Phrenic Nerve Stimulation in the Treatment of Central Sleep Apnea

National Government Services has completed the review of a request to reconsider and revise the local coverage determination (LCD) for Category III CPT® Codes (LCD ID Number L33392) specifically, CPT 0424T-0436T procedure codes. The response discusses the four published articles received and provides a determination. The fifth article accepted for publication was read but was not reviewed.

Ponikowski et al. (2012)\(^1\) conducted a prospective, non-randomized trial to determine the feasibility of using unilateral transvenous phrenic nerve stimulation for the treatment of central sleep apnea (CSA) in patients with heart failure (HF). Thirty-one patients from six centers were selected; 16 were able to undergo two nights of polysomnography (PSG) and were enrolled in the study. Measurements of apnea-hypopnea index (AHI), central apnea index (CAI), obstructive apnea index (OAI), hypopnea index, arousal index, and 4% oxygen index (ODI 4%) were performed prior to and after phrenic nerve stimulation of 271 ± 71 minutes. The AHI, CAI, arousal index and ODI 4% significantly improved although there were no significant changes in the hypopnea index or OAI. The AHI remained elevated at 23 (12-27) events/hour. There were two adverse events of a lead thrombus and an episode of ventricular tachycardia, neither of which was considered directly related to the phrenic nerve stimulation therapy. The authors stated the study provided a strong proof of concept and that large-scale, long-term randomized controlled trials using an implanted system were needed. The study was supported by Respicardia, Inc. and six of the authors were paid consultants and one an employee of this company.

Abraham et al. (2015)\(^2\) prospectively studied 57 non-randomized patients with CSA and treated with unilateral transvenous phrenic nerve stimulation in multiple centers to determine feasibility, safety and efficacy. Eligible patients had an AHI of at least 20 and at least one-half of the events were of central origin. Patients with obstructive events >20% were excluded. Obstructive apnea was defined as absence of airflow with respiratory effort for >10 seconds (sec). Central apnea was defined as the absence of airflow and respiratory effort for >10 sec and mixed apnea was considered a minimum of three respiratory efforts with absent inspiratory effort at the beginning of the episode. A >30% reduction in airflow lasting at least 10 sec and accompanied by a 4% decrease in arterial oxyhemoglobin saturation was defined as hypoventilation. Attended PSGs were performed at baseline and one month after implantation of the device. Programming for maximal stimulation parameter was the stimulation parameter that maximized the reduction in AHI while minimizing sleep disruption. Follow-up was monthly for the first three months and at six months with PSG. Ten patients did not have the device implanted: 7 had anatomical issues and 1 had a severe reaction to anesthesia which resulted in device dislodgement. Forty-seven of the 57 (82%) were available for study at three months and 44 (77%) at six months. There was a statistically significant reduction in AHI of 27.1 ± 17.7 episodes per hour, but the AHI still remained elevated at 22.4 ± 13.6. Central apnea index and mixed apnea index also showed statistically significant changes. There were significant improvements in sleep efficiency, rapid eye movement (REM) sleep, arousals, and
oxygenation. Forty-four patients were available for the six month visit and the improvements were sustained. Regarding feasibility, there were some problems with lead positioning which resolved in the last 20 implantations. Regarding safety, one patient died due to end-state heart failure and three of the 47 (6%) were judged to have serious adverse events related to the device: hematoma; migraine; and atypical chest pain the first night with therapy being restarted the following night without further symptoms. Epworth Sleepiness Scores (EPS) were improved at six months and 36 patients with HF showed improvement by an average of 10 points in the Minnesota Living With Heart Failure Questionnaire (MLWHF) (p = 0.0009). No other outcome measures were obtained. Respicardia, Inc. funded the study. Five of the physician authors had received consulting fees and two other authors were consultants for this company.

Jagielski et al. (2016)³ reported on the 12-month outcomes of the 47 patients in the article immediately above. PSGs were obtained on 41/47 (87%) at about 12 months post-implant. The ESC, MLWHF, and a patient global assessment were administered and adjudicated by an independent data and safety monitoring board. Heart failure was the predominant CSA etiology (78%) with another 12% having other cardiac disorders. Nearly half (49%) had a concomitant cardiac device, e.g., an automatic cardioverter defibrillator, cardiac desynchronization therapy-defibrillator, or a pacemaker already implanted when the phrenic nerve stimulator was placed. The AHI continued to be reduced from baseline to 27.5 ± 18.3 events but also continued to be elevated. The CAI and MAI were also reduced, the OAI remained stable, and there was significant improvement in the 4%ODI. Time spent with peripheral capillary oxygen saturation (SpO₂ <90%) showed no statistically significant improvement. Sleep efficiency and REM sleep time improved and the ESC showed a trend towards improvement. Quality of life assessments combined for mild, moderate or marked improvements were 70.8% at 3 months, 75.6% at 6 months, and 83.0% at 12 months. The MLWHF score for 30 of the patients with symptoms of HF as baseline showed a trend towards sustained improvement. There were three patient deaths over the 12-month period which were not judged to be related to the device. Five patients had adverse events including the three described above, one with impending pocket perforation and another related to lead failure. There was no evidence of interaction between the study device and other cardiac devices already implanted. Seventeen of 35 patients had an 18-month visit and PSG with results similar to those at 12 months. Five of the authors reported personal fees and non-financial support from Respicardia, Inc. that also supported the study. One author reported grants from Respirationics received outside the submitted work.

Costanzo et al. (2016)⁴ performed a randomized prospective trial in 31 hospital centers in Germany, Poland, and the United States. Patients with central sleep apnea were randomized to receive transvenous phrenic nerve device placement with 73 of 151 (52%) subjects having the device activated and 78 serving as controls with no activation until after the first six month effectiveness evaluation. Exclusions decreased the numbers to 68 in the treatment and 73 in the control group. Patients had to have been stable for at least 30 days, have had appropriate guideline-based therapy, and an AHI of at least 20 events/hour shown on PSG. Central apneas needed to be ≥ 50% of the apneas, happen at least 30 times per night, and the obstructive apnea
index apnea index (OAI) needed to be \( \leq 20\% \). The primary effectiveness endpoint was the proportion of the treatment patients versus controls who achieved a 50\% or greater reduction in AHIs measured in a PSG lab. The primary safety endpoint was freedom from adverse events during the 12 months. Physicians and patients were not blinded but the PSG core laboratory staff were blinded. The system was activated one month after insertion and activation gradually increased in the treatment group until diaphragmatic capture without disrupting sleep was accomplished. Baseline AHIs were 48.8 \( \pm \) 19.3 in the treatment and 43.7 \( \pm \) 16.8 in the control group. The device could be inserted on the first attempt in 147 of the patients. Lead modification was need in five and achieved in four. More of the treatment patients (35/68 or 51\%) had a 50\% or more statistically significant reduction in AHIs from baseline to six months compared to the controls (8/73 or 11\%). However, the mean AHI still remained elevated at a mean of 25 although 26 of the 35 had an AHI \(< 20\). Other statistically significant improvements between the groups were the arousal events per hour, the percent of REM sleep, the oxygen desaturation \( \geq 4\% \), and the Epworth Sleepiness Scale. Treatment patients also had higher scores on the patient global assessment. During the first six month evaluation period, two deaths were seen in the treatment group, occurring in the daytime when the device was not activated and two in the control group due to heart failure progression. Three additional deaths occurred in the second six months but considered not related to the device. Resplicardia, Inc. funded the study and was involved in the study design, data collection, and data analysis from this company and one other author reported support from other device companies.

In summary, the research on the use of transvenous phrenic nerve stimulation of individuals with central sleep apnea is in its beginning stages. One randomized trial\(^4\) with 140 patients has been published in which the PSG staff were blinded but the patients and physicians were not. The initially activated patients were assessed at six and twelve months; the activation in the controls allowed observation for six months. Improvements in AHI, arousal index, REM sleep, sleep quality, and quality of life at six months were observed. However, the AHIs still remained elevated and there were no measures of cardiovascular outcomes. Further randomized trials are needed to test these outcomes and long-term safety. There is currently insufficient evidence to show transvenous phrenic neurostimulation is reasonable and necessary for the treatment of illness (SSA § 1862 (a)(1)(A) in the Medicare population.
