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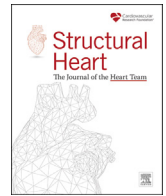
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## Original Research

# Synchronized Diaphragmatic Stimulation for Heart Failure With a Reduced Left Ventricular Ejection Fraction Using the VisONE System: A First-in-Patient Study With Extended Population



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## ABSTRACT

**Background:** Synchronized diaphragmatic stimulation (SDS) produces localized contractions of the diaphragm gated to the cardiac cycle to transiently modulate intrathoracic pressures, thereby impacting cardiac function for heart failure patients with reduced ejection fraction (HFrEF). This study prospectively evaluated the safety and 1-year effectiveness of SDS in an expanded first-in-patient cohort using multiple implant methods.

**Methods:** Symptomatic patients with HFrEF despite guideline-directed therapy were enrolled. Patients were evaluated at 3, 6 and 12 months for adverse events, quality of life (SF-36 QOL), echocardiography and 6-minute hall walk distance. The SDS system consists of 2 bipolar, active-fixation leads, and an implantable pulse generator.

**Results:** Nineteen men were enrolled (age 63 [57, 67] years, New York Heart Association class II [53%]/III [47%], N-terminal pro B-type natriuretic peptide 1779 [886, 2309] pg/mL, left ventricular ejection fraction 27 [23, 33] %). Three implant techniques (abdominal laparoscopy: sensing and stimulating leads on the inferior diaphragm (n = 15); subxiphoid access for an epicardial sensing lead and abdominal laparoscopy for stimulation on the inferior diaphragm (n = 2); thoracoscopy to place an epicardial sensing lead and a stimulating lead on the superior diaphragm (n = 2)) were employed with 100% success. Patients were unaware of diaphragmatic stimulation. From discharge to 12 months, 6-minute hall walk distance increased (315 [296, 332]m to 340 [319, 384]m;  $p = 0.002$ ), left ventricular end-systolic volume decreased (135 [114, 140]mL to 99 [90, 105]mL;  $p = 0.04$ ), and SF-36 QOL improved (physical scale 0 [0, 0] to 25 [0, 50],  $p = 0.004$ ; emotional scale 0 [0, 33] to 67 [33, 67],  $p = 0.001$ ). N-terminal pro B-type natriuretic peptide was lower (1784 [944, 2659]pg/mL vs. 962 [671, 1960]pg/mL;  $p = ns$ ) and left ventricular ejection fraction increased (28 [23, 38]% vs. 35 [31, 40]%;  $p = ns$ ) although neither reached statistical significance. There were no procedure- or SDS-related adverse events.

**Conclusions:** These data demonstrate that SDS can be delivered using alternative implantation methods without raising safety concerns and suggest improved outcomes over 1 year of follow-up. Adequately powered randomized trials are now needed to confirm these findings.

## ABBREVIATIONS

CRT, cardiac resynchronization therapy; HFrEF, heart failure reduced ejection fraction; SDS, synchronized diaphragmatic stimulation; LVEF, left ventricular ejection fraction; GDMT, guideline-directed medical therapy; ECG, electrocardiogram; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; LBBB, left bundle branch block.

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## Introduction

Cardiac resynchronization therapy (CRT) is often an effective treatment for patients in sinus rhythm with heart failure reduced ejection fraction (HFrEF) and prolonged QRS duration (e.g., LBBB). Despite guideline-directed medical therapy, the majority of patients with HFrEF are not candidates for CRT and HF disease progression proceeds with frequent episodes of decompensation, diminishing quality of life, and poor prognosis. Alternative device-based therapies for these patients are desirable, resulting in an increase in the number of HF devices under development and seeking U.S. Food and Drug Administration approval.<sup>1</sup>

Synchronized diaphragmatic stimulation (SDS) is a recent HF therapy which stimulates the diaphragm in a manner imperceptible to the patient<sup>2</sup> and at a specific timepoint in each cardiac cycle, thereby modulating intrathoracic pressure and pericardial restraint to increase systemic venous return and improve cardiac performance.<sup>3–6</sup> Previous studies used modified CRT devices with the stimulating lead attached to the superior left hemisphere of the diaphragm to deliver diaphragmatic stimulation synchronized to biventricular pacing.<sup>3–5</sup> In this manner, Beeler et al., using a small, randomized cross-over trial design,<sup>4</sup> found that 3 weeks of diaphragmatic stimulation improved dyspnea, functional capacity, and left ventricular ejection fraction (LVEF), and these improvements may have continued for up to 1 year<sup>5</sup> without adverse events related to diaphragmatic function. A case report<sup>6</sup> of a dedicated SDS system (VisONE) successfully implanted using a minimally invasive abdominal laparoscopic approach with the stimulating lead attached to the inferior left hemisphere of the diaphragm demonstrated enhanced quality of life, exercise tolerance, and cardiac function. Full results of the VisONE first-in-human study (n = 15) have recently been reported.<sup>7</sup>

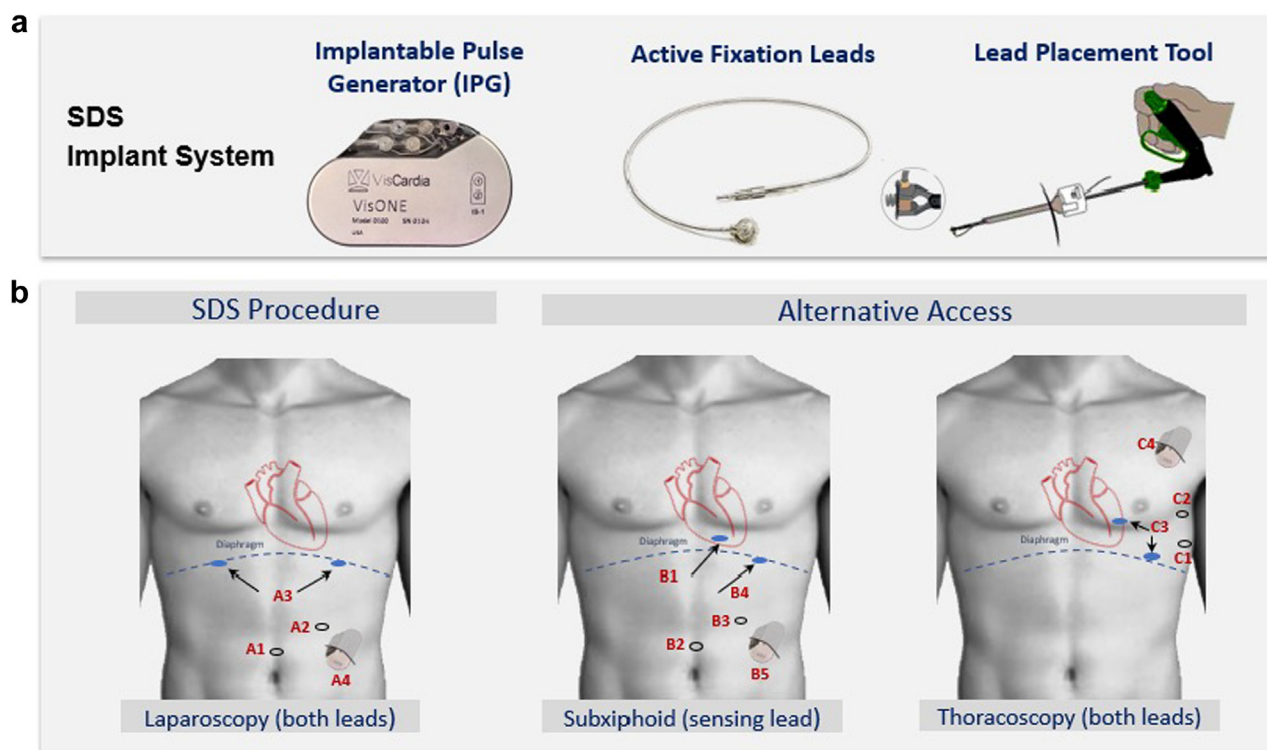
Herein we report the 1 year results of the VisONE first-in-human heart failure study with an extended population using alternative implant techniques on symptomatic HFrEF patients despite guideline-directed pharmacological therapy.

## Methods

### Study Design

This was a prospective, multicenter, multinational, observational study to investigate the safety and efficacy of delivering SDS to patients with HFrEF not indicated for CRT who were symptomatic despite guideline-directed medical therapy (GDMT) as defined by the European Society of Cardiology/American Heart Association guidelines.<sup>8,9</sup> This included the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRA). Use of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 inhibitors (SGLT2) was lower given the expense and lack of access in Georgia where the study was conducted. Patient-specific GDMT was left up to the discretion of the site investigators. There was no independent review committee. The initial cohort of patients was implanted with the SDS system using a minimally invasive abdominal laparoscopic approach and the extended population was implanted using thoracoscopy or subxiphoid mediastinotomy. The study protocol was approved by the local ethics committee and complied with the Declaration of Helsinki. All patients provided written informed consent.

The primary safety outcome was freedom from implant procedure or therapy-related serious complications or adverse events at 3 and 12



**Figure 1.** a) Components of the VisONE SDS system. b) Main surgical procedure steps for laparoscopic implant: 1. Midline incision [A1] to place trocar and laparoscope. 2. Incision lateral [A2] to place trocar and introduce leads. 3. Two leads placed on inferior diaphragm [A3]. 4. Create subcutaneous pulse generator pocket [A4]. Subxiphoid mediastinotomy: 1. Create subxiphoid access to place epicardial sensing lead [B1]. 2. Midline incision [B2] to place trocar and laparoscope. 3. Incision lateral [B3] to place trocar and introduce stimulation lead [B4]. 4. Create subcutaneous pulse generator pocket [B5]. Thoracoscopy. 1. Incision to place trocar for left ventricular access [C1]. 2. Incision to place trocar for superior-lateral diaphragm access [C2]. 3. Leads placed on left ventricular epicardium and superior diaphragm [C3]. 4. Create subcutaneous pulse generator pocket [C4]. Abbreviation: SDS, synchronized diaphragmatic stimulation.

**Table 1**

Baseline characteristics of participating patients

Characteristic	All participants (n = 19)	% SDS ≥80% group (n = 13)	% SDS <80% group (n = 6)
Age, years	63 [57, 67]	66 [61, 69]	56 [53, 60]*
Men	19 (100%)	13 (100%)	6 (100%)
Medical history			
Hypertension	13 (68.4%)	10 (76.9%)	3 (50%)
T2DM	7 (36.8%)	5 (38.5%)	2 (33.3%)
IHD	18 (94.7%)	12 (92.3%)	6 (100%)
CABG	7 (36.8%)	5 (38.5%)	2 (33.3%)
PTCA	11 (57.9%)	6 (46.1%)	5 (83.3%)
CVA/TIA	1 (5.3%)	1 (7.7%)	0 (0%)
Clinical characteristics			
NYHA class			
II	10 (52.6%)	9 (69.2%)	1 (16.7%)
III	9 (47.4%)	4 (30.8%)	5 (83.3%)
BMI, kg/m <sup>2</sup>	28 [26, 30]	28 [26, 29]	28 [28, 31]
Heart rate, bpm	74 [63, 87]	74 [60, 87]	78 [69, 95]
BP systolic, mm Hg	127 [118, 130]	127 [117, 129]	124 [118, 133]
BP diastolic, mm Hg	69 [65, 76]	70 [66, 78]	68 [63, 70]
SpO <sub>2</sub> , %	97 [97, 98]	97 [97, 98]	97 [97, 98]
QRSd, ms	117 [102, 123]	113 [103, 123]	118 [100, 125]
Ejection fraction, %	27 [23, 33]	30 [23, 34]	25 [23, 33]
6MHW	308 [292, 327]	308 [295, 335]	307 [293, 311]
distance, m			
NT-proBNP, pg/mL	1779 [886, 2309]	1025 [830, 2249]	1859 [911, 2546]
Creatinine, μmol/L	119 [108, 133]	119 [106, 137]	119 [110, 130]
Sodium, mmol/L	138 [136, 139]	137 [136, 140]	138 [137, 139]
Potassium, mmol/L	4.4 [4.1, 5.0]	4.3 [4.1, 4.8]	4.9 [4.3, 5.2]
Hemoglobin, g/dl	139 [127, 148]	134 [126, 147]	143 [139, 158]
eGFR, mL/min	67 [56, 77]	67 [56, 77]	68 [65, 80]
FEV1, liters	2.6 [2.4, 2.8]	2.6 [2.4, 2.8]	2.6 [2.3, 2.8]
FVC, liters	3.2 [3.0, 3.4]	3.1 [3.0, 3.4]	3.4 [3.1, 3.8]

Notes. Values are presented as median and [Q1, Q3] or for categorical variables, n (%).

6MHW, 6-minute hall walk; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; FVC, forced vital capacity; FEV1, forced expiratory volume, first recording; IHD, ischemic heart disease; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTCA, percutaneous transluminal coronary angioplasty; QRSd, QRS duration; TIA, transient ischemic attack; T2DM, type 2 diabetes mellitus; SDS, synchronized diaphragmatic stimulation.

\*  $p < 0.05$ .

months. Assessments made prior to discharge with SDS therapy off and at follow-up with SDS therapy on at 3, 6, and 12 months included: quality of life (Short Form [36] Health Survey, SF-36), 6-minute hall walk distance, New York Heart Association (NYHA) functional class, device-based activity, spirometry, N-terminal pro B-type natriuretic peptide (NT-proBNP), and LVEF and left ventricular end-systolic volume by echocardiography.

### Inclusion and Exclusion Criteria

Patients were included if they were in sinus rhythm with <10% ventricular ectopy, NYHA class II/III, on GDMT with an LVEF ≤35% and NT-proBNP >500 pg/mL (>250 pg/mL if on loop diuretics). The exclusion criteria included contraindications to the implant procedure, QRS duration ≥140 ms, significant pulmonary disease, or an acute coronary syndrome, cardiac procedure or sustained ventricular arrhythmia within the previous 3 months.

### Echocardiographic Imaging

Two-dimensional and Doppler echocardiography was performed by trained personnel following American Society of Echocardiography standards in a recumbent left-lateral position using a Philips ClearVue 550 system (Philips, USA). A blinded analysis of the echocardiographic images from the initial cohort was performed by a core echocardiography laboratory (University Heart Center, Zurich, Switzerland) while the extended population of 4 patients was analyzed by an independent, blinded investigator. LVEF was calculated using the biplane Simpson's method and ventricular volumes were measured using the biplane technique.

### SDS System

The SDS system consists of an implantable pulse generator (IPG), 2 sutureless sensing/stimulating leads and a custom laparoscopic tool to assist with lead placement, Figure 1a. The SDS system senses the intrinsic QRS complex and then, at a programmed delay, stimulates the left hemidiaphragm. Adjustable settings for stimulation (pulse width and amplitude), sensitivity for sensing, and synchronized delay for stimulation timing gated to the cardiac cycle are programmed using an external programmer. The IPG also stores the hourly activity level and the percentage of QRS complexes followed by diaphragmatic stimulation (% SDS, the SDS "dose-response"). The QRS complex must be detected by the IPG but electromyographic noise from the diaphragmatic muscle during respiration can contaminate the sensing signal making detection difficult especially in patients with low-amplitude R-waves. A threshold of 80% SDS was determined offline during data analysis for presented results after analysis of diagnostic data stored within the IPG because it appeared to identify responders. A group of patients with %SDS ≥80% (n = 9) in the original group of 15 patients was identified by approximately 3 months providing an informal opportunity to assess the dose response to SDS.

### SDS Implantation Procedures

#### Placement of SDS Sensing and Stimulation Leads Via Laparoscopy

An initial 1 cm midline incision was made to place the trocar and laparoscope (Figure 1b, A1), and the abdomen insufflated to allow adequate visualization of the diaphragm and surrounding organs. Another small incision was made laterally (Figure 1b, A2) to place another trocar for lead-insertion using a specialized tool to attach the stimulating lead to the left diaphragm and the sensing lead to the right at positions (Figure 1b, A3) relative to anatomical markers. A subcutaneous pocket was created for the IPG (Figure 1b, A4), and the leads tunneled to connect to it. After device testing the pocket and all open port locations and incisions were surgically sealed.

#### Alternative Placement of SDS Sensing Lead Via Subxiphoid Mediastinotomy

As an alternative to sensing the electrocardiogram (ECG) through the placement of epiphrenic leads on the inferior side of the diaphragm, an epicardial lead placement via a subxiphoid access was performed prior to the placement of the diaphragm stimulation lead via laparoscopy. The surgeon performed a subxiphoid incision to expose the right ventricle (Figure 1b, B1) and created a pericardial window to attach an active-fixation bipolar lead to the myocardium. Once that sensing lead was placed and tested to confirm adequate sensing, the placement of the diaphragm stimulation was performed via a laparoscopic access (Figure 1b, B2 thru B4 similar to the above laparoscopic method). A subcutaneous pocket was created for the IPG (Figure 1b, B5) and both leads were tunneled to connect to the IPG. Sensing and stimulating thresholds were tested and the diaphragmatic capture threshold determined before the pocket and all open port locations and incisions surgically sealed.

**Table 2**

Change in laboratory and spirometry variables following SDS

Parameter	Discharge	3-mo follow-up	6-mo follow-up	12-mo follow-up
NT-proBNP, pg/mL				
All (n = 19)	1784 [944, 2659]	1190 [884, 2411]*	1061 [898, 1708]	962 [671, 1960]
% SDS $\geq$ 80%, initial cohort (n = 9)	1020 [968, 1898]	1024 [871, 1797]*	1020 [910, 1400]	962 [736, 1673]
% SDS $\geq$ 80%, all (n = 13)	1020 [968, 2068]	1024 [871, 1981]*	975 [760, 1445]*	921 [596, 1583]*
Creatinine, $\mu$ mol/L				
All (n = 19)	121 [108, 129]	115 [101, 127]	110 [94, 117]	116 [100, 122]
% SDS $\geq$ 80%, initial cohort (n = 9)	115 [107, 133]	115 [107, 118]	102 [97, 117]	114 [95, 116]*
% SDS $\geq$ 80%, all (n = 13)	115 [107, 133]	115 [95, 118]	106 [96, 116]	115 [99, 119]
Forced expiratory volume (FEV), L				
All (n = 19)	2.6 [2.5, 2.7]	2.5 [2.4, 2.7]	2.6 [2.5, 2.7]	2.5 [2.4, 2.7]
% SDS $\geq$ 80%, initial cohort (n = 9)	2.8 [2.6, 2.9]	2.9 [2.7, 3.0]*	2.9 [2.8, 2.9]	2.8 [2.5, 3.0]
% SDS $\geq$ 80%, all (n = 13)	2.8 [2.6, 2.8]	2.7 [2.5, 2.9]	2.8 [2.7, 2.8]	2.7 [2.4, 2.9]
Forced vital capacity (FVC), L				
All (n = 19)	3.1 [3.0, 3.4]	3.3 [3.0, 3.4]	3.1 [3.0, 3.4]	3.1 [2.9, 3.3]
% SDS $\geq$ 80%, initial cohort (n = 9)	3.1 [2.9, 3.2]	3.2 [3.0, 3.4]	3.0 [2.9, 3.2]	3.0 [2.9, 3.2]
% SDS $\geq$ 80%, all (n = 13)	3.1 [3.0, 3.2]	3.2 [3.0, 3.4]	3.1 [3.0, 3.3]	3.1 [2.9, 3.2]

Notes. Values are median and [quartiles].

One patient with SDS &lt;80% died before the 6-month assessment.

One patient with SDS &lt;80% died before the 12-month assessment.

NT-proBNP, N-terminal pro-B-type natriuretic peptide; SDS, synchronized diaphragmatic stimulation.

\* p-value &lt;0.05 follow-up compared to discharge.

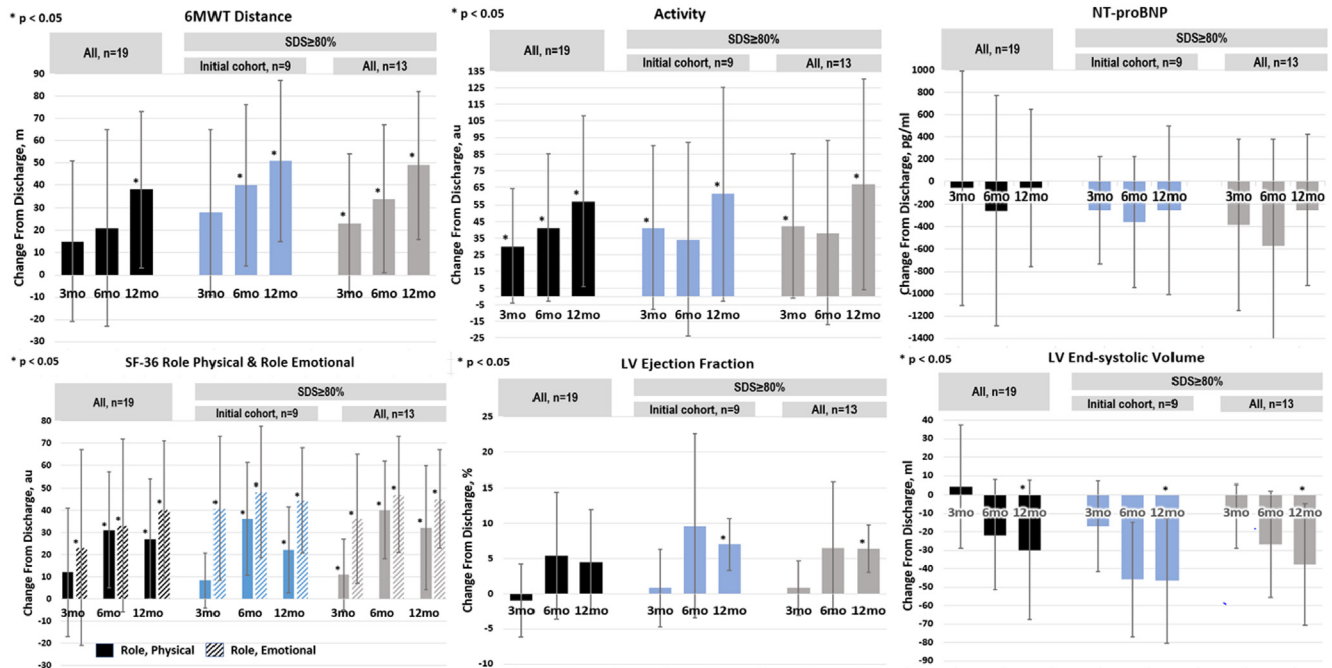
**Alternative Placement of SDS Sensing Lead Via Thoracoscopy**

The patient was intubated using a single or dual lumen endotracheal tube to allow for selective ventilation of the right lung and selective deflation of the left lung. Two thoracoscopy ports were placed in an appropriate intercostal space on the left chest to access the left ventricular (LV) apex and superior-lateral diaphragm (Figure 1b, C1). A bipolar active-fixation lead was attached to the superior left diaphragm, and another was attached to the LV lateral wall near the apex (Figure 1b, C2 and C3). A subcutaneous pocket was created for the IPG (Figure 1b, C4), and the leads tunneled for connection. Sensing and stimulating thresholds were tested and the diaphragmatic capture threshold determined. The pocket and thoracic

port locations were surgically sealed and a temporary thoracostomy tube inserted for reinflation of the left lung after surgery. A final programmed device test was performed to confirm appropriate sensing and pacing thresholds before the surgical procedure was completed.

**Statistical Analysis**

Continuous variables are presented as the median with [interquartile range] and categorical variables are presented as N (%). Categorical variables were compared using the Fisher exact test. For comparison of continuous variables at follow-up to discharge values, a Wilcoxon ranked



**Figure 2.** Change from discharge to 3, 6, and 12 months postimplant in 6MWT distance, device-based activity, NT-proBNP, QOL parameters (SF-36 role physical and role emotional), and echocardiographic parameters (LVEF and LVESV) for all patients (n = 19) and patients with synchronized % SDS  $\geq$  of cardiac beats from the initial cohort (n = 9) and the extended population (n = 13). p-values compared to discharge.

Abbreviations: 6MWT, 6-minute hall walk distance; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro B-type natriuretic peptide; QOL, quality of life.



**Table 3**  
Change in exercise status, quality of life, activity, and echocardiography following SDS

Parameter	Discharge	3-mo follow-up	6-mo follow-up	12-mo follow-up
6-min walk test distance, m				
All (n = 19)	315 [296, 332]	333 [303, 350]*	342 [322, 357]*	340 [319, 384]*
% SDS $\geq$ 80%, initial cohort (n = 9)	315 [292, 318]	336 [319, 349]*	347 [329, 357]*	346 [328, 385]*
% SDS $\geq$ 80%, all (n = 13)	308 [295, 335]	336 [296, 351]*	348 [327, 365]*	368 [334, 386]*
SF-36 Role limitations, physical				
All (n = 19)	0 [0, 0]	25 [0, 25]	50 [0, 50]*	25 [0, 50]*
% SDS $\geq$ 80%, initial cohort (n = 9)	0 [0, 0]	0 [0, 25]	50 [25, 50]*	25 [0, 50]*
% SDS $\geq$ 80%, all (n = 13)	0 [0, 0]	25 [0, 25]	50 [44, 50]*	25 [12, 50]
SF-36 Role limitations, emotional				
All (n = 19)	0 [0, 33]	33 [0, 67]*	67 [33, 67]*	67 [33, 67]*
% SDS $\geq$ 80%, initial cohort (n = 9)	0 [0, 0]	67 [0, 67]*	67 [33, 67]*	33 [33, 67]*
% SDS $\geq$ 80%, all (n = 13)	0 [0, 0]	67 [33, 67]*	67 [33, 67]*	67 [33, 67]*
LV ejection fraction, %				
All	28 [23, 38]	31 [21, 39]	39 [27, 44]	35 [31, 40]
% SDS $\geq$ 80%, initial cohort (n = 9)	28 [23, 38]	39 [34, 43]	42 [39, 51]	34 [34, 38]*
% SDS $\geq$ 80%, all (n = 13)	28 [23, 37]	38 [25, 40]	41 [38, 46]	35 [34, 41]*
LV end-systolic volume, ml				
All (n = 19)	135 [114, 140]	123 [100, 169]	110 [94, 139]*	99 [90, 105]*
% SDS $\geq$ 80%, initial cohort (n = 9)	136 [125, 155]	102 [83, 161]	115 [72, 133]	98 [90, 105]*
% SDS $\geq$ 80%, all (n = 13)	130 [114, 138]	102 [92, 142]	104 [83, 128]*	99 [91, 105]*
LV end-diastolic volume, mL				
All (n = 19)	180 [175, 221]	180 [158, 241]	188 [137, 237]	165 [136, 183]*
% SDS $\geq$ 80%, initial cohort (n = 9)	183 [176, 250]	180 [154, 231]	187 [136, 254]	150 [136, 168]*
% SDS $\geq$ 80%, all (n = 13)	180 [175, 194]	171 [154, 196]	174 [135, 212]	165 [137, 169]
Device-based activity, au				
All (n = 19)	63 [41, 96]	98 [78, 131]*	115 [90, 140]*	152 [128, 161]*
% SDS $\geq$ 80%, initial cohort (n = 9)	84 [51, 119]	110 [98, 145]	119 [102, 136]	151 [127, 163]
% SDS $\geq$ 80%, all (n = 13)	55 [40, 109]	109 [76, 143]*	107 [80, 139]	154 [128, 163]*

Notes. Values are median and [quartiles].

One patient with SDS <80% died before the 6-month assessment.

One patient with SDS <80% and one patient with SDS  $\geq$  80% died before the 12-month assessment.

LV, left ventricular; SDS, synchronized diaphragmatic stimulation.

\*  $p$ -value < 0.05 follow-up compared to discharge.

signed test for paired values was performed which excluded missing data, in particular from patients who died over the progression of the study. A two-sided  $p$ -value <0.05 was used to indicate statistical significance. Statistical analyses were performed using R, version 3.4.1 (2017-06-30 for Windows), MedCalc Statistical Software, version 20.113 (MedCalc Software Ltd., Ostend, Belgium) and Excel for Microsoft 365, version 16.0 (Microsoft Corporation, Washington, USA).

## Results

### Baseline Demographics and Medications

Twenty-three symptomatic HF patients were invited to participate, and 19 men were enrolled in this study. All patients were in sinus rhythm and all but one (95%) had ischemic heart disease. Use of GDMT was high with all patients on diuretics and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and 11 patients on beta-blockers. Few medication changes occurred: one patient had bisoprolol 2.5 mg/d discontinued at 6 months, another discontinued amlodipine 10 mg/d at 3 months, one patient had carvedilol changed from 6.25 to 12.5 mg twice daily prior to the 12-month follow-up, one patient had Concor at 2.5 mg once daily changed to Coraxan 5 mg twice daily at 3 months, and one patient had ramipril 10 mg once daily decreased to 5 mg once daily prior to the 12-month follow-up. The median age was 63 [57, 67] years, LVEF was 27 [23, 33] %, QRS duration was 117 [102, 123] ms, 53% were NYHA Class II and the others NYHA Class III, and median plasma NT-proBNP was 1779 [886, 2309] pg/mL (Table 1).

### Implant Procedure

Fifteen patients were implanted with the VisONE system using an abdominal laparoscopic approach with the sensing and stimulating leads affixed to the right and left inferior diaphragmatic hemispheres,

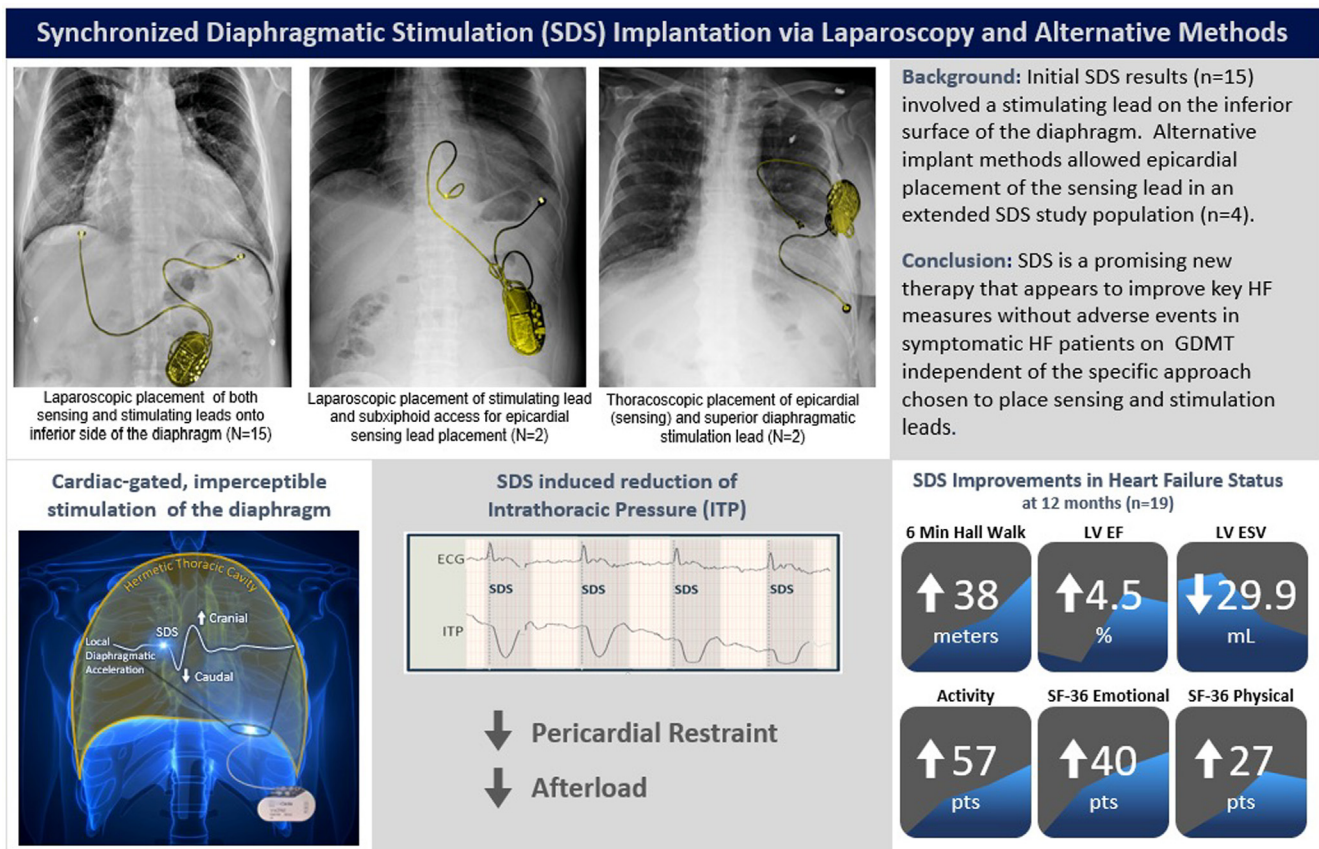
respectively. The average procedure time for the laparoscopic implant was 73 minutes. Two patients received an epicardial SDS sensing lead via subxiphoid incision. Two patients were implanted with the epicardial sensing lead via thoracoscopy and the stimulating lead on the superior surface of the left diaphragm. Implantation resulted in no device or procedure-related adverse events independent of the implant procedure method. Minimum stimulation energy to capture the diaphragm was 2.5 [2.0, 3.0] V at pulse widths of 0.4 [0.4, 0.4] ms. The diaphragmatic stimulation capture threshold was identified by palpation of the abdomen while adjusting the stimulation energy. Prior to discharge, the stimulation energy (voltage and/or pulse-width) was increased until the patient became aware of the stimulus. The IPG was set to deliver a stimulus well below this threshold and all patients were discharged with SDS therapy on at an imperceptible stimulation output.

### Follow-Up

Throughout the study, lead impedances were monitored, revealing a reduction within a few hours after implantation and no significant changes during follow-up. At implant, lead impedance was 1458 [1419, 1739]  $\Omega$ , at discharge 528 [476, 598]  $\Omega$ , at 6 months 499 [420, 583]  $\Omega$ , and 451 [374, 482]  $\Omega$  at 12 months. Capture and symptomatic thresholds were determined at each follow-up. No significant adjustments were necessary. Programmed stimulation voltages at discharge were 3.0 [2.5, 4.5] V, at 3 months 2.5 [1.8, 3.5] V, at 6 months 2.5 [1.8, 3.5] V, and 2.5 [1.8, 4.3] V at 12 months. Interrogation of the IPG found that 13 patients had  $\geq$ 80% SDS (9 from the initial laparoscopic cohort and all 4 alternative implant methods) and 6 had <80% SDS.

### Safety and Adverse Events

There was one serious adverse event (pneumothorax) due to central line placement, 3 mild adverse events (superficial wound infection,



**Figure 3.** Illustration for synchronized diaphragmatic stimulation for heart failure.

Abbreviations: GDMT, guideline-directed medical therapy; HF, heart failure; LV EF, left ventricular ejection fraction; LV ESV, left ventricular end-systolic volume; SF-36, Short Form (36) Health Survey.

transient second-degree AV block, worsening diabetic angiopathy of the right foot), 2 moderate adverse events (sprained ankle, decompensation of HF), and 3 severe adverse events (cholecystectomy due to cholelithiasis, acute decompensation of HF, amputation of the right lower leg due to diabetic angiopathy) during the study. One patient with undisclosed pre-enrollment and ongoing pulmonary effusions, constituting a protocol violation, was considered ineligible for the safety analysis. This patient (SDS <80%) died just prior to his 6-month follow-up from HF. Another patient (SDS <80%) died 11 months into the study due to an infection unrelated to SDS while hospitalized for nephrolithotomy. A third patient (SDS ≥80%) died suddenly prior to his 12-month follow-up witnessed by his wife and without new symptoms (etiology unclear; no autopsy performed). Other than the superficial wound infection, no adverse events related to the SDS procedure, device or leads were reported during the 12-month study period. No patient complained of symptoms due to diaphragmatic stimulation.

#### Laboratory Data and Spirometry Results

There were no significant changes in forced expiratory volumes, forced vital capacity, or serum creatinine over 12 months. Plasma concentrations of NT-proBNP were not significantly different over 1 year (discharge 1784 [944, 2659] vs. 12 months 962 [671, 1960] pg/mL,  $p = ns$ ), although there was a trend for lower values (Table 2).

#### Effect of SDS on Functional Status, Exercise Capacity and Quality of Life

Six-minute hall walk distance increased from discharge to follow-up at 12 months (discharge 315 [296, 332] vs. 12 months 340 [319, 384] m,  $p = 0.002$ ) with slightly greater improvements when SDS was ≥80%

(Figure 2 and Table 3). Quality of life, as assessed by the SF-36 questionnaire, also improved both for physical (discharge 0 [0, 0] vs. 6 months 50 [0, 50],  $p < 0.001$ ; 12 months 25 [0, 50] au,  $p = 0.004$ ) and emotional components (discharge 0 [0, 33] vs. 6 months 67 [33, 67],  $p = 0.004$ ; 12 months 67 [33, 67] au,  $p = 0.001$ ) with the effect greater when SDS was ≥80%. Daytime device-based activity increased between 3 and 12 months, with values being higher, as expected, than activity recorded during the 3 days after discharge (Table 3). During 12 months of follow-up, LV end-systolic volume fell from 135 [114, 140] mL to 99 [90, 105] mL ( $p = 0.04$ ) with greater decrease in patients with SDS ≥80%. LV end-diastolic volume decreased over 12 months (discharge 180 [175, 221] vs. 12 months 165 [136, 183] mL,  $p = 0.006$ ). A trend to increasing LVEF in the overall cohort (28 [23, 38] % to 35 [31, 40] %,  $p = 0.08$ ) was significant for those with SDS ≥80% (28 [23, 37] % vs. 35 [34, 41] %,  $p = 0.008$ ).

#### Discussion

A previous report<sup>7</sup> of the initial cohort of the VisONE first-in-human study demonstrated that SDS can be successfully deployed through the placement of epiphrenic sensing and stimulation leads via abdominal laparoscopy as a minimally invasive surgical technique that allows for outpatient implantation. There can be circumstances where an alternative access for the placement of SDS leads is preferred. The purpose of this extended study was to demonstrate the safety and feasibility of alternate surgical techniques, namely a subxiphoid mediastinotomy and/or thoracoscopy to place the SDS leads.

We report the feasibility of both minimally invasive abdominal laparoscopic and alternative implant procedures with a low rate of complications. SDS implant via any approach can be an outpatient



procedure while the abdominal laparoscopic procedure has the additional benefit of being extra-cardiac in nature and not occupying space in the thoracic cavity where other devices might be located. However, in cases where the abdominal laparoscopic approach is not deemed optimal other surgical access as reported here is possible. Although limited in the number of patients, it appears that SDS stimulation can be successfully delivered over 12 months from both the inferior and superior surfaces of the diaphragm. SDS was delivered without causing symptoms from diaphragmatic stimulation similar to previous results<sup>2-4</sup> and there were no therapy-related adverse events.

Our results confirm those of previous studies using modified CRT devices either in a temporary application of stimulation or longer use of diaphragmatic stimulation therapy. Roos et al.,<sup>3</sup> studied 35 patients who during bypass surgery had a temporary stimulation lead attached to the superior diaphragm and found all patients could be stimulated without symptoms with improvements to an acoustic cardiography parameter acting as a marker for systolic function. Beeler et al.,<sup>4</sup> using a cross-over trial design (3-week treatment periods) and a modified CRT device on chronic HFrEF patients, found that SDS improved NYHA class, dyspnea, exercise capacity, and LVEF when SDS was optimized within the cardiac cycle. Continued SDS therapy for a year on these patients,<sup>5</sup> suggested that stimulation thresholds were stable without reported patient symptoms from diaphragmatic stimulation.

The SDS therapy dose response (%SDS) is defined as the number of cardiac complexes appropriately sensed so that diaphragmatic stimulation can be effectively delivered. It appears that patients who received more SDS did better on measures of exercise tolerance, quality of life, and functional cardiac parameters. The 80% SDS dose threshold was chosen, not prespecified, for the results we present after analysis of diagnostic data stored within the IPG because it appeared to identify responders. SDS stimulation is imperceptible to the patient and the % SDS dose was determined offline during data analysis, therefore both the patient and investigators were blinded to the dose delivered. The first-generation device sensing software was not always successful in identifying QRS complexes due to interference from diaphragmatic electromyographic activity especially in the presence of low amplitude R waves in patients with a sensing lead on the diaphragm, which reduced the % SDS for some patients. Patients with an epicardial sensing lead had %SDS close to 100%. The ECG detection filter has been optimized for future studies including an upcoming randomized controlled trial using data collected by the IPG and will be used to enhance the next generation VisONE system. Future studies should also prespecify SDS thresholds for investigation of treatment response. We consider it reasonable to believe that successful delivery of SDS therapy might be associated with better outcomes, but we also admit that this could reflect confirmation bias in the post hoc analysis particularly for the patients with diaphragmatic sensing leads.

The mechanisms of action of SDS are not fully understood but we can propose several possibilities. Diaphragmatic movement during inspiration increases systemic venous return by reducing intrathoracic and increasing intra-abdominal pressures. Right atrial and right ventricular volume increase while left atrial and LV volume decrease during inspiration. Pericardial restraint may also be reduced.<sup>10</sup> SDS produced biphasic changes in intrathoracic pressure as shown in Figure 3 with data acquired from continuous ECG and intrathoracic pressure recordings in a porcine model.<sup>11</sup> Two research groups, Pinsky et al. and Peters et al., completed a series of canine and porcine model to determine the impact of transient changes of intrathoracic pressure relative to the cardiac cycle.<sup>12-15</sup> Their findings suggest that short transient increased or decreased in intrathoracic pressure alters both cardiac and large vessel pressures and flows including LV stroke volume. Pinsky et al. found that increased intrathoracic pressure changes from high-frequency jet ventilation during systole improved cardiac performance<sup>13,14</sup> due to changes in LV afterload and impedance and in venous return.

The limitations of this study include a small sample size with limited diversity, in particular with respect to sex and underlying HF etiology.

The total number of patients implanted with alternative methods was limited. There was no control group for comparison. The echocardiography analysis for the patients with alternative lead placements was not performed by the same group as the initial cohort. There was no evaluation of right ventricular function or diaphragm properties other than spirometry. Values at discharge were used for comparison.

In conclusion, SDS appears to have a reasonable safety profile with options for the implantation procedure and delivering asymptomatic and long-term SDS. Larger randomized clinical trials of SDS are warranted and soon to be performed in an upcoming randomized controlled study.

## Disclosure statement

T. Shaburishvili received grant/research support, and Michael Mirro received stock options from VisCardia and is the Medical Director for VisCardia. Michael Mirro, Lee Goldberg, and Marat Fudim are on the VisCardia Scientific Advisory Board. The other authors had no conflicts to declare.

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