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Synchronized Diaphragmatic Stimulation for the Treatment of Symptomatic Heart Failure: A Novel Implantable Therapy Concept

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Research Letter

Synchronized Diaphragmatic Stimulation for the Treatment of Symptomatic Heart Failure

A Novel Implantable Therapy Concept

Despite successes in pharmacologic and device therapy for patients with heart failure with reduced ejection fraction (HFrEF), the majority of patients remain symptomatic, quality of life is often impaired, and episodes of decompensation are common with a shortened life expectancy. For patients with HFrEF in sinus rhythm and prolonged QRS duration, cardiac resynchronization therapy (CRT) is often highly effective. There is an unmet need for patients with HFrEF who are not candidates for CRT but remain symptomatic despite maximally tolerated guideline-directed medical therapy, which inspired the US Food and Drug Administration to grant Breakthrough Device Designations for promising technologies to close that treatment gap.[1] Synchronized diaphragmatic stimulation (SDS) is recognized by the U.S. Food and Drug Administration as a breakthrough device. SDS is a novel approach designed to improve cardiac function, symptoms, and, ultimately, outcomes for patients who are symptomatic for HFrEF.

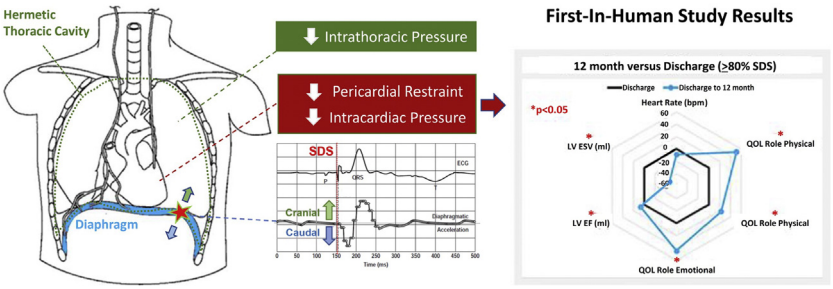
Elevated intracardiac pressures are the hallmark of heart failure (HF) and a key pathological driver of disease progression and limited exertional capacity. The degree of cardiac pressure elevation is determined by preload, afterload, and pericardial restraint. The pericardium restrains the heart, and the degree of restraint is determined by the pericardial structure itself and the intrathoracic pressure. This aspect of HF pathophysiology is among the fundamental drivers behind the SDS therapy concept. SDS induces a temporal modulation of intrathoracic pressure with a resultant reduction in pericardial restraint, leading to improved cardiac filling and reduced afterload. When applied at the right time in the cardiac cycle, SDS can improve cardiac filling, cardiovascular pressure conditions, and systolic cardiac performance.[2] SDS modulates the intrathoracic pressure through a localized contraction of the diaphragm facilitated by stimulating the diaphragmatic muscle in concert with the cardiac cycle. Because the stimulation is not targeting the phrenic nerve but rather the slow responding type-I diaphragmic muscle fibers, the corresponding diaphragmatic "twitch" is clinically impactful yet does not affect respiration and is also not perceptible to the patient.[2,3]

The SDS concept has been validated through a series of preclinical studies and human pilot studies. In humans, SDS has been investigated in the acute setting[3] of post coronary artery bypass graft surgery and in the chronic setting of CRT, where Beeler et al[2] reported on a small, randomized crossover trial that used a CRT device to deliver diaphragmatic stimulation synchronized to atrioventricular delay optimized and simultaneous biventricular pacing. Three weeks of diaphragmatic pacing improved breathlessness, exercise capacity, and left ventricular ejection fraction (LVEF) over CRT therapy alone. Improvements in LVEF were sustained for up to 1 year.[4] In this study, the stimulation lead was placed on the superior side of the diaphragm at the end of the coronary artery bypass graft procedure, and the lead was connected to the pulse generator when the CRT implant occurred weeks later. While this approach is attractive for patients indicated for coronary artery bypass graft procedure as well as pacing therapy, it would only address a segment of patients who are symptomatic for HF that are no longer responding to guideline-directed medical therapy.

An implantable SDS therapy system has been developed that overcomes those restrictions with a minimally invasive implantation technique and a low-risk profile that allows outpatient implantation. The system consists of an implantable pulse generator, stimulating/sensing leads suitable for an inferior diaphragmatic placement, and a tailored surgical delivery tool to facilitate implantation through a laparoscopic procedure.

Editor's Note: To view the authors' full presentation at TCTMD Shark Tank, please visit https://www.jacc.org/journal/basic-translational/tht-2022-shark-tank

FIGURE 1 SDS Mechanism of Action and Study Results



Synchronized diaphragmatic stimulation (SDS) is delivered through a novel extracardiac device by stimulating the diaphragm in concert with the cardiac cycle. SDS improved exercise tolerance, quality of life (QOL), and echocardiographic functional measures over 12 months. LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic function.

The first-in-human, single-arm, open-label study with the SDS therapy system enrolled 15 men who were symptomatic for HFrEF, New York Heart Association functional class II/III, and ischemic heart disease.[5] Implant success was 100%. Patients were evaluated at 3, 6, and 12 months for device- or lead-related complications, quality of life (determined by SF-36 QOL survey), 6-minute hall walk distance, and by echocardiography. No implantation procedure or SDS-related adverse event occurred throughout 12-month follow-up, and patients did not sense the ongoing diaphragmatic stimulation. Significant changes in HF-relevant parameters were observed at 6 months postdischarge, in particular if a synchronization level of ≥80% was achieved. By 12 months, the median values decreased for the following: left ventricular end-systolic volume 136 (IQR: 123-170) to 98 (IQR: 89-106) mL ($P = 0.05$); 6-minute hall walk distance (at discharge 315 [IQR: 300-330] vs at 12 months 340 [IQR: 315-368] m; $P = 0.004$), and SF-36 QOL for physical scale (at discharge 0 [IQR: 0-0] vs at 6 months 38 [IQR: 0-50] arbitrary units [AU]; $P = 0.002$; at 12 months 25 [IQR: 0-50] AU; $P = 0.006$). And median values for emotional scale (at discharge 0 [IQR: 0-33] vs at 6 months 50 [IQR: 0-67] AU; $P = 0.02$; at 12 months 33 [IQR: 33-67] AU; $P = 0.001$) improved significantly in all patients, with numerically larger changes in the subgroup with SDS ≥80% as shown in **Figure 1**. Whereas LVEF numerically improved in all patients (median: 28% [IQR: 23%-40%] to 34% [IQR: 29%-38%]; P = NS), only LVEF changes in the SDS ≥80% subgroup (median: 28% [IQR: 23%-40%] vs 34% [IQR: 34%-38%]; $P = 0.005$) reached statistical significance.

In summary, encouraging preclinical and first-in-human results indicate that SDS is a promising novel long-term therapy concept with US Food and Drug Administration Breakthrough Designation for the treatment of patients with HFrEF, who remain symptomatic despite maximal guideline-directed medical therapy. Encouraging study results to date now need to be validated in a randomized clinical trial.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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