ESC HEART FAILURE
*ESC Heart Failure* 2022; **9**: 2207–2214
Published online 26 May 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13984

ORIGINAL ARTICLE

# Synchronized diaphragmatic stimulation for heart failure using the VisONE system: a first-in-patient study

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## Abstract

**Aims** Synchronized diaphragmatic stimulation (SDS) modulates intrathoracic and intra-abdominal pressures with favourable effects on cardiac function for patients with a reduced left ventricular ejection fraction (LVEF) and heart failure (HFrEF). VisONE-HF is a first-in-patient, observational study assessing the feasibility and 1 year effects of a novel, minimally invasive SDS device.

**Methods and results** The SDS system comprises a pulse generator and two laparoscopically delivered, bipolar, active-fixation leads on the inferior diaphragmatic surface. Fifteen symptomatic men with HFrEF and ischaemic heart disease receiving guideline-recommended therapy were enrolled (age 60 [56, 67] years, New York Heart Association class II [53%] /III [47%], LVEF 27 [23, 33] %, QRSd 117 [100, 125] ms, & N terminal pro brain natriuretic peptide [NT-proBNP] 1779 [911, 2,072] pg/mL). Implant success was 100%. Patients were evaluated at 3, 6, and 12 months for device-related or lead-related complications, quality of life (SF-36 QOL), 6 min hall walk distance (6MHWd), and by echocardiography. No implant procedure or SDS-related adverse event occurred, and patients were unaware of diaphragmatic stimulation. By 12 months, left ventricular end-systolic volume decreased (136 [123, 170] mL to 98 [89, 106] mL; $P$ = 0.05), 6MHWd increased (315 [300, 330] m to 340 [315, 368] m; $P$ = 0.004), and SF-36 QOL improved (physical scale 0 [0, 0] to 25 [0, 50], $P$ = 0.006; emotional scale 0 [0, 33] to 33 [33, 67], $P$ = 0.001). Although neither reached statistical significance, LVEF decreased (28 [23, 40]% vs. 34 [29, 38]%; $P$ = ns) and NT-proBNP was lower (1784 [920, 2540] pg/mL vs. 1492 [879, 2028] pg/mL; $P$ = ns).

**Conclusions** These data demonstrate the feasibility of laparoscopic implantation and delivery of SDS without raising safety concerns. These encouraging findings should be investigated further in adequately powered randomized trials.

**Keywords** Congestive heart failure; Synchronized diaphragmatic stimulation; Acute cardiac haemodynamics

*Received: 8 January 2022; Revised: 28 February 2022; Accepted: 6 May 2022*
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## Introduction

Despite successes in pharmacological and device therapy for patients with a reduced left ventricular ejection fraction (LVEF) and heart failure (HFrEF), many patients remain symptomatic, quality of life is often persistently poor; episodes of decompensation are not uncommon; and for patients whose congestion cannot be controlled, the prognosis is poor. For patients with HFrEF in sinus rhythm and a prolonged QRS duration, cardiac resynchronization therapy (CRT) is often highly

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effective. For patients with HFrEF who are not candidates for CRT, there is some evidence, although not robust, to support cardiac contractility modulation devices[1] and baroreflex activation therapy.[2]

Synchronized diaphragmatic stimulation (SDS) is a novel concept designed to deliver cardiac-cycle-gaited reductions in intrathoracic pressure by stimulating the diaphragm at the appropriate time in the cardiac cycle, thereby increasing systemic venous return but reducing atrial pressure.[3] The stimulus and diaphragmatic contraction are imperceptible to the patient. A small, randomized cross-over trial that used the atrial lead from a CRT device to deliver diaphragmatic pacing synchronized to bi-ventricular pacing suggested that 3 weeks of diaphragmatic pacing could improve breathlessness, exercise capacity, and LVEF.[4] Haemodynamic effects may have been sustained for up to 1 year.[5]

Here, we present the results of the VisONE-HF first-in-human study where patients with symptomatic HFrEF despite guideline-recommended pharmacological therapy received continuous SDS for 1 year using the laparoscopically implanted VisONE SDS system. This presents the first study to investigate the effect of chronic diaphragmatic stimulation in heart failure.

# Methods

## Study design

This first-in-human study was a prospective, multicentre, multinational, observational study investigating the feasibility of delivering SDS to patients with HFrEF who remained symptomatic despite guideline-recommended therapy and who were not indicated for CRT. The main safety outcome was freedom from serious complications or adverse events at 3 and 12 months. The research protocol was approved by the local ethics committee and complied with the Declaration of Helsinki. All patients were required to provide written informed consent.

New York Heart Association (NYHA) functional class, quality of life (SF-36), 6 min hall walk distance, spirometry, plasma concentrations of N terminal pro brain natriuretic peptide (NT-proBNP), and LVEF and left ventricular end-systolic volume by echocardiography were assessed prior to discharge with SDS programmed off, and at 3, 6, and 12 months, with SDS programmed on (*Figure 1*).

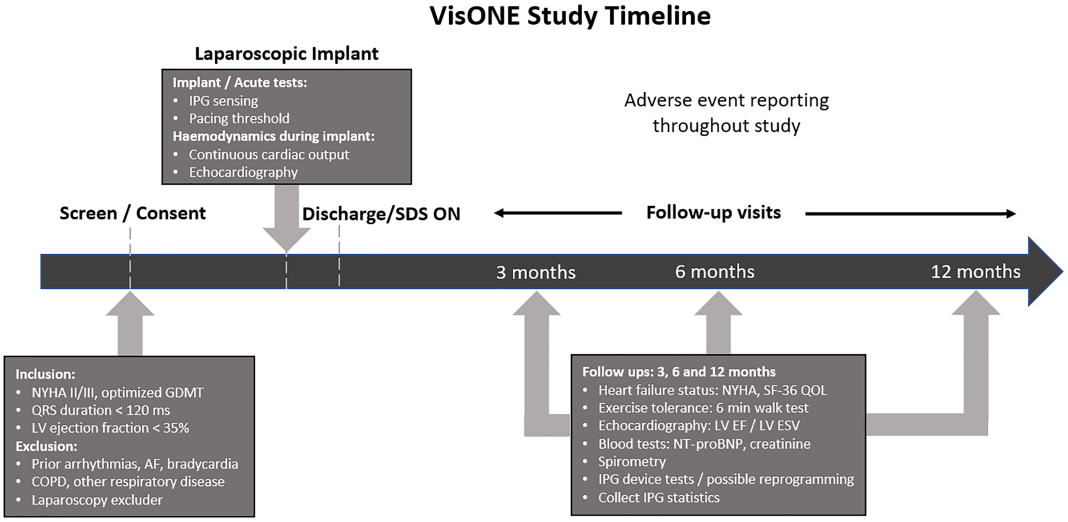
## Inclusion and exclusion criteria

Patients in NYHA class II/III on guideline-recommended treatment with an LVEF $\leq$ 35%, NT-proBNP $>$ 500 pg/mL ($>$250 pg/mL if on loop diuretics), in sinus rhythm with $<$10% ventricular ectopy were included. The main exclusion criteria were substantial pulmonary disease, contraindications to laparoscopy, QRS duration $\geq$140 ms or, within the previous 3 months, an acute coronary syndrome, cardiac procedure, or sustained ventricular arrhythmia.

## Echocardiographic imaging

Two-dimensional and Doppler echocardiography were done in a recumbent left-lateral position by trained personnel following American Society of Echocardiography standards

**Figure 1** Study design for the VisONE heart failure study.



using a Philips iE33 system (Philips, Bothell, WA, USA). A blinded analysis was performed by a core echocardiography laboratory (University Heart Center, Zurich, Switzerland). LVEF was calculated using the biplane Simpson's method.

## Synchronized diaphragmatic stimulation system

The SDS system consists of an implantable pulse generator (IPG), two suture-less pacing/sensing leads and a tailored laparoscopic delivery tool to place the leads onto the inferior surface of the diaphragm (*Figure 2*A). An external programmer is used to synchronize diaphragmatic pacing to the cardiac cycle with an adjustable delay. The IPG also records accelerometer-based hourly activity.

## Implantation procedure for synchronized diaphragmatic stimulation

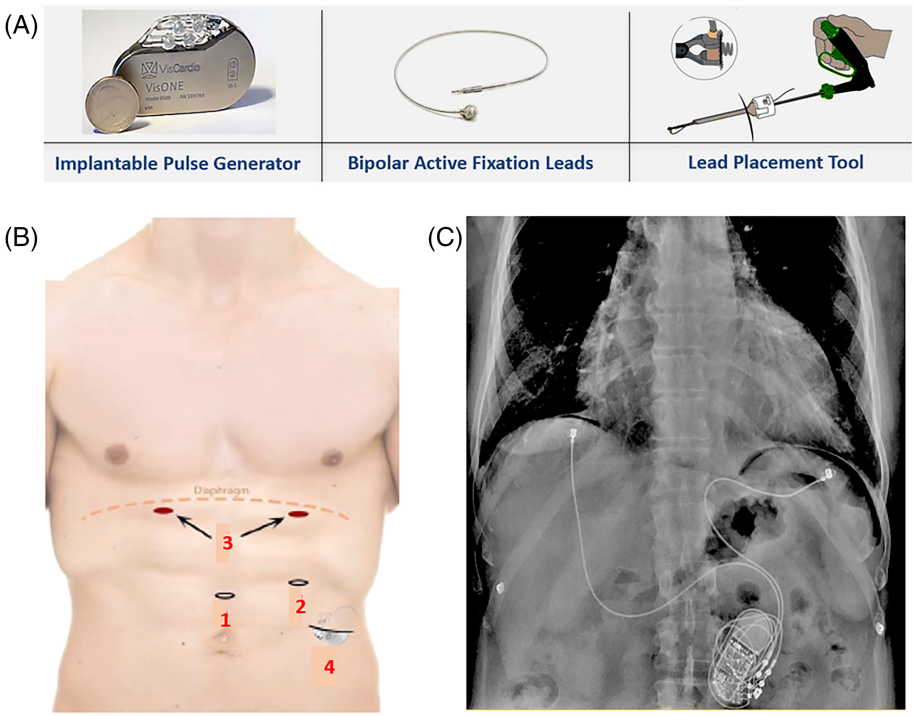
Using a sterile laparoscopic technique, the SDS leads were implanted via minimally invasive abdominal access (*Figure 2*B). An initial 1 cm midline incision was made to place the trocar and laparoscope; the abdomen was insufflated to allow adequate visualization of the diaphragm and surrounding organs. Another small incision was made laterally 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. A subcutaneous pocket was created for the IPG, and the leads tunnelled to connect to it. Sensing and stimulating thresholds were then tested, and the diaphragmatic capture threshold was determined. To document lead placement, a lateral chest X-ray was done (*Figure 2*C). After the effects of general anaesthesia had resolved, the acute effect of SDS on cardiac function was measured using a thermodilution catheter (Edwards Lifesciences) and echocardiography.

The SDS system senses the intrinsic QRS complex and then, at a programmed delay, stimulates the left hemi-diaphragm. This information is stored on the IPG. The SDS 'dose–response' (% SDS) is defined by the percentage of QRS complexes followed by diaphragmatic pacing.

## Statistical analysis

Continuous variables are presented as the median with [interquartile range]. Categorical variables are presented as *N* (%). For comparisons of continuous variables, the *t*-test or

**Figure 2** (A) Components of the implantable SDS therapy system; (B) anatomic locations used during laparoscopic implant of the SDS system: (1) trocar location for the laparoscope, (2) trocar location for insertion of sensing/stimulating leads, (3) diaphragmatic lead attachment locations, and (4) subcutaneous pocket; (C) chest X-ray imaging of fully implanted IPG and leads; visualization of the inferior left hemisphere of the diaphragm with pacing lead attached, post-implant procedure with residual infra-diaphragmatic gas accumulation (expected).





DOI: 10.1002/ehf2.13984

paired *t*-test was used as appropriate. 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) and Excel for Microsoft 365, Version 16.0 (Microsoft Corporation, Washington, USA).

# Results

## Baseline demographics

Nineteen patients were invited to participate in this study, and 15 men agreed. Median age was 60 [56, 67] years, 53% were in NYHA Class II and the others in NYHA Class III, LVEF was 27 [23, 33] %, QRS duration was 117 [100, 125] ms, and median plasma NT-proBNP was 1779 [911, 2072] pg/mL (*Table 1*). All patients were in sinus rhythm and had ischaemic heart disease. Prescription of guideline-recommended pharmacological therapy for heart failure was high. There were very few adjustments to these prescriptions during follow up: one patient had bisoprolol 2.5 mg/day discontinued at 6 months and another discontinued amlodipine 10 mg/day at 3 months.

## Implant procedure and acute changes with synchronized diaphragmatic stimulation

The average procedure time was 73 min. All patients underwent SDS implantation with no device or procedure-related adverse events. Average minimum stimulation energy to capture the diaphragm was 2.5 [1.75, 2.75] V at pulse widths of 0.4 [0.4, 0.4] ms. For all patients, while conscious, the diaphragmatic stimulation capture threshold was identified by palpation of the abdomen. The energy (voltage or pulse-width) was increased until the patient became aware of the stimulus. The IPG was then set to deliver a stimulus well below this threshold (6.0 [5.0, 7.5] V at pulse widths of 0.4 [0.4, 0.4] ms). Temporary activation of SDS for approximately 5 min in conscious patients was associated with a 17% increase in cardiac output (SDS off: 4.8 [4.0, 5.4] vs. SDS on: 5.7 [4.7, 5.9] L/min, Wilcoxon paired $P < 0.001$) with little change in heart rate (SDS off: 81 [72, 88] vs. SDS on: 82

**Table 1** Baseline characteristics of participating patients

| Characteristic | All participants ($n = 15$) | % SDS $\geq$ 80% group ($n = 9$) |
|---|---|---|
| Age (years) | 61, 60 [56, 67] | 64, 66 [58, 68] |
| Men | 15 (100%) | 9 (100%) |
| Medical history | | |
| Hypertension | 10 (66.7%) | 7 (77.8%) |
| T2DM | 5 (33.3%) | 3 (33.3%) |
| IHD | 15 (100%) | 9 (100%) |
| CABG | 6 (40.0%) | 4 (44.4%) |
| PTCA | 10 (66.7%) | 5 (55.6%) |
| CVA/TIA | 1 (6.7%) | 1 (11.1%) |
| Clinical characteristics | | |
| NYHA class | | |
| II | 8 (53.3%) | 7 (77.8%) |
| III | 7 (46.7%) | 2 (22.2%) |
| BMI (kg/m$^2$) | 28, 28 [26, 31] | 28, 28 [26, 29] |
| Heart rate (b.p.m.) | 74, 71 [63, 87] | 70, 68 [60, 82] |
| BP systolic (mmHg) | 122, 120 [116, 131] | 122, 120 [118, 128] |
| BP diastolic (mmHg) | 69, 68 [65, 78] | 71, 68 [67, 78] |
| SpO2 (%) | 97, 98 [97, 98] | 97, 98 [97, 98] |
| QRSd (ms) | 114, 117 [100, 125] | 115, 113 [104, 120] |
| Ejection fraction (%) | 28, 27 [23, 33] | 29, 30 [26, 32] |
| 6MHW distance (m) | 304, 308 [295, 323] | 305, 308 [302, 332] |
| NT-proBNP (pg/mL) | 1579, 1779 [911, 2072] | 1437, 1025 [965, 1901] |
| Creatinine (μmol/L) | 122, 119 [105, 137] | 120, 119 [105, 137] |
| Sodium (mmol/L) | 139, 138 [137, 140] | 139, 139 [137, 140] |
| Potassium (mmol/L) | 4.6, 4.7 [4.1, 5.0] | 4.5, 4.2 [4.1, 4.9] |
| Haemoglobin (g/dL) | 139, 139 [127, 153] | 135, 132 [127, 149] |
| eGFR (mL/min) | 71, 67 [56, 78] | 66, 67 [56, 77] |
| FEV1 (L) | 2.6, 2.7 [2.5, 2.8] | 2.5, 2.7 [2.5, 2.8] |
| FVC (L) | 3.2, 3.2 [3.1, 3.4] | 3.1, 3.2 [3.0, 3.4] |

6MHW, 6 min hall walk; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; FCV, forced vital capacity; FEV1, forced expiratory volume, first recording; IHD, ischemic heart disease; PTCA, percutaneous transluminal coronary angioplasty; QRSd, QRS duration; TIA, transient ischaemic attack; T2DM, type 2 diabetes mellitus.
Values are presented as mean, median, and [quartiles] or for categorical variables, *n* (%).

[74, 88] b.p.m.). All patients were discharged with SDS turned on at a stimulation output imperceptible to the patient.

## Follow up

Changes in lead impedance were monitored throughout the study, revealing a reduction within a few hours after implantation and no significant changes thereafter. Average lead impedance was 1608 [1434, 1874] Ω at implant, 528 [469, 605] Ω at discharge, 493 [413, 581] Ω at 3 months, 503 [466, 573] Ω at 6 months, and 451 [361, 493] Ω at 12 months. Capture and symptomatic thresholds were determined at each follow up. No significant adjustments were necessary. Programmed stimulation voltages were 2.5 [2.0, 4.5] V at discharge, 2.5 [1.75, 3.5] V at 3 months, 2.5 [1.75, 3.5] V at 6 months, and 2.5 [2.0, 3.5] V at 12 months. Interrogation of the IPG found that nine patients had ≥80% SDS and six had <80% SDS (refer to Supporting Information, *Figures S1–S2*).

## Safety and adverse events

One patient was considered ineligible for the safety analysis due to undisclosed, pre-enrolment, and ongoing pulmonary effusions, which constituted a protocol violation. This patient, who had SDS <80%, died just prior to his 6 month follow up from heart failure. One patient, who had SDS <80%, died 11 months into the study due to an infection while hospitalized for nephrolithotomy unrelated to SDS. During the study, there was one serious adverse event (pneumothorax) due to central line placement, one mild adverse event (superficial wound infection), two moderate adverse events (sprained ankle, decompensation of heart failure), and two severe adverse events (cholelithiasis, acute decompensation of heart failure). 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, and no patient complained of symptoms due to diaphragmatic stimulation.

## Laboratory data and spirometry results

Plasma concentrations of NT-proBNP were similar at baseline and 1 year (*Table 2*), although there was a trend for lower values when SDS was ≥80% (*Table 3*). Serum creatinine was lower at 12 months when SDS was ≥80% (discharge 1.26 [1.21, 1.33] vs 12-months 1.17 [1.08, 1.29] mg/dL, $P = 0.03$). There were no significant changes in forced expiratory volumes or forced vital capacity.

## Effect of synchronized diaphragmatic stimulation on functional status, exercise capacity, and quality of life

Six-minute hall walk (6MHW) distance increased from discharge to follow up at 12 months (discharge 315 [300, 330] vs. 12 months 340 [315, 368] m, $P = 0.004$) with slightly greater improvements when SDS was ≥80% (*Figure 3* & *Table 3*). QOL, as assessed by the SF-36 questionnaire, also improved both for physical (discharge 0 [0, 0] vs. 6 months 38 [0, 50], $P = 0.002$; 12 months 25 [0, 50] au, $P = 0.006$) and emotional aspects (discharge 0 [0, 33] vs. 6 months 50 [0, 67], $P = 0.02$; 12 months 33 [33, 67] au, $P = 0.001$). Again, the effect was greater when SDS was ≥80%. Day-time activity increased between 3 and 12 months, with both values being higher, as expected, than activity recorded during the 3 days after discharge (*Table 3*). During 12 months follow up, LV end-systolic volume fell from 136 [123, 170] to 98 [89, 106] mL ($P = 0.05$); the effect was not greater in patients with SDS ≥80%. A trend to increasing LVEF in the overall cohort (28 [23, 40] % to 34 [29, 38] %, $P$ = ns) was significant for those with SDS ≥80% (28 [23, 40] % vs. 34 [34, 38] %, $P = 0.005$).

**Table 2** Change in laboratory and spirometry variables following SDS

| Parameter | Discharge | 3 month follow up | 6 month follow up | 12 month follow up |
|---|---|---|---|---|
| NT-proBNP (pg/mL) | | | | |
| All ($n = 15$) | 1669, 1784 [920, 2540] | 1775, 1190 [871, 2059] | 1556, 1161 [910, 1708] | 1488, 1492 [879, 2028] |
| % SDS ≥ 80% ($n = 9$) | 1470, 1020 [968, 1898] | 1215, 1024 [871, 1797] | 1110, 1020 [910, 1400] | 1218, 962 [736, 1673] |
| Creatinine (μmol/L) | | | | |
| All ($n = 15$) | 115, 111 [107, 125] | 120, 115 [100, 131] | 107, 104 [93, 127] | 108, 106 [97, 120] |
| % SDS ≥ 80% ($n = 9$) | 115, 111 [107, 118] | 112, 115 [100, 118] | 106, 98 [93, 117] | 104, 103 [95, 114]* |
| Forced expiratory volume (FEV) (L) | | | | |
| All ($n = 15$) | 2.6, 2.6 [2.5, 2.8] | 2.6, 2.5 [2.4, 2.8] | 2.6, 2.6 [2.5, 2.7] | 2.5, 2.5 [2.3, 2.7] |
| % SDS ≥ 80% ($n = 9$) | 2.4, 2.6 [2.5, 2.6] | 2.5, 2.5 [2.5, 2.7] | 2.5, 2.6 [2.5, 2.7] | 2.4, 2.5 [2.2, 2.7] |
| Forced vital capacity (FVC) (L) | | | | |
| All ($n = 15$) | 3.2, 3.1 [2.9, 3.5] | 3.2, 3.2 [3.0, 3.4] | 3.1, 3.1 [3.0, 3.5] | 3.0, 3.1 [2.9, 3.2] |
| % SDS ≥ 80% ($n = 9$) | 3.0, 3.1 [2.9, 3.2] | 3.1, 3.2 [3.0, 3.4] | 3.1, 3.0 [3.0, 3.2] | 2.9, 3.0 [2.9, 3.2] |

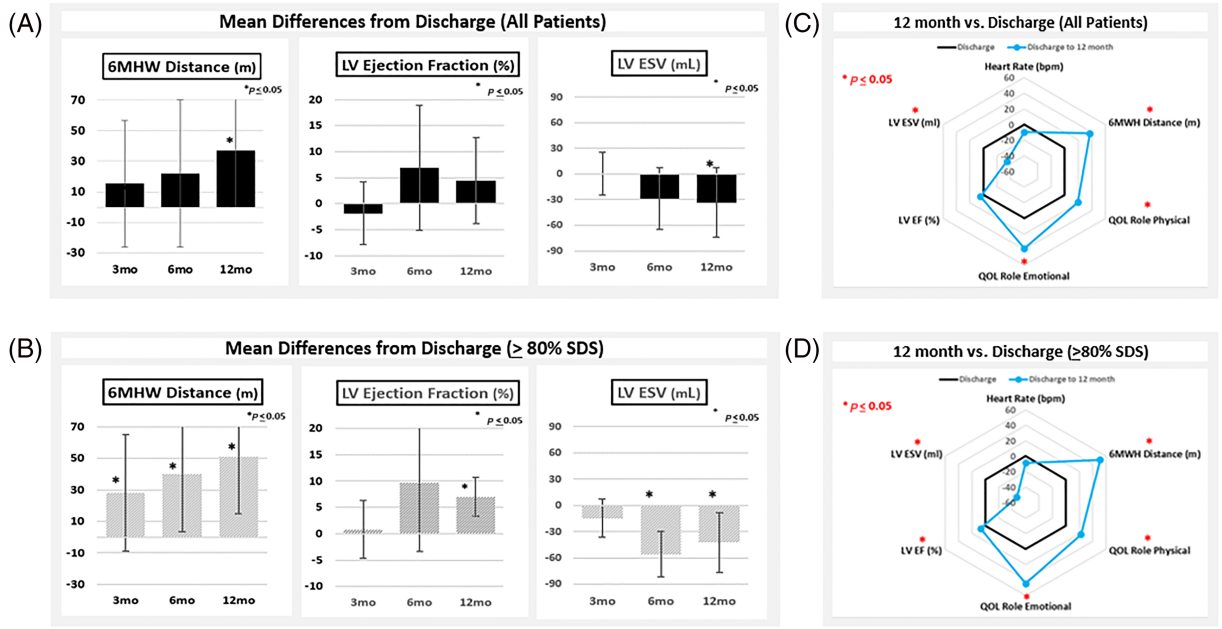
Values are mean, median, and [quartiles]. One patient with SDS < 80% died before the 6 month assessment. One patient with SDS < 80% died before the 12 month assessment.
*$P$ value < 0.05 follow up compared with discharge.

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

| Parameter | Discharge | 3 month follow up | 6 month follow up | 12 month follow up |
|---|---|---|---|---|
| 6 min walk test distance (m) | | | | |
| All ($n$ = 15) | 305, 315 [300, 330] | 321, 333 [310, 349] | 324, 336 [322, 350] | 336, 340 [315, 368]* |
| % SDS ≥ 80% ($n$ = 9) | 293, 315 [292, 318] | 321, 336 [319, 349] | 333, 347 [329, 357]* | 344, 346 [328, 385]* |
| SF-36 Role limitations, physical | | | | |
| All | 7, 0 [0, 0] | 17, 0 [0, 25] | 29, 38 [0, 50]* | 21, 25 [0, 50]* |
| % SDS ≥ 80% | 3, 0 [0, 0] | 11, 0 [0, 25] | 39, 50 [25, 50]* | 25, 25 [0, 50]* |
| SF-36 Role limitations, emotional | | | | |
| All | 16, 0 [0, 33] | 38, 67 [0, 67] | 41, 50 [0, 67]* | 46, 33 [33, 67]* |
| % SDS ≥ 80% | 4, 0 [0, 0] | 44, 67 [0, 67]* | 52, 67 [33, 67]* | 48, 33 [33, 67]* |
| LV ejection fraction (%) | | | | |
| All | 30, 28 [23, 40] | 30, 31 [20, 39] | 40, 39 [28, 51] | 35, 34 [29, 38] |
| % SDS ≥ 80% | 31, 28 [23, 40] | 39, 39 [34, 43] | 45, 43 [39, 51] | 36, 34 [34, 38]* |
| LV end-systolic volume (mL) | | | | |
| All | 146, 136 [123, 170] | 162, 125 [91, 203] | 136, 132 [77, 150] | 103, 98 [89, 106]* |
| % SDS ≥ 80% | 144, 136 [125, 140] | 118, 102 [91, 154] | 105, 115 [77, 132] | 97, 98 [91, 105]* |
| Device-based physical activity (au) | | | | |
| All | 81, 80 [58, 115] | 108, 109 [84, 140] | 121, 119 [106, 140] | 135, 151 [127, 160] |
| % SDS ≥ 80% | 83, 84 [51, 119] | 115, 110 [98, 145] | 122, 119 [102, 136] | 135, 151 [127, 163] |

Values are mean, median, and [quartiles]. One patient with SDS < 80% died before the 6 month assessment. One patient with SDS < 80% died before the 12 month assessment.
*$P$ value < 0.05 follow up compared with discharge; activity follow up compared with 3 month.

**Figure 3** Change from discharge to 3, 6, and 12 months post-implant in 6MHW distance and echocardiographic parameters (LVEF and LVESV) for A (all patients) and B (patients with synchronized % SDS ≥ of cardiac beats). Radar charts show changes from discharge to 12 months post-implant for 6MHW distance, LVEF, LVESV, and SF-36 QOL parameters for C (all patients) and D (patients with synchronized % SDS ≥ of cardiac beats).




## Discussion

Synchronized diaphragmatic stimulation (SDS) is a novel approach to try to improve cardiac function, symptoms, and ultimately, outcome for patients with HFrEF. This study takes several important steps towards realizing the therapeutic potential of SDS. It demonstrates the feasibility of a minimally invasive implant procedure with a low rate of complications. It also shows that SDS can be delivered without causing untoward symptoms from diaphragmatic pacing and that this can be maintained for at least 1 year. However, this was an observational study and cannot distinguish outcomes with

an intervention from the response to it, which require randomized trials.[6,7] However, investigators were blind to the percentage of SDS successfully delivered, and therefore, the observation that patients who received more SDS appeared to do better provides some further encouragement.

This is the first study of the VisONE system. Investigators rapidly developed the technical skills to deliver diaphragmatic leads laparoscopically. The average procedure time was 73 min. Laparoscopic surgeons had a training session with a simulator, thus there was no evidence of a learning curve in clinical practice for the routine laparoscopic approach. The procedure does require an anaesthetic but could be done as an outpatient procedure.

Phrenic nerve and diaphragmatic pacing are potential complication of CRT, which may cause hiccoughs. Consistent with previous reports,[3,8] this study shows that it is possible to stimulate the diaphragm asymptomatically and without causing diaphragmatic fatigue. The rapid fall in lead impedance after implantation suggests that the energy required for diaphragmatic capture may fall over the first year; hopefully, this will be maintained longer term.

The Epiphrenic II pilot cross-over trial (3 week treatment periods) found that SDS, using a modified CRT device, improved dyspnoea, exercise capacity, and LVEF in patients with chronic HFrEF.[4] Observing patients for a further year, with SDS programmed on,[5] suggested that diaphragmatic pacingdid not cause adverse symptoms and that stimulation thresholds were stable.

The potential mechanisms of action of SDS require further elucidation. Diaphragmatic movement during inspiration reduces intrathoracic and increases intra-abdominal pressure, increasing systemic venous return. The fall in intrathoracic pressure increases pulmonary venous capacitance and reduces flow into the left atrium, but transmural atrial pressures gradients may be maintained or increase.[9] RA and RV volume will increase and LA and LV volume decrease during inspiration (refer to *Figure S3*). Reduction in pericardial restraint may also occur.[9] In a porcine model with continuous intrathoracic pressure recording, SDS produced biphasic changes in intrathoracic pressure and increased cardiac output.[10] Using high-frequency, jet-ventilation, Pinsky *et al*. found that increased intrathoracic pressure pulses during systole improved cardiac performance[11,12] due to changes in LV afterload and impedance and in venous return. Recently, a device for intrathoracic pressure regulation has been developed to decrease intrathoracic pressure to improve cardiac function in emergency situations.[13]

The SDS therapy dose response is defined by the number of cardiac beats appropriately sensed (% SDS) so that diaphragmatic stimulation can be effectively delivered. For the results presented herein, the 80% SDS dose threshold was chosen, not pre-specified, after analysis of diagnostic data stored within the IPG (refer to *Figure S1*) because it appeared to identify responders. We consider it reasonable to suggest that successful delivery of the intended intervention might be associated with a better response, but we also admit that this could reflect confirmation bias in a post hoc analysis. As SDS stimulation is imperceptible to the patient and the % SDS determination was done offline during data analysis, both the patient and investigators were blinded to the dose delivered. The software in this first-generation device was not always successful in identifying QRS complexes due to interference from diaphragmatic electromyographic activity especially in the presence of low amplitude R waves, which reduced the % SDS for some patients. Using data collected by the IPG, a database was developed to optimize the ECG detection filter, which will be used to enhance the next generation VisOne system. Future research will pre-specify SDS thresholds for investigation of treatment response.

This study has several limitations. Only a few patients were enrolled that cannot reflect the great diversity of HFrEF and it had no control group. The study also provided limited insights into the potential mechanisms by which SDS might benefit patients with HFrEF and did not evaluate RV function.

In conclusion, this study demonstrates the feasibility of delivering, asymptomatic, long-term SDS by a minimally invasive procedure. It appears safe. These encouraging observational data now need to be validated in randomized trials.

## Conflict of interest

T. Shaburishvilli received grant/research support and Mike Mirro received stock options from VisCardia. Mike Mirro, Lee Goldberg, John Cleland, and Marat Fudim are on the VisCardia Scientific Advisory Board. All other authors have no conflicts of interest to declare.

## Funding

The work was supported by the Schweizerische Herz und Kreislauf-Stiftung (SHK), Switzerland, and VisCardia Inc., Portland, OR, USA.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Dose-response (% SDS) over 12 months on a per patient basis: SDS should be delivered for each heart beat at the appropriate time in the cardiac cycle. To achieve this goal, the ECG (R-wave) must be detected by sensor-leads attached to the diaphragm, but this can be contaminated with electromyographic (EMG) noise from diaphragmatic muscle

during respiration. The first-generation VisONE IPG did not optimally remove diaphragmatic EMG noise, which impaired ECG R-wave detection (sensing) for some patients, especially those with low amplitude R-waves. The IPG maintains statistics on the sensing performance (% synchronized stimulation, %SDS), which can be downloaded at clinic visits. The figure shows %SDS for the patients in this study over 12 months. By approximately 3 months, a group of patients with %SDS ≥80% (n=9) was identified, providing an opportunity to assess, informally, the dose-response to SDS.

**Figure S2.** Examples of original device (1st generation) filter results for sensing the ECG from the diaphragm and the 2nd generation filter results optimized to remove EMG noise artifact.

**Figure S3.** Illustration of proposed acute and chronic effects of SDS. Abbreviations: RA- right atrial, RV- right ventricular, LA- left atrial, LV- left ventricular.

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