate the right phrenic nerve (see Figure 3). Placement of the sensing electrode is similar; after selective exploration with a suitable catheter it is positioned into the azygos vein, as close to the diaphragm as possible. When the guidance catheters are removed, electrode fixation follows and the aggregate is placed into a prepared subfascial pouch. After implantation, the device is tested by a programmer.

Initial experience with this phrenic nerve stimulation device is positive. Patients tolerated stimulation well and PSG recordings showed good suppression of CSA. An initial first multicentre clinical trial in 31 patients reported statistically significant reductions in CSA with the phrenic nerve stimulation device compared with no treatment (control night prior to device implantation).³⁴ Longer term six-month follow-up data are available for a cohort of 47 patients, 70 % of whom had symptomatic HF with reduced systolic left ventricular ejection fraction (LVEF, 31 ± 12 %) and severe CSA (mean AHI 50 ± 15 per hour and mean central apnoea index [CAI] 28 ± 14 per hour). PSG performed after three and six months documented significant reductions in CSA (baseline to three months: AHI from 50 ± 15 per hour to 22 ± 14 per hour, $p < 0.0001$; CAI from 28 ± 14 per hour to 5 ± 9 per hour, $p < 0.0001$). This study also reported significant improvements in QoL, assessed using the Minnesota Living with Heart Failure questionnaire ($p = 0.0012$), and New York Heart Association functional class ($p < 0.0001$).^{35–37} AHI was reduced, but not to normal levels, and there was no data on the effects of therapy on cardiac performance and patient prognosis.

There is also an implantable device available for patients with OSA. This stimulates the hypoglossus nerve to prevent upper airway collapse. Implantation of the electrodes for this device is more complex and requires surgery on the neck because direct access and preparation of the nerve are necessary. Furthermore, video endoscopic sleep examination is mandatory to identify appropriate candidates for this procedure. As such, this device has limited clinical application³⁸ but the first clinical data are promising. Over 12 months

of follow-up in 31 patients, respiratory events and clinical parameters were improved.³⁹ Final validation and clinical endpoint studies for this implantable device are not yet available, but initial data from a multicentre, prospective, cohort study, the Stimulation Therapy for Apnoea Reduction (STAR) trial, show that use of an upper-airway stimulation device in 126 patients with OSA who had difficulty either accepting or adhering to CPAP therapy, decreased median AHI at 12 months by 68 % (from 29.3 to 9.0 per hour, $p < 0.001$). Participants with a response to therapy were then included in a randomised, controlled trial of therapy withdrawal, which showed a rebound increase in the AHI when upper airway stimulation was withdrawn (to 25.8 per hour from 7.6 per hour, $p < 0.001$). The rate of procedure-related serious adverse events was $< 2\%$.⁴⁰

Conclusions, Outlook and Clinical Perspective

SDB is a highly prevalent comorbidity in patients with cardiac dysrhythmia, HF and in those with implanted cardiac devices. Today's pacemaker, ICD or CRT devices have the ability to constantly monitor transthoracic impedance making them capable of detecting and quantifying SDB. Results from the first studies of new devices are promising and they reveal the potential of this technology.

Detected SDB events and severity show good correlation with PSG, the gold standard for diagnosing SDB. The latest implantable device technology even allows treatment of SDB, via selective stimulation of the hypoglossus nerve for OSA and via phrenic nerve stimulation for CSA. Clinical studies are underway to determine the usefulness of the latter approach for the treatment of CSA and the suppression of CSR. One of the benefits of the new phrenic nerve stimulation device is that it is inserted using a well-known transvenous implantation procedure.

The main limitation of the new implantable devices is that they do not record oximetry or sleep and breathing parameters. Nevertheless, the ability of implantable cardiac devices to detect SDB could have clinical utility, not only for SDB screening but also to monitor SDB severity and document the effectiveness of SDB treatment. Implantable devices are also able to measure additional parameters, including intrathoracic fluids, heart rate variability, and activity parameters. This type of information may allow early detection of worsening of HF and facilitate the prevention of clinical events. There are currently no randomised, controlled clinical trials looking at this utility, but this is an area for future research. ■

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