Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augustini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham, for the remedé System Pivotal Trial Study Group

Summary

Background Central sleep apnoea is a serious breathing disorder associated with poor outcomes. The remedé system (Respicardia Inc, Minnetonka, MN, USA) is an implantable device which transvenously stimulates a nerve causing diaphragmatic contraction similar to normal breathing. We evaluated the safety and effectiveness of unilateral neurostimulation in patients with central sleep apnoea.

Methods We recruited patients from 31 hospital-based centres in Germany, Poland, and the USA in this prospective, multicentre, randomised trial. Participants had to have been medically stable for at least 30 days and have received appropriate guideline recommended therapy, be aged at least 18 years, be expected to tolerate study procedures, and willing and able to comply with study requirements. Eligible patients with an apnoea-hypopnoea index (AHI) of at least 20 events per h, tested by a polysomnography, underwent device implantation and were randomly assigned (1:1) by a computer-generated method stratified by site to either stimulation (treatment) or no stimulation (control) for 6 months. The primary effectiveness endpoint in the intention-to-treat population was the comparison of the proportions of patients in the treatment versus control groups achieving a 50% or greater AHI reduction from baseline to 6 months, measured by a full-night polysomnography assessed by masked investigators in a core laboratory. The primary safety endpoint of 12-month freedom from serious adverse events related to the procedure, system, or therapy was evaluated in all patients. This trial is active, but not recruiting, and is registered with ClinicalTrials.gov (NCT01816776).

Findings Between April 17, 2013, and May 28, 2015, we randomly assigned 151 eligible patients to the treatment (n=73) or control (n=78) groups. In the analysis of the intention-to-treat population, significantly more patients in the treatment group (35 [51%] of 68) had an AHI reduction from baseline of 50% or greater at 6 months than had those in the control group (eight [11%] of 73; difference between groups 41%, 95% CI 25–54, p<0·0001). 138 (91%) of 151 patients had no serious-related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group. Seven patients died (unrelated to implant, system, or therapy), four deaths (two in treatment group and two in control group) during the 6-month randomisation period when neurostimulation was delivered to only the treatment group and was off in the control group, and three deaths between 6 months and 12 months of follow-up when all patients received neurostimulation. 27 (37%) of 73 patients in the treatment group reported non-serious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients, but was unresolved in one (1%) patient.

Interpretation Transvenous neurostimulation significantly reduced the severity of central sleep apnoea, including improvements in sleep metrics, and was well tolerated. The clinically meaningful effects of the therapy are supported by the concordant improvements in oxygenation and quality of life, making transvenous neurostimulation a promising therapeutic approach for central sleep apnoea.

Funding Respicardia Inc.

Introduction

Central sleep apnoea is distinguished by a temporary interruption of neural output from the respiratory control centre, resulting in loss of respiratory stimulation and airflow cessation.1 2 Central sleep apnoea has a high prevalence across diverse populations,3 including patients with a broad range of cardiovascular and cerebrovascular diseases.4 5

Similar to obstructive sleep apnoea, central sleep apnoea is associated with hypoxia and sympathetic activity surges,6 7 which lead to increased blood pressure, preload, and afterload8 and promotes myocardial ischaemia and arrhythmias.9 10 Hypoxia in the setting of sleep disordered breathing has been associated with an increased risk of unfavourable outcomes.11 Central sleep apnoea enhances oxidative stress, causing endothelial dysfunction, inflammation, and activation of neurohormonal systems, which contribute to progression of underlying diseases.4 This pathophysiology might account for the association between central sleep apnoea and poor outcomes that has been observed in some populations.12 13 14

Currently available treatments for central sleep apnoea are not widely accepted because of sparse effectiveness data, poor patient adherence, and potential safety risks.15 16 Transvenous unilateral neurostimulation is a unique
physiological approach to the treatment of central sleep apnoea. The remedé system (Respicardia Inc, Minnetonka, MN, USA; appendix) aims to stimulate a nerve to cause diaphragmatic movement producing changes in carbon dioxide concentrations and tidal volumes similar to normal breathing. Unilateral transvenous neurostimulation does not produce a “hiccup-type” diaphragmatic response such as that noted with neurostimulation for the treatment of central sleep apnoea. Several studies have observed an association between the presence of central sleep apnoea and poor prognosis, even after adjustment for other important prognostic markers. Thus, treatment of central sleep apnoea is an appropriate therapeutic target. Pharmacological therapies are few and continuous positive airway pressure is limited by patient tolerability, acceptance, and adherence. Neurostimulation causes diaphragmatic contraction, creating negative intrathoracic pressure that mimics normal breathing. Pilot studies done with this technology showed that implantation of the device was safe and stimulation reduced the occurrence of apnoeas, hypopnoeas, oxygen desaturation events, and arousals and improved measures of sleep quality.

**Added value of this study**

In our prospective, multicentre, randomised controlled trial we included a population of patients with severe central sleep apnoea who had serious underlying comorbidities, including heart failure, which produced evidence of the efficacy and safety for use of transvenous neurostimulation. Neurostimulation resulted in a greater proportion of patients who had a 50% or greater reduction in the apnoea–hypopnoea index from baseline to 6 months compared with the control group. Importantly, the stimulation therapy was well tolerated and safe. This study adds to the evidence generated from pilot studies testing neurostimulation for central sleep apnoea.

**Implications of all the available evidence**

Our results support and expand the available evidence that neurostimulation is a novel physiological treatment for patients with central sleep apnoea. In addition to showing improvements in sleep indices, sleep architecture, and quality of life, this is the first randomised trial, to our knowledge, to show improvements in arousals and rapid eye movement sleep in patients with this condition. Transvenous neurostimulation in this study was shown to be efficacious and safe, with a low rate of serious device-related events reported. Transvenous neurostimulation works automatically and continuously throughout the night for every hour of sleep and does not depend on patient adherence.
and in the study design report. All patients provided written informed consent.

Randomisation and masking
All patients undergoing an implant attempt were randomly assigned (1:1) to neurostimulation (treatment) or no stimulation (control). Random assignment of patients was based on computer-generated random numbers stratified by site with random blocks of size two and four within each site. The randomisation schedule was loaded into the electronic data capture system as prepared by an independent, third-party statistician (Manya R Harsch, MS of Technomics Research, LLC, Minneapolis MN, USA). Although patients and physicians were aware of treatment assignment, the polysomnography core laboratory remained masked throughout the study. Patients and physicians were aware of treatment assignment when the health-related quality-of-life assessments were completed. No stimulation artifact on the respiratory or electroencephalogram waveforms was noted on the scored polysomnography signals, which would have revealed the randomisation assignment of patients to the core laboratory.

Procedures
The treatment and control groups had the remedē system device implanted, which consisted of a neurostimulator (similar in appearance to a standard pacemaker), a stimulation lead, and a sensing lead (appendix). The neurostimulator was placed in either the left or right pectoral region, the stimulation lead was placed in either the left pericardiophrenic or right brachiocephalic vein to stimulate a nerve. The placement of the lead was verified under fluoroscopy by observation of movement of the diaphragm with stimulation. Placement of the neurostimulator was based on individual patient venous anatomy. If possible, the device was placed on the right side of the upper chest area to accommodate an existing device or for a possible future cardiac device placement. The sensing lead was placed in a thoracic vein, such as the aygos vein, to sense respiration by thoracic impedance. The system aimed to automatically stimulate the phrenic nerve during the scheduled time at night when the patient was asleep and in a reclining position, which was detected by a position and motion sensor present in the device. All patients had a study visit 1 month after implantation, after which we set the timings of subsequent follow-up visits and assessments done at the 3-month intervals (until trial end) for a physical examination and to check the implanted device. The system was activated in the treatment group at the 1-month visit, according to a proprietary algorithm that applied a stimulation pattern that enabled full diaphragmatic contraction while the patient continued to sleep (appendix). The ranges of pulse stimulation used were 0–1–10·0 mA for 60–300 μs at 10–40 Hz. Over about 12 weeks, stimulation was gradually increased in the treatment group until diaphragmatic capture was consistently achieved without disrupting sleep.

Patients completed a full night polysomnography that was evaluated by a single scorer at the core laboratory (Registered Sleepers, Leicester, NC, USA), with quality assured by an intra-scorer quality control process, 6 months after the 1-month visit in all participants to assess the primary effectiveness endpoint. The Sleep Scoring Methodology is in the appendix. The system remained turned off in the control group throughout the 6-month effectiveness assessment, after this time therapy was initiated and remained switched on until trial end (appendix).

Outcomes
The primary effectiveness outcome was a comparison of the proportion of patients in the treatment versus control groups achieving a reduction in AHI of 50% or greater from baseline to 6 months. This timepoint was considered sufficient to show the effect of neurostimulation, and it was deemed inappropriate by the physician investigators and the scientific advisory board when the protocol was developed to withhold therapy longer than 6 months in patients with known severe central sleep apnoea. The primary safety endpoint was absence of serious adverse events associated with the implantation procedure, the system, or delivered therapy in both study groups reported at 12 months’ follow-up.

If the primary effectiveness endpoint was met, pre-specified secondary endpoints from baseline to 6 months were hierarchically tested in the per-protocol population in the following order: mean reduction in the central apnoea index (CAI), AHI, and arousal index; mean increase in percent of time spent in rapid eye movement (REM) sleep; the proportion of patients with moderate or marked improvement in the Patient Global Assessment (PGA) health-related quality of life instrument; mean reduction in the oxygen desaturation index of 4% or more (ODI4); and mean reduction in the Epworth Sleepiness Scale (ESS). Secondary endpoints for additional analyses of changes at 6 months and 12 months after initiation visit were tested in the per-protocol population; these will be reported elsewhere. An independent data and safety monitoring board evaluated safety and was responsible for recommending potential sample size adjustment after a planned interim analysis. An independent clinical events committee reviewed and adjudicated all adverse events (appendix).

Statistical analysis
We chose a target sample of 173 patients to achieve 132 patients reaching the 6-month assessment of the primary effectiveness endpoint. We calculated this sample size to provide 80% power at an overall one-sided α error rate of 0·025 and was based on the assumptions of the response rates of 50% in the treatment group and
25% in the control group, a 15% implantation failure, and a 10% drop-out.

A pre-specified interim analysis was done by an independent statistician (Tyson Rogers, Minneapolis, MN, NAMSA) after 50% of patients had completed 6 months of follow-up (appendix). No recommendation was made for an increase in sample size by the data safety monitoring board.

The primary effectiveness endpoint was evaluated in the intention-to-treat population, which is defined as all patients who were randomised and had an implant attempt, with the following criteria for missing data. Patients in the treatment group without an AHI result at 6 months’ follow-up were imputed as treatment failures if they did not successfully receive an implant, missed the 6-month visit because of ongoing titration effects, or withdrew from the study before 6 months for a reason related to the procedure, device, or therapy. Patients in the treatment group without an AHI result at 6 months who withdrew because of reasons unrelated to the therapy, device, or implantation procedure (decided by the clinical events committee), and patients in the control group without a 6-month AHI result who withdrew for any reason before 6 months were excluded from the analytical intention-to-treat cohort. To test the endpoint we used a one-sided Fisher’s exact test with a type I error rate of 0·025. We did a tipping-point sensitivity analysis to evaluate the effect of these missing data on the primary effectiveness endpoint (appendix). The primary safety endpoint of freedom from serious adverse events at 12 months’ follow-up was assessed in all study participants undergoing an implant attempt.

Secondary and exploratory endpoints were analysed in the per-protocol population. Patients excluded from the per-protocol population were those with unsuccessful implants, who did not meet inclusion criteria, had therapy programmed to off, or did not have 6-month polysomnography results. A hierarchical closed-test procedure was used to test the secondary endpoints in a pre-specified order to preserve the overall type I error level at 0·025. The PGA endpoint was tested with Fisher’s exact test; continuous endpoints of AHI, ODI4, and arousal index were tested with two-group Student’s t tests; and CAI, REM sleep, and ESS were evaluated with the Mann-Whitney U test. Our statistical analysis plan specified that each secondary endpoint would be evaluated for statistical significance only if the primary effectiveness endpoint and all previous analyses of secondary endpoints were significant. We specified statistical significance if a p value was less than 0·025. We did statistical analyses using SAS (version 9.4) and StatXact (version 11.1). This trial is active, but not recruiting, and is registered with ClinicalTrials.gov, number NCT01816776.

Role of the funding source
The funder was involved in the study design, data collection, and data analysis, which were verified by an independent statistician (RH). All authors had full access to all the data and made the decision to submit for publication.

Results
Between April 17, 2013, and May 28, 2015, we recruited and screened patients for eligibility. 151 patients were implanted with the remedē system device, which was switched on for only patients in the treatment group. (B) Per-protocol population was analysed for secondary outcomes.
the intention-to-treat population was 68 patients in the treatment group and 73 patients in the control group (figure 1A), and the per-protocol population was 58 patients in the treatment group and 73 patients in the control group (figure 1B). Adherence to study visits was 98% up to the 6-month primary effectiveness evaluation.

Baseline demographics and clinical characteristics were similar between groups (table 1). Six (4%) patients had no documented comorbidities. Baseline mean AHI was 48.8 events per h (SD 19.3) in the treatment group and 43.7 events per h (16.8) in the control group. Concomitant cardiac rhythm devices were present in 64 (42%) patients.

First implant attempt of the remedē system device was successful in 147 (97%) of 151 patients. Four (3%) patients (two per group) did not receive an implant because of anatomical issues that prevented lead placement. The mean time for implantation was 2.7 h (SD 0.8). After the initial implant, five (3%) of 147 patients required lead modification, which was successful in four patients.

A significantly higher proportion of patients in the treatment group (35 of 68, 51%, 95% CI 39–64) had a 50% or higher reduction in AHI from baseline to 6 months of follow-up than in the control group (eight of 73, 11%, 95% CI 5–20; table 2). The difference between groups was 41% (95% CI 25–54, p<0.0001; table 2). The percentage change in AHI for each patient in the two groups is shown in figure 2 and the appendix. Achievement of the primary endpoint allowed analysis of the pre-specified hierarchical secondary endpoints in the per-protocol population. The mean change from baseline to 6 months of follow-up in all pre-specified secondary endpoints was significantly improved in the treatment group compared with the control group (table 2 and figure 3). Further exploratory, sex subgroup, post-hoc analyses of additional polysomnography measures and sleep architecture variables are in the appendix. We reported significant reductions in the treatment group AHI with a mean 23.9 events per h (SD 18.6); with a mean 19.1 OD14 events per h (18.4), and a reduction in the percentage of sleep time spent with oxygen saturation below 90% of absolute 5.1% (SD 12.6).

All patients completed their follow-up visit at 12 months. At 12 months' follow-up in the intention-to-treat population, 138 (91%) of 151 patients (95% CI 86–95) had no serious adverse events due to implant procedure, system, or delivered therapy (table 3). Of 73 patients in the treatment group, 27 (37%) patients reported non-serious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients, but was unresolved in one (1%) patient. During the 6 months after the 1-month initiation visit, four deaths occurred. Two deaths were in the treatment group (one sudden non-arrhythmic [per the cardiac device interrogation] out of hospital and one sustained tachyarrhythmia; appendix); both deaths occurred during the daytime when stimulation was off. In the control group, the two deaths were due to heart failure progression. After therapy had been activated in all patients, three additional deaths (unrelated to implant, system, or therapy) were reported between 6 months and 12 months of follow-up: one from progressive heart failure, one from cardiac surgery complications, and one from lung cancer (appendix). In 64 (42%) patients with implantable cardiac devices, no ventricular arrhythmias were adjudicated as attributable to neurostimulation. One case of oversensing resulted in inappropriate defibrillation, which was
corrected by remedé system reprogramming without recurrences.

In the per-protocol population, 50% or higher reduction in AHI occurred in 35 (60%) of 58 patients, and in 26 (74%) of 35 of these patients, AHI dropped to lower than 20 events per h (appendix). The tipping-point sensitivity analysis showed that missing data had no effect on the primary outcome (appendix). Exploratory post-hoc comparison of patients with heart failure versus those without heart failure was done in the per-protocol population. 22 (63%) of 35 patients with heart failure in the treatment group had a 50% or greater reduction in AHI at 6 months compared with two (4%) of 45 patients with heart failure in the control group (p<0·0001). In patients without heart failure, 13 (57%) of 23 patients in the treatment group had a 50% or greater reduction in AHI at 6 months compared with six (21%) of 28 patients in the control group (p=0·0108). The p value for the homogeneity of odds ratios between the strata was 0·0648 (data not shown).

**Discussion**

The results of this trial indicate that transvenous neurostimulation produces significant improvements in reducing the severity of central sleep apnoea, as measured by several pre-specified sleep indices obtained during polysomnography and scored by masked investigators in a core laboratory. Improvements were observed with use of the device in the arousal index, REM sleep, PGA scores, and ESS quality of life measures at 6 months' follow-up. The therapy was well tolerated, with only two patients who were unable to adjust to therapy, and first implant success was high. Procedural complications, including lead dislodgements, were comparable with other implantable devices using transvenous lead technology. On the basis of an

<table>
<thead>
<tr>
<th><strong>Baseline</strong></th>
<th><strong>6 months' follow-up</strong></th>
<th><strong>Change from baseline</strong></th>
<th><strong>Between-group difference</strong></th>
<th><strong>One-sided p value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥50% reduction in apnoea-hypopnoea index from baseline*</td>
<td>35 (51%, 29–64)†</td>
<td>8 (21%, 5–20)</td>
<td>27 (25–54)</td>
<td>&lt;0·0001‡</td>
</tr>
<tr>
<td><strong>Secondary endpoints§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central apnoea index (events per h)</td>
<td>31·7 (18·6)</td>
<td>26·2 (16·2)</td>
<td>6·0 (9·2)</td>
<td>23·3 (17·4)</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index (events per h)</td>
<td>49·7 (18·9)</td>
<td>43·9 (17·3)</td>
<td>25·9 (20·5)</td>
<td>45·0 (20·3)</td>
</tr>
<tr>
<td>Arousal index (events per h)</td>
<td>45·6 (18·9)</td>
<td>44·0 (19·5)</td>
<td>25·4 (14·3)</td>
<td>38·9 (19·5)</td>
</tr>
<tr>
<td>Percent of sleep in rapid eye movement</td>
<td>40·6 (34·1 to 63·6)</td>
<td>43·6 (29·0 to 55·3)</td>
<td>21·9 (15·8 to 32·5)</td>
<td>36·6 (24·5 to 55·8)</td>
</tr>
<tr>
<td>Patients with marked or moderate improvement in patient global assessment**</td>
<td>35/58 (60%, 47–73)</td>
<td>4/72†† (6%, 2–14)</td>
<td>31/58 (54%, 41–66)</td>
<td>3/72 (4%, 2–7)</td>
</tr>
</tbody>
</table>

Data are n (%), 95% CI, n/N (%), 95% CI, mean (SD), or median (IQR). *Assessed in intention-to-treat population. †N=68. ‡p value from Fisher's exact test. §Assessed in the per-protocol population. ¶p value from Mann-Whitney U test for difference in change from baseline between groups. ¶p value from two-group Student's t test for difference in change from baseline between groups. **In questionnaire patients were asked "Specifically in reference to your overall health, how do you feel today as compared to how you felt before having your device implanted? Markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse, or markedly worse". ††One patient in the control group did not complete the patient global assessment.

Table 2: Primary effectiveness and secondary hierarchically-tested endpoints.
independent clinical events committee’s adjudication, we showed that 138 (91%) patients at the 12-month visit were free from device, implant, and therapy-related serious adverse events.

The improvement in AHI demonstrated in this trial shows significant reductions in the burden of central sleep apnoea, ODI4 events per h, and in the percentage of sleep time spent with oxygen saturation below 90%. In several small studies of patients with central sleep apnoea and heart failure, a reduction in AHI was associated with improvements in patient symptoms, left ventricular ejection fraction, and B-type natriuretic peptide levels. As Oldenburg and colleagues showed, time with oxygen saturation below 90% was an independent predictor of all-cause mortality.

The improvement in the arousals index and REM sleep accompanying the reduction in AHI suggest amelioration of poor sleep quality, which might have contributed to the improvement of PGA and ESS scores. The consistency of improvement in both sleep and quality of life measures indicates that the effects of neurostimulation are clinically relevant.

The magnitude of AHI improvement we report is similar to that in the CANPAP trial (21 events per h), which used continuous positive airway pressure (CPAP), the most used treatment for central sleep apnoea. Our trial had a high mean baseline AHI of 46·2 events per h. On the basis of the results of CANPAP, if the mean baseline AHI was similarly high, CANPAP would have had an AHI similar to that seen with neurostimulation at the end of follow-up. Additionally, if our trial had been limited to patients with an AHI of lower than 50 events per h (with a mean baseline AHI of 35 events per h [SD 9]), we calculated that the mean AHI change from baseline at 6 months after the 1-month initiation visit could have been 17·9 events per h. Unlike CPAP, the delivery of neurostimulation does not depend on patient adherence.

Table 3: Serious adverse events associated with procedure, device, or therapy at 12 months' follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment (n=73)</th>
<th>Control (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>6 (8%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Investigational device implant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impending pocket erosion</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Implant site haematoma</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Implant site infection</td>
<td>2 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Investigational device system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra-respiratory stimulation</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Concomitant device interaction</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Lead component failure</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Lead dislodgement</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Abnormal laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
ventricular dysfunction similar to the population in the
only 59 (39%) had heart failure severity and left
96 (64%) patients in this study had previous heart failure,
neurostimulation in a different population. Although
advanced heart failure also apply to the effects of
servoventilation (ASV) on the outcomes of patients with
appropriate or valid to assume that the effects of adaptive
12 months’ follow-up. However, it might not be
31·0 events per h at baseline to 6·6 events per h at
mortality (p=0·0060) despite a reduction in AHI from
unexpected increase in the risk of cardiovascular
Vol 388   September 3, 2016 981
www.thelancet.com
articles

 Aside from a few idiopathic cases, central sleep apnoea occurs in the setting of specific disease states and comorbidities. Heart failure is the most common condition associated with central sleep apnoea. Indeed in this study, designed to enrol patients with central sleep apnoea irrespective of cause, 96 (64%) enrolled patients had previous heart failure. Data from our trial do not permit us to know whether heart failure was the primary cause or merely a contributing factor for the occurrence of central sleep apnoea in participants. However, our exploratory post-hoc analyses suggested that the effects of neurostimulation in the subgroups of patients with heart failure and those without heart failure were consistent with the findings in the overall trial population.

Results from the SERVE-HF trial\(^\text{33}\) showed an unexpected increase in the risk of cardiovascular mortality (p=0.0060) despite a reduction in AHI from 31-0 events per h at baseline to 6-6 events per h at 12 months’ follow-up. However, it might not be appropriate or valid to assume that the effects of adaptive servoventilation (ASV) on the outcomes of patients with advanced heart failure also apply to the effects of neurostimulation in a different population. Although 96 (64%) patients in this study had previous heart failure, only 59 (39%) had heart failure severity and left ventricular dysfunction similar to the population in the SERVE-HF trial.\(^\text{33}\) The authors of the SERVE-HF trial\(^\text{33}\) considered two hypotheses to explain the increased mortality risk associated with ASV: that positive airway pressure itself had detrimental haemodynamic effects or that central sleep apnoea could be a beneficial compensatory mechanism in patients with advanced heart failure. The mechanism of action of neurostimulation is different, and actually opposite to that of ASV. Specifically, while ASV delivers positive airway pressure, the diaphragmatic contraction triggered by neurostimulation generates negative intrathoracic pressure.\(^\text{11-14}\) The intermittent hypoxia and norepinephrine release associated with central sleep apnoea events make it unlikely that this sleep disorder confers any long-term benefits to patients with heart failure.

Our study has some limitations. Despite recruitment efforts, a low percentage of women and mostly white people met the eligibility criteria (appendix). In our study subjective patient assessments of health status (PGA and ESS) could be biased by the knowledge of treatment assignment. However, the primary endpoint and five secondary pre-specified objective sleep measures were scored by a masked core laboratory, which could mitigate the risk of bias. Daytime central apnoea events might occur in some patients with central sleep apnoea.\(^\text{15}\) Theoretically, improvements in sleep quality resulting from night-time neurostimulation might attenuate the detrimental effects of daytime central apnoea events.\(^\text{16}\) However, we did not assess the effect of neurostimulation on daytime central apnoea events since therapy occurred at night while the patient was asleep and in a reclining position. Future studies including mechanistic studies of the haemodynamic effects of negative intrathoracic pressure in patients with heart failure, large registry databases, and outcomes trials are expected to provide supportive results and extend the findings in this study.

Transvenous neurostimulation resulted in significant reductions in the severity of central sleep apnoea as well as improvements in the arousal index, self-reported sleepiness, REM sleep, and quality of life measures at 6 months. Since it is automatically activated every night, neurostimulation does not depend on patient adherence. To our knowledge, it is one of the first therapies for central sleep apnoea to demonstrate improvements in arousals index and REM sleep in a randomised multicentre trial, with most patients without serious adverse events related to the implant procedure, system, or therapy. Transvenous neurostimulation might offer a new therapeutic approach to the treatment of central sleep apnoea.

Acknowledgments
We thank the contributions of the investigators and coordinators at each participating centre. We thank Wendy Gattis Stough for scientific writing...
assistance, who was funded by Respircardia Inc and worked under the direction and supervision of Medical Research Council; and thank Manya R Harsh and Tyson Rogers for their statistical support.

References
24. Linde C, Abraham WT, Gold MR, St John SM, Ghiu S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52: 1834–43.