Review Article

Transvenous phrenic nerve stimulation, a novel therapeutic approach for central sleep apnea

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Abstract: Central sleep apnea (CSA) is common in heart failure (HF) patients. Traditional treatment of CSA, including continuous positive airway pressure (CPAP), adaptive servo ventilation (ASV), oxygen therapy, and CO_2 inhalation, has respective limitations. Transvenous phrenic nerve stimulation (PNS), a novel therapeutic approach for CSA, was proved to be effective and safe. The remedē® system and related transvenous PNS methods was approved by FDA in 2017, for treating moderate to severe CSA.

Keywords: Central sleep apnea (CSA); phrenic nerve stimulation; remedē® system

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Heart failure (HF) is a common disorder with a poor prognosis that can be improved by treating associated conditions such as sleep apnea. The combined prevalence of obstructive (OSA) and central (CSA) sleep apnea in HF patients has been estimated at 40–80% (1). CSA presents as apnea with a duration longer than 10 seconds without simultaneous thoracic and abdominal respiratory movement. Cheyne-Stokes respiration (CSR) is a special type of CSA characterized by a cyclic pattern of waxing and waning ventilation interrupted by episodes of central apnea or hypopnea that cause arousal, hypoxemia, reduced sleep quality, enhanced sympathetic nerve activation, pulmonary artery hypertension, and increased risk of sudden death (2).

Pathogenesis of CSA

There are at least three physiological causes of CSA. The first is increased central sensitivity to changes in blood $PaCO_2$ that leads to hyperventilation followed by CSA induced by even small oscillations in partial pressure (3). This is regarded as the most important cause, as treatment by phrenic nerve stimulation (PNS) elevates end-tidal CO_2 levels and improves CSA (4). The second is delayed circulation time. HF can prolong blood circulation time that results in a delay in detection of instantaneous changes of $PaCO_2$ y chemoreceptors and the responses of effector organs such as the lungs. If the negative feedback response to hypocapnia becomes positive feedback because of delayed circulation time, then CSA is aggravated (5). The third cause is enhanced loop gain (LG). Increased of LG (LG >1) always associated with decreased of $PaCO_2$, leading to the occurrence of CSA (6). PNS may influence LG, and it would be interesting to investigate the nature of the feedback loop, describe the changes in LG that occur during PNS, and determine whether LG can predict the suppressive effect of PNS on CSR in chronic HF (CHF) patients (7).

Current opinion is that CSR in CHF patients is associated with hypersensitivity to $PaCO_2$ during sleep (8). The key pathophysiological cause of CSR is the oscillation of blood CO_2 levels below and above the apneic threshold, and $PaCO_2$ is normally maintained within a narrow range. Patients with CHF and CSA have a brisker ventilatory response to CO_2 than those without CSA (9).

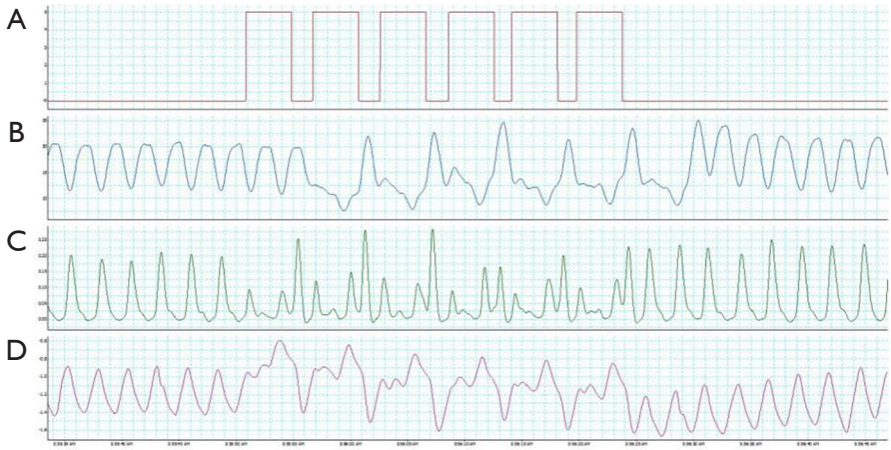

Figure 1 Effects of acute temporary PNS on normal breath. (A) PNS signals; (B) $ETCO_2$ (mmHg); (C) airflow pressure (cmH_2O); (D) abdominal belt. During PNS, the respiratory rate was reduced and the $ETCO_2$ was slightly elevated. PNS, phrenic nerve stimulation.

Traditional treatment of CSA

The current CSA treatments include continuous positive airway pressure (CPAP), adaptive servo ventilation (ASV), oxygen therapy, and CO_2 inhalation. Each treatment is effective, but each has limitations. Compliance to CPAP treatment by HF patients is lower than that to other treatments (10). ASV was reported not to improve 6-month cardiovascular outcomes (11), and oxygen therapy was found to be only weakly effective (12). CO_2 inhalation requires close monitoring during treatment, poses a risk of improper hypercapnia, and is difficult in home use (13). Novel and effective CSA treatments would be of great benefit.

Principle and mechanisms of PNS

PNS was first described by Sarnoff in 1951 (14), who reported that application of unilateral electric PNS resulted in reversible temporary inhibition of central respiratory control. However, the practical application and clinical significance of this phenomenon was not realized at that time. In spontaneously breathing animals, central inhibition of breathing is induced by selective activation of feedback from stretch receptors in the lung via the afferent vagal pathway.

An understanding of the anatomy of the phrenic nerve pathway is essential for performing PNS. After leaving the brain, the phrenic nerve passes through the neck and the thoracic cavity before finally reaching the diaphragm. Isolation of the phrenic nerve in the neck via open surgery is invasive and poses undue risk to surrounding vital nerves and disruption of the neck musculature. The phrenic nerve passes along the wall of the thoracic cavity adjacent to several veins, which allows transvenous electrode stimulation of the nerve. To stimulate phrenic nerve within thoracic cavity, a transvenous approach is not only anatomically feasible but also non- or minimally invasive.

The phrenic nerves pass close to the right wall of the superior vena cava or the right brachiocephalic vein in right thoracic cavity and along the wall of the left pericardiophrenic vein in left thoracic cavity. In several previous studies, the stimulation electrode was placed within the brachiocephalic or in left pericardiophrenic vein, as these sites are easily reached and fixed using percutaneous routes. In our previous study (7), PNS slowed the breathing rate during hyperpnea and increased $PaCO_2$ by detecting the start of a hyperventilation episode, unilaterally stimulating the phrenic nerve to reduce the effect of spontaneous breathing and allowing $PaCO_2$ to rise, and keeping CO_2 above the apneic threshold, thus preventing apnea (*Figure 1*).

To position the leads connected to the phrenic nerve stimulator (Respicardia Inc., Minnetonka, MN, USA), venous access was obtained via the right subclavian vein. The lead used to provide PNS was positioned in the right brachiocephalic vein (7,8), and a sensing lead was placed in the azygos vein to record CSR. After successful performance of the transvenous PNS, an implantable pulse generator was placed in the right pectoral area (*Figure 2*). Selection of the optimal location of the stimulation electrode was guided by fluoroscopic visualization of diaphragm movement,

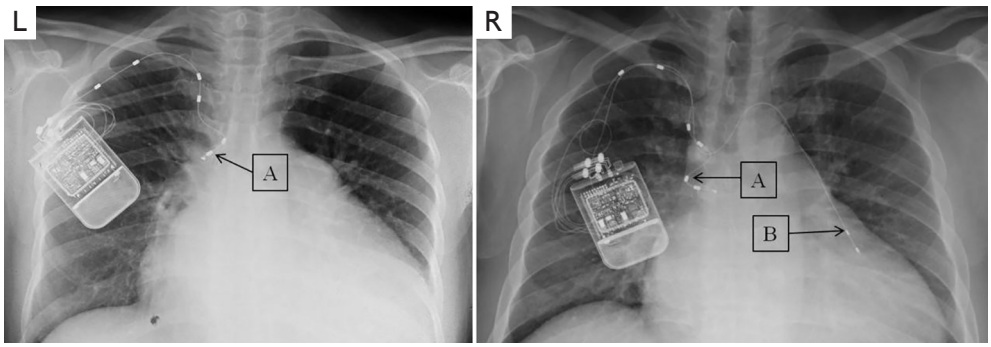

Figure 2 The implanted PNS device and leads are shown in this chest X-ray film. The left figure shows the first patient with an implanted remedē® system. Only a stimulation lead was implanted in the azygous vein (L: A). Treatment was applied manually when CSA appeared. The right figure shows the second implanted patient who had a neurostimulator implanted in the right pectoral area. The right subclavian approach was used to place the stimulation lead in the left pericardiophrenic vein (R: B) and the sensing lead in the azygous vein (R: A). PNS, phrenic nerve stimulation; CSA, central sleep apnea.

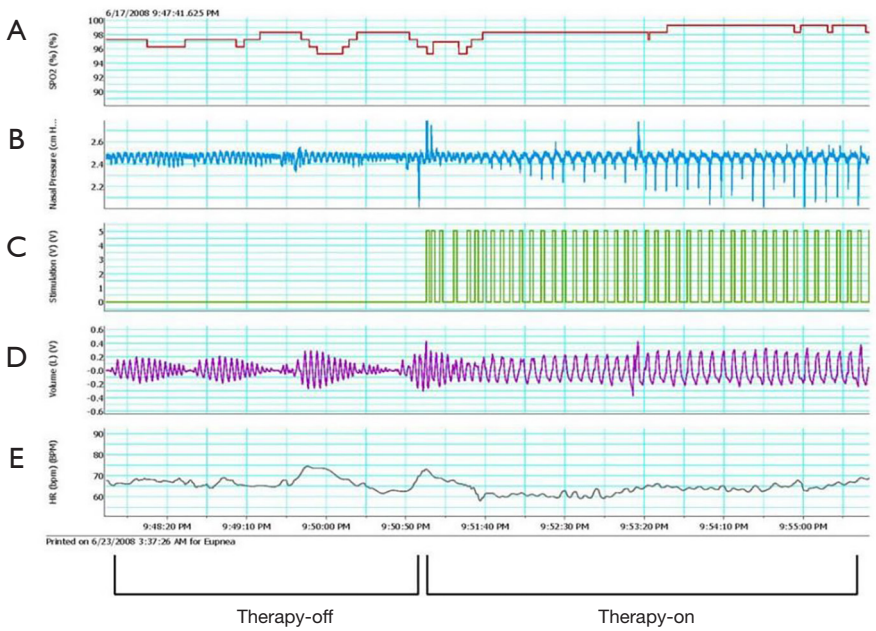

Figure 3 Effects of PNS therapy. (A) SpO_2; (B) abdominal belt; (C) PNS signals; (D) airflow pressure (cmH_2O); (E) heart rate. When continuous PNS (C) was applied following a series of CSR events, there was a disappearance of CSA events (D), improved oxygen saturation (A) and stable heart rate (E). PNS, phrenic nerve stimulation; CSR, Cheyne-Stokes respiration; CSA, central sleep apnea.

palpation of the diaphragm, and patient feedback. After implantation, the amount of PNS was titrated monthly as needed to eliminate CSR events without arousing the patient from sleep (15). The intensity of PNS was modulated transdermally by an external magnetic guide device (Respicardia Inc., Minnetonka, MN, USA). PNS was automatically performed nightly following the patient's regular sleeping and waking times (*Figure 3*).

Studies of PNS with the remedē® system for treating CSA

Fourteen studies describing the use of transvenous PNS have been published (*Table 1*); five are original research

Table 1 Remedē® system publications

Journal	Year	First author	Article type
European Heart Journal	2011	Ponikowski (8)	Original Article
Chest	2012	Zhang (7)	Original Article
Chest	2012	Cao (16)	Editorial
Herzschrittmacherther Elektrophysiol	2012	Augostini (17)	Editorial
European Heart Journal	2012	Floras (18)	Editorial
Herz	2014	Oldenburg (19)	Editorial
Cardiovasc Revasc Med	2014	Germany (20)	Editorial
Journal of Cardiac Failure	2015	Costanzo (21)	Clinical Trial Design
JACC Heart Fail	2015	Abraham (22)	Original Article
JACC Heart Fail	2015	Naughton (23)	Editorial
Lancet	2016	Costanzo (24)	Original Article
Eur J Heart Fail	2016	Jagielski (25)	Original Article
Int J Cardiol	2016	Joseph (26)	Review
Clinical Respiratory Journal	2017	Zhang (15)	Original Article

Table 2 Original research on PNS treatment using the remedē® system

Journal	Year	First author	Cases	Short/chronic study	AHI (events/h)			CAI (events/h)		
					No therapy	Therapy	P	No therapy	Therapy	P
European Heart Journal	2011	Ponikowski (8)	16	Short	45 [39-59]	23 [12-27]	0.002	27 [11-38]	1 [0-5]	<0.001
Chest	2012	Zhang (7)	19	Short	33.8±9.3	8.1±2.3	<0.001	–	–	–
JACC Heart Fail	2015	Abraham (22)	47	Chronic[#]	49.5±14.6	25.9±20.5	<0.001	28.0±14.2	4.7±8.6	<0.001
Lancet	2016	Costanzo (24)	151*	Chronic[##]	48.8±19.3	43.7±16.8	<0.001	–	–	–
Eur J Heart Fail	2016	Jagielski (25)	82**	Chronic[###]	49.9±15.1	27.5±18.3	<0.001	28.2±15.0	6.0±9.2	<0.001
Clinical Respiratory Journal	2017	Zhang (15)	7	Chronic[####]	32±9	13±6	<0.001	26±7	5±3	<0.001

*, of 151 patients, 73 received PNS, 78 were controls; **, of 82 patients, 41 received PNS, 41 were controls; [#], follow-up was at 3 and 6 months; baseline and 6-month results are shown; [##], follow-up was at 6 and 12 month; baseline and 12-month results are shown; [###], follow-up was at 3, 6 and 12 months; baseline and 12-month results are shown; [####], follow-up was at 1, 2, 3, 4, 5, and 6 months; baseline and 6-month results are shown. PNS, phrenic nerve stimulation; AHI, apnea hypopnea index; CAI, central apnea index.

articles (*Table 2*). A total of 322 patients were included, 35 with temporary transvenous PNS without stimulator implantation and 287 patients with permanent transvenous PNS and stimulator implantation.

Ponikowski's group and our team are the pioneers of this method, and were the first to report the successful clinical use of the remedē transvenous PNS stimulator or treatment of CSA/CSR in HF patients (7,8). The first PNS stimulator was implanted after completion of clinical trials of temporary PNS, and a total of seven HF patients experienced successful implantation with 6 months of follow-up. Remarkable efficacy was observed in these patients (15). A large multicenter study conducted in Europe and the USA found therapeutic efficacy, with elimination of CSA events and elevation of SpO_2 compared with no PNS during long-term follow-up of 151 HF patients (24). A prospective randomized controlled study of 173 patients is underway. The most common adverse events

reported included concomitant device interaction, implant site infection, swelling and local tissue damage, or pocket erosion. The remedē® system should not be used by patients with an active infection or by patients who are known to require magnetic resonance imaging.

On October 6, 2017, the FDA approved the use of the remedē® system to treat moderate to severe CSA (27). The device is not intended for use in patients with OSA, a condition in which the patient attempts to breathe, but the upper airway is partially or completely blocked. In conclusion, remedē® system and related PNS methods provide a novel treatment option for CSA patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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