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DISSERTATION

Different Treatment Modalities of Sleep Apnea in Patients with Heart Failure
Unterschiedliche Behandlungsmodalitäten der Schlafapnoe bei Patienten mit Herzinsuffizienz

zur Erlangung des akademischen Grades
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List of abbreviations

ACEIs: angiotensin-converting enzyme inhibitors
AHI: apnea-hypopnea index
AI: arousal index
ARNI: angiotensin-receptor neprilysin inhibitor
ASV: adaptive servo-ventilation
BF: breathing frequency
CA: central apnea
CAVI: transcatheter valve implantation
CABG: coronary artery bypass graft
CPET: cardiopulmonary exercise test
CPAP: continuous positive airway pressure
CO_2: carbon dioxide
COPD: chronic obstructive pulmonary disease
CRT: cardiac resynchronization therapy
CSA: central sleep apnea
DR: duty ratio
DT: deceleration time
eGFR: estimated glomerular filtration rate
FEV1: forced expiratory volume for one second
HR: heart rate
HF: heart failure
HFrEF: HF with reduced ejection fraction
ICD: implantable cardioverter-defibrillator
IVRT: isovolumetric relaxation time
LA-Index: left atrial index
LVEDD: left ventricular end-diastolic diameter
LVEF: left ventricular ejection fraction
LVESD: left ventricular end-systolic diameter
LVEDV: left ventricular end-diastolic volume
LVESV: left ventricular end-systolic volume
LG: loop gain
MAPSE: mitral annular plane systolic excursion

Max VO2: maximal oxygen uptake

NYHA: New York Heart Association

NT-pro BNP: N-terminal-pro-B-type natriuretic peptide

OA: obstructive apnea

ODI: oxygen desaturation index

OSA: obstructive sleep apnea

PAP: pulmonary arterial pressure

PCWP: pulmonary capillary wedge pressure

RA: right atrium

REI: respiratory event index

Ref: reference

RV-FAC: right ventricular fractional area change

RV-s`: right-ventricular systolic velocity

RV-IVRT: right-ventricular isovolumetric relaxation time

RV-AT: right-ventricular acceleration time

SaO_2: oxygen saturation

SA: sleep apnea

SBP: systolic blood pressure

SDB: sleep-disordered breathing

SV: sacubitril-valsartan

s`: systolic velocity in tis-sue doppler imaging

Sys PAP: systolic pulmonary artery pressure

TAPSE: tricuspid annular plane systolic excursion

TR: tricuspid regurgitation

T90: the time spent with oxygen saturation <90%

TTVI: transcatheter tricuspid valve interventions

Vp: velocity of flow progression

Zusammenfassung

Herzinsuffizienz (HF) ist eine komplexe und lebensbedrohliche Erkrankung, die durch eine hohe Morbidität und Mortalität gekennzeichnet ist. Weltweit sind fast 63 Millionen Menschen von HF betroffen. Schlafapnoe ist eine häufige Komorbidität bei Patienten mit HF und steht in Verbindung mit einer schlechten Prognose. Es besteht ein wach-sendes Interesse an der Behandlung von Komorbiditäten und der Optimierung der HF. In dieser Studie wurde versucht, die Wirkungen von Transkatheter Klappenimplantati-on (CAVI) und Sacubitril-Valsartan (SV) bei Patienten mit HF und Schlafapnoe zu be-werten. Achtunddreißig HF-Patienten, die sich einem tragbaren Apnoe-Aufzeichnungsgerät, einer echokardiografischen Untersuchung und einem kardi-opulmonalen Belastungstest (CPET) unterzogen, wurden in die Studie aufgenommen. In der ersten Studie wurde CAVI als eine relativ neue Behandlungsoption für HF-Patienten bewertet. Jedoch wurden keine signifikanten Veränderungen bei den Schlafvariablen nach der CAVI beobachtet. In der zweiten Studie untersuchten wir die Wirkung von SV auf zentrale Apnoe (CA) / obstruktive Apnoe (OA) bei HF-Patienten. Die Ergebnisse zeigten, dass die SV-Behandlung mit einer signifikanten Verringerung des respiratorischen Ereignisindex (REI) verbunden war. SV könnte eine vielverspre-chende therapeutische Option für CA sein. Weitere und längerfristige prospektive Fol-gestudien sind erforderlich.

Abstract

Heart failure (HF) is a complex and life-threatening disease characterized by high mobidity and mortality. Nearly 63 million people worldwide are affected by HF. Sleep apnea is a common comorbidity in patients with HF and is associated with a poor prognosis. There is a growing interest in treating comorbidities and optimizing HF. This study attempted to assess the effects of transcatheter valve implantation (CAVI) and sacubitril-valsartan (SV) in patients with HF and sleep apnea. Thirty-eight HF patients who underwent portable apnea recording device, echocardiographic evaluation, cardiopulmonary exercise test (CPET) were enrolled. The first trial evaluated CAVI as a relatively new treatment option for patients with HF. However, no significant changes were observed in sleep variables after CAVI. In the second trial, we aimed to investigate the impact of SV on central apnea (CA) / obstructive apnea (OA) in HF subjects. The results showed that SV treatment was associated with a significant reduction in respiratory event index (REI). SV could be a promising therapeutic option for CA. More and longer-term follow-up prospective studies are needed.

1. Introduction

Sleep disordered breathing (SDB) consists of two main categories, obstructive sleep apnea (OSA) and central sleep apnea (CSA). Patients who have SDB experience apnea and hypopnea events during their sleep [1]. Breathing can stop completely, possibly as a result of airway collapse or decreased respiratory drive and cessation of inspiratory effort [2]. The apnea-hypoventilation index (AHI) is the number of episodes of apnea or hypoventilation during a 1 hour of sleep and helps determine the severity of sleep apnea (SA) [3, 4].

Heart failure (HF) is a common disease in developed countries, affecting at least 1-2% of adults [5]. Despite significant advances in treatment, the prognosis for patients with CHF remains poor: within 5 years, approximately half of all elderly or hospitalized HF subjects die [6]. SA is common in patients with HF. Statistically, almost 81% of patients with HF have SA. The most common type is OSA, with a prevalence of 15-20% in middle-aged adults. OSA is present in up to 60 percent of individuals with heart failure. CSA is predominantly seen in patients with HF, with an estimated prevalence of 30-50%. Notably, OSA and CSA can occur in a mixture in the same patient, but one is the predominant one [7-10]. Current mechanisms of HF in apnea patients include intermittent hypoxia, increased sympathetic nervous system activity, increased cardiac load, and vascular endothelial dysfunction.

Clinical studies have demonstrated that optimization of HF treatment could improve cardiac function and CSA [11, 12]. Reduced cardiac output and increased preload are the key pathogenic mechanisms of CSA [13]. Thus, CSA events are more severe during HF exacerbations [14]. Similarly, jugular vein congestion can lead to upper airway instability, which can exacerbate potential OSA, particularly when the patients are in their supine position during sleep [15]. A study showed that volume shifts in the lower extremity during sleep are associated with increased AHI in SA in patients with HF [16]. Volume overload appears to be a direct cause of jugular venous congestion, which exacerbates OSA, and interstitial lung congestion, which promotes CSA. As a result, deteriorating HF may result in an increase in central and obstructive apnea [17]. So, optimizing HF therapy is still the most important first step in treatment. For people with high blood pressure, medicines and medical devices can help them sleep better. This is because they can cut

back on volume overload and keep more of it from moving into the lungs and neck [18]. Treatment guidelines for HF are a standard of care in modern HF management in developed nations, and the HF team is constantly improving them. As a result, it is unknown how important HF optimization is in the therapeutic therapy of newly diagnosed CSA or OSA in stable HF patients [19]. However, optimizing HF may be critical in determining whether to commence PAP therapy for SDB, which is diagnosed in patients who have not yet received optimal HF-based guideline therapy. In these instances, it may be prudent to review the kind and severity of SDB after initiating appropriate HF treatment. CSA has been treated with adaptive servo-ventilation (ASV), continuous positive airway pressure (CPAP), bi-level positive airway pressure with back-up respiratory rate, and drugs such as theophylline and acetazolamide[20]. None of these treatment options are effective in the long term. The optimal method for managing CSA in CHF remains debatable. Therefore, multiple therapy options are now being studied.

Tricuspid regurgitation (TR) is a common symptom of HF and is linked to an increased risk of death [21]. Current guidelines recommend surgical reconstruction or replacement of the tricuspid valve as the primary treatment strategy followed by drug therapy [22, 23]. However, new treatment options are needed as the elderly cannot tolerate surgery [24, 25]. Transcatheter caval valve implantation (CAVI) is a promising therapeutic option that has been proposed. It is designed to address the problem of luminal regurgitation that occurs late in severe TR. In a study of CSA subjects with HF, a decrease in AHI was found after heart transplantation and pharmacological treatment [26]. Another study found that a 64-year-old man with CSA also had improved sleep and breathing disorders after mitral valve transplantation[27]. Nevertheless, some studies have indicated that transcatheter aortic valve replacement does not alleviate sleep apnea in subjects with CHF [28, 29].

Sacubitril-valsartan (SV) has been characterized as an angiotensin-receptor neprilysin inhibitor (ARNI) for the therapy of congestive HF with decreased ejection fraction (HFrEF). A considerable number of studies have displayed that angiotensin-converting enzyme inhibitors (ACEIs) are effective in patients with HF and CSA [30]. Treatment with SV was suggested in a study to reduce overall mortality and HF-related hospitalizations compared with ACEI treatment [31]. The pathogenesis of OSA and CSA such as sympathetic nervous system activation in patients with CHF may be countered by SV combined therapy, which has a known mechanism of action [32]. Thus, SV

interferes with the neurohumoral system and ameliorates CHF by reducing renin-angiotensin-aldosterone and sympathetic activity, two more potential contributors in the pathogenesis of SA [33]. Therefore, it is an excellent option for the correction of SA in CHF patients. SV is currently the cornerstone of clinical therapy in subjects with HFrEF who remain symptomatic despite adequate treatment with ACEIs, β-blockers, and mineralocorticoid receptor antagonists [34]. Although combination therapy is associated with improved HF, to our knowledge, studies on the impact of SV on central apnea (CA) /obstructive apnea (OA) are still scarce [35].

In this thesis, I aimed to assess; 1) Could CAVI and SV be used to enhance sleep variables? 2) Is it possible for CAVI and SV treatment to have a beneficial effect on echocardiographic parameters? 3) Could CAVI and SV affect CPET parameters? 4) Could CAVI and SV have an impact on N-terminal-pro-B-type natriuretic peptide (NT-pro BNP)?

2. Methodology

All methods used are described in detail in selected publications. In this section, only the main materials and methods relevant to the results and experimental purposes are summarized.

2.1 Clinic data collection

Publication 1[36] investigated associations between CAVI and sleep apnea (Figure 1). Publication 1 followed the inclusion criteria (Laule et al., 2019): (1) TR is at least severe; (2) NYHA II-IV; (3) older than age 50 years; and (4) high risk with surgery. Exclusion criteria: (1) inferior vena cava (IVC) diameter $\geqslant$ 31 mm; (2) ongoing SA treatment; (3) reluctance to use Apnealink; (4) serum creatinine concentration $\leqslant$ 3.0 mg/dl; (5) declined to sign informed consent form; (6) chronic kidney disease requiring scheduled dialysis; (7) Left ventricular ejection fraction (LVEF) $\leqslant$ 30%.

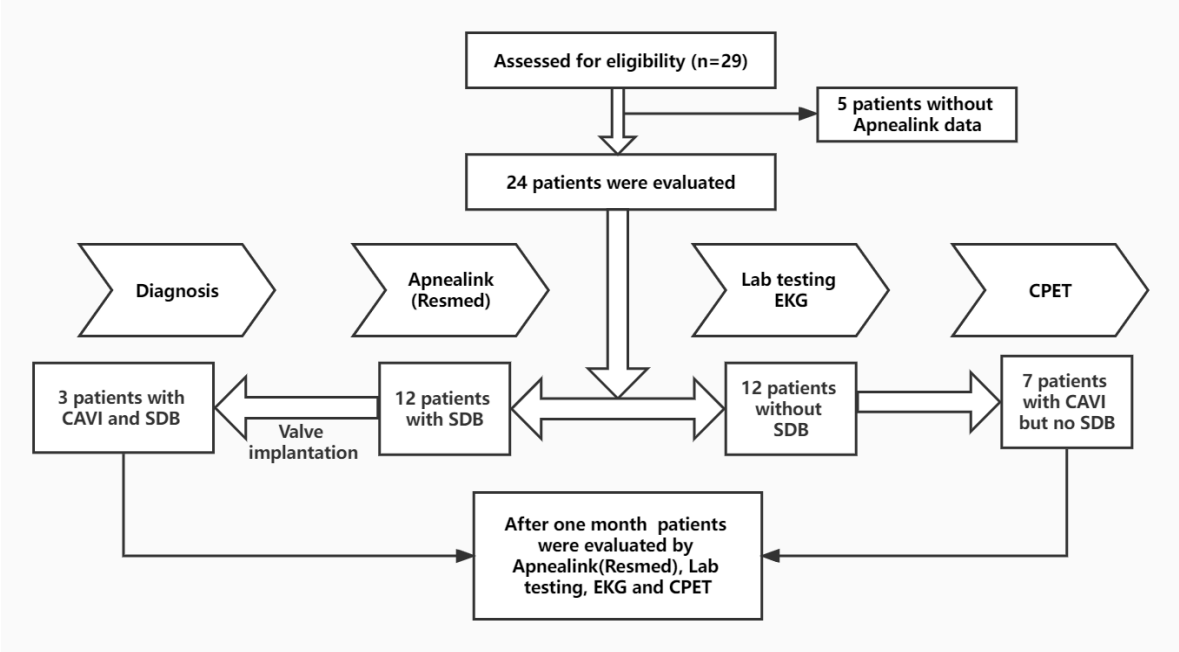

Figure 1 CAVI study flow chart (own representation).

Publication 2 [37] focused on the impact of initiating SV on CA/OA patients and enrolled 18 participants with HFrEF (Figure 2). The following data were collected: age, height, weight, NYHA functional class, systolic and diastolic blood pressure, medications, and basic diseases such as arterial hypertension and diabetes mellitus. The following criteria

were used to determine inclusion: subjects (age ⩾ 60) with HF (NYHA class II-IV); LVEF ⩽ 40%; patients must have received stable doses of standard-of-care HF medication for at least one month before the study; a blood test result of serum potassium ⩽ 5.2 mmol/L, estimated glomerular filtration rate (eGFR) ⩾ 30 ml/min/1.73 m^2 and systolic blood pressure (SBP) ⩾ 100 mmHg. Those with severe valvular disease, hypertrophic obstructive cardiomyopathy, previous or planned heart transplantation, and unstable angina within 6 months were excluded. All patients completed an informed consent form and were performed with the approval of the local ethics committee.

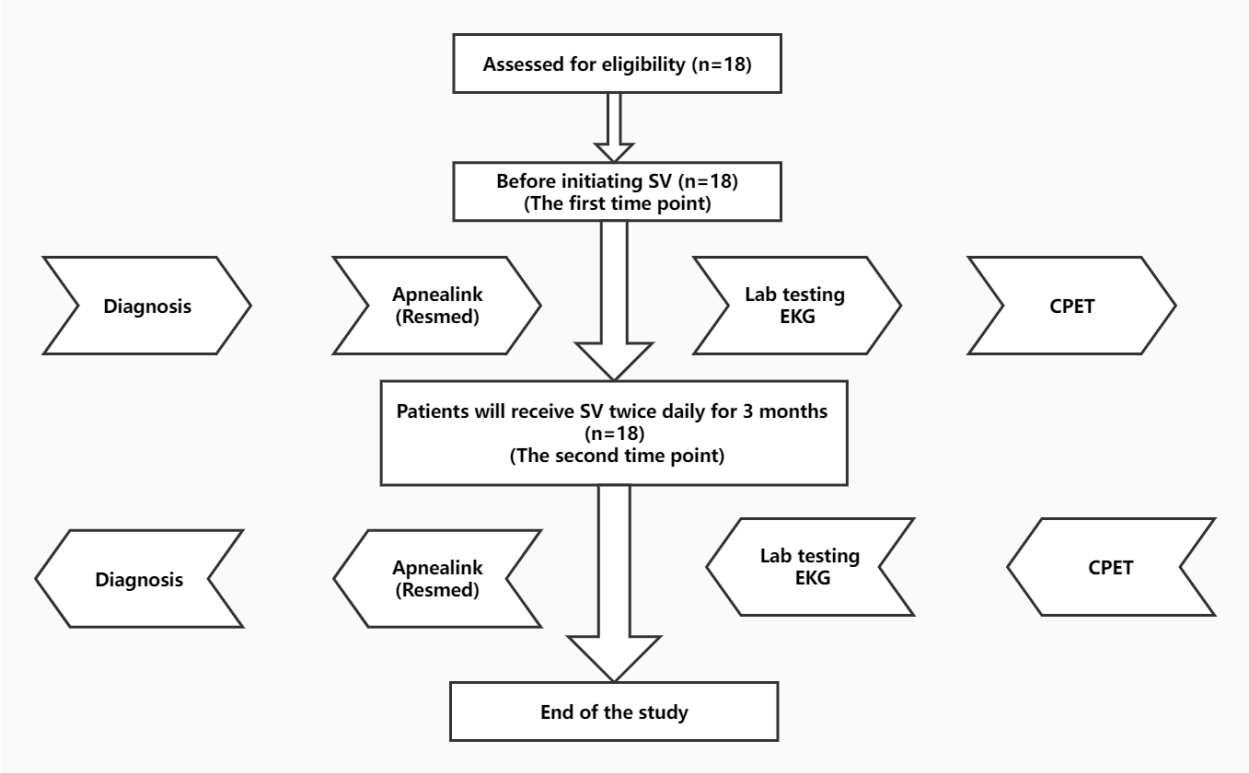

Figure 2 SV study flow chart(own representation).

2.2 Portable Monitoring

Apnealink (ResMed, Germany) was used to assess pulse oximetry and nasal flow in Publication 1[36] and Publication 2[37]. Participants are instructed by researchers with comprehensive training in the standard use of the equipment. Apnea was defined as a sustained reduction in airflow of greater than 90% from baseline that lasted more than 10 seconds. The respiratory event index (REI) is defined as the number of apnea and hypopnea occurrences observed per hour during a specified period.

2.3 Treatment

In Publication 1[36], self-expanding valve for implantation in the IVC to protect abdominal vessels from high blood pressure and systolic backflow in people who have a lot of TR. Using this device, you don't have to worry about blocking hepatic venous inflow below your diaphragm. The proximal stent segment is then attached to a three-leaf porcine pericardial valve. A sleeve is then placed inside the valve up to the base of the leaflet to keep it from leaking. All implantations were conducted under local anesthetic and via transfemoral venous access with transthoracic echocardiography.
In Publication 2[37], patients will receive SV twice daily, adjusted for renal function and hemodialysis tolerance, at the dose permitted by the European Union. Patients will be encouraged to take the study drug daily in conjunction with their usual prescription, according to approved instructions that follow the best medical treatment recommendations in current European HF guidelines.
The formula for duty ratio (DR) is:

$$DR = \frac{ventilatory\ duration}{cycle\ duration}$$

The formula to calculate loop gain (LG) is:

$$LG = \frac{2\pi}{(2\pi * DR - \sin(2\pi * DR))}$$

2.4 Laboratory Testing, Echocardiography and CPET

In Publication 1[36] and Publication 2[37], the blood sample will be taken by the nurse for evaluation. The eGFR was determined using a biochemical auto-analyzer. All patients had routine transthoracic and transesophageal echocardiogram in two- and three-dimensions. LVEF, tricuspid annular plane systolic excursion (TAPSE), and other EKG parameters were all analyzed. All recordings were made using ultrasound equipment. All patients underwent symptom-limited CPET on a cycle ergometer, which entailed pedaling at 60 rpm with a burden of 20 W, followed by a stepwise 20-W increment every 2 minutes until exhaustion.

2.5 Statistical analysis

To describe baseline characteristics, descriptive statistics (means and standard deviations) were utilized. Numbers (n) and percentages (%) are used to express categorical variables.

In Publication 1[36], data were followed a normal distribution and analyzed using paired t-test and independent samples t-test for intra- and inter-group comparisons, respectively. In Publication 2[37], due of the dependency on both populations before and after, paired t-tests were performed (for data with a normal distribution) and Wilcoxon tests (for data with an abnormal distribution). $P < 0.05$ was chosen as the threshold for statistical significance. To evaluate the statistical data, SPSS version 25.0 was employed (IBM, Armonk, NY, USA).

3. Results

The studies' findings are detailed in the "Selected Publications" paper. Only the most important results are summarized and briefly described in this section.

In Publication 1[36], baseline characteristics are shown in Table 1. During the trial period, no medication was changed. After CAVI, no significant changes were observed in echocardiographic, blood testing, or sleep parameters ($P > 0.05$) (see Table 2 and Figure 3).

Table 1 Patient demographics and baseline characteristics of CAVI study (own representation).

	Patients (n = 29)
Age (years)	75.17 ± 8.38
Male (%)	9 (31)
BMI（kg/m^2）	25.10 ± 4.25
NYHA class	
I	1 (3.4)
II	26 (89.7)
III	2 (6.9)
TR (severe)	29 (100)
Pulmonary hypertension	
No	11 (37.9)
Primary	4 (13.8)
Secondary	7 (24.1)
Combined	3 (10.3)
PAP mean (mmHg)	27 ± 11.48
PCWP mean (mmHg)	16 ± 5.49
Arterial hypertension	29 (100)
Nicotine abuse	5 (17.2)
Obstruction COPD	8 (27.6)
GFR (ml/min)	47.65 ± 18.85
Renal insufficiency	

Normal	0
Mild	6 (20.7)
Moderate	14 (48.3)
Severe	6 (20.7)
Diabetes mellitus	
No	21 (72.4)
Type 1	1 (3.4)
Type 2	7 (24.1)
LVEF (%)	57.21 ± 7.29

PAP: pulmonary arterial pressure.

Table 2 Comparison of echocardiographic findings between CAVI-pre and CAVI-post after 1 month (own representation).

	CAVI-pre (n = 3)	CAVI-post (n = 3)	P value
LEVEF, %	54 ± 10	49 ± 9	0.383
TR vmax, m/s	2.8 ± 0.28	2.43 ± 0.29	0.5
RVFAC, %	12	30 ± 2	-
RV S', cm/s	7.95 ± 0.5	8.37 ± 1.7	0.892
TAPSE, mm	17± 11	17 ± 9	0.853
RV strain mid, %	-16	-24 ± 5.66	-
Stroke volume index, L/min/m^2	29 ± 9.9	23.93 ± 1.79	0.548
Cardiac index, l/min	2.2 ± 0.14	2.2 ± 0.56	0.205

Data are presented as mean ± SD. RVMPI: right ventricular myocardial performance index.

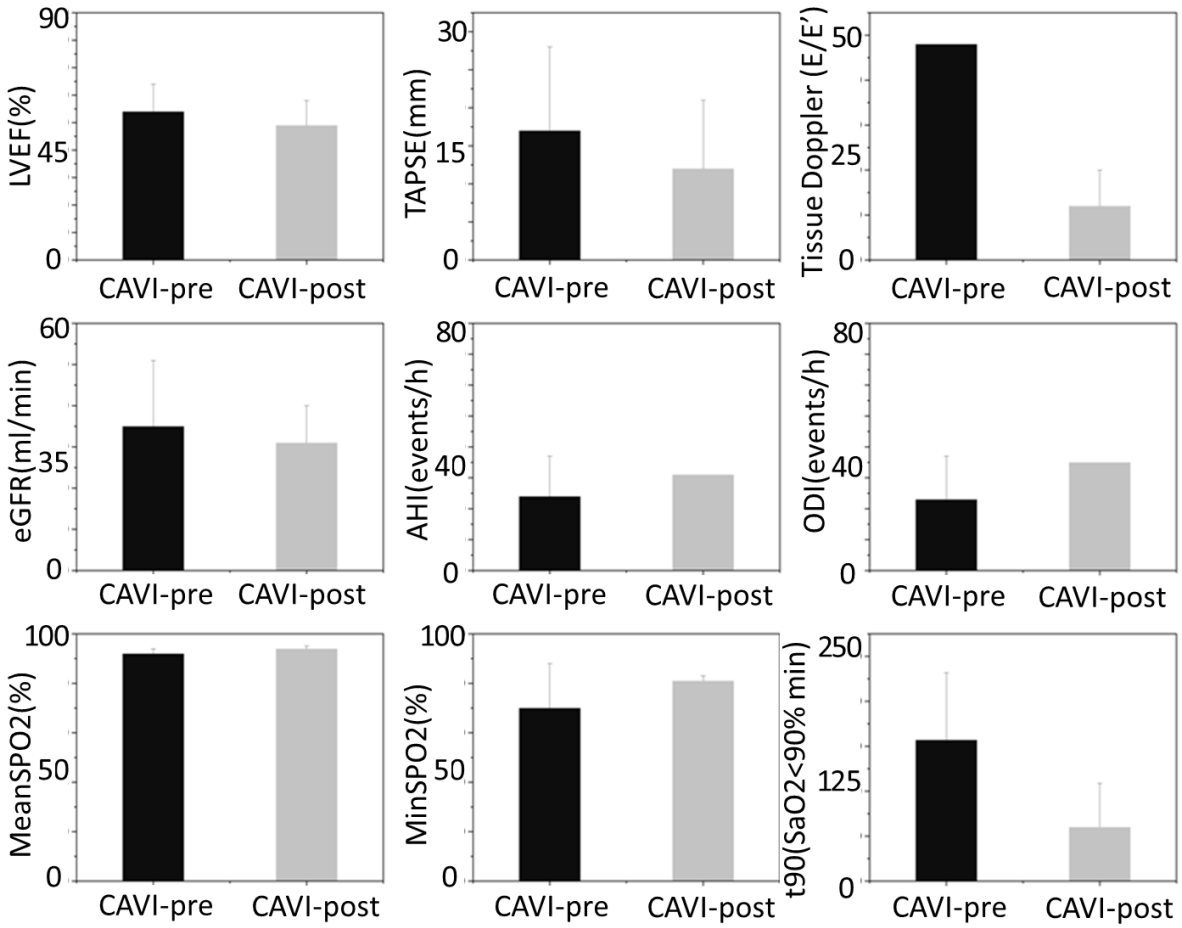

Figure 3 Comparison between CAVI-pre and CAVI-post group (own representation). SaO2: oxygen saturation; HR: heart rate; T90: SaO2 < 90% min.

In publication 2[37], baseline characteristics are displayed in Table 3. SV has been demonstrated to be related to a statistically significant reduction in NT-pro BNP (see Figure 4). As compared to the portable monitoring variables between baseline and three months after SV titration, there were significant differences in AHI, apnea length, cycle length, ODI, RI, T90, DR, loop gain, and circulatory delay (all $P < 0.05$). After optimization of HF-treatment with SV, we saw a complete significant decrease of T90 (time of oxygen saturation under 90%) and a marked reduction of AHI, cycle length, apnea length and circulatory delay (Table 4).

Enhanced systolic and diastolic function of the left ventricle (LV), as measured by a rise in LV end-diastolic diameter, and enhanced LV reverse re-modeling, as indicated by an increase in LVEF, were also associated with SV. However, there were no

statistically significant changes in TAPSE (p = 0.392) or systolic pulmonary artery pressure (sPAP) (see Figure 4). Echocardiography showed a significant increase of the RV-FAC (P = 0.001) and cardiac index (p = 0.078). ECG findings are listed in Table 5. CPET variables showed no differences after SV treatment. The effect of SV was significantly associated with a reduction in REI in the subgroup of patients with OA (p = 0.039). Furthermore, in the CA subgroup, SV was related to a reduction in REI (p = 0.018). SV may reduce the minimum oxygen saturation and the amount of time spent with T90 (all p < 0.05) (see Figure 5).

Table 3 Baseline characteristics of SV study (own representation).

	Patients (n = 18)
Age (years)	66.67 ± 10.73
Male	15 (83.33)
BMI（kg/m^2）	43.80 ± 50.22
NYHA class	
II	9 (50)
III	9 (50)
NT-pro BNP (pg/ml)	1792.06 ± 1271.25
Comorbities	
Atrial fibrillation / flutter	4 (22.22)
Valvular heart disease	4 (22.22)
LVEF (%)	57.21 ± 7.29
Diabetes	3 (16.67)
Hypertension	14 (77.78)
COPD	5 (27.78)
Myocarditis	2 (11.11)
Peripheral artery/ cerebrovascular/ aortic disease	4 (22.22)
Cardiac infarction	4 (22.22)
Active smoker	4 (22.22)
Hyperlipidemia	8 (44.44)
Medications	
Beta blocker	16 (88.89)

Loop diuretics	13 (72.2)
Others	
CABG	4 (22.22)
ICD	13 (72.22)
CRT	3 (16.67)

COPD: chronic obstructive pulmonary disease.

Table 4 Changes of sleep parameters after SV (own representation).

	SV-pre (n=18)	SV-post (n=18)	P value
Cycle length (s)	68 ± 15	53 ± 13	**＜0.001***
Ventilation length (s)	41 ± 10	36 ± 10	**0.018***
Apnea length (s)	27±10	17±11	**＜0.001***
ODI (e/h)	16 ± 15	9 ± 7	**0.016***
SO2 basal (%)	93 ± 2	95 ± 2	0.053*
min SO2 (%)	80 ± 4	80 ± 8	0.812*
min HR (bpm)	50 ± 9	48 ± 8	0.631*
max HR (bpm)	106 ± 24	100 ± 22	0.458*
mean HR (bpm)	66 ± 9	62 ± 7	0.137*
Circulatory delay (s)	43 ± 10	31 ± 10	**＜0.001***
DR	0.60 ± 0.09	0.69 ± 0.16	**0.006***
LG	1.57 ± 0.53	1.51 ± 1.06	0.734*
AHI (e/h)	20 ± 23	7 ± 7	**0.003#**
RI (e/h)	19 ± 18	10 ± 7	**0.011#**
T90 (SO2 <90% in min)	119 ± 128	42 ± 86	**0.001#**
Cycle length (s)	68 ± 15	53 ± 13	**＜0.001***
Ventilation length (s)	41 ± 10	36 ± 10	**0.018***
Apnea length (s)	27 ± 10	17 ± 11	**＜0.001***

P* stands for the paired T test. P# stands for Wilcoxon test. DR: duty ratio; LG: loop gain.

Table 5 Echocardiographic findings (own representation).

	SV-pre (n=18)	SV-post (n=18)	P value

LVEF (%)	31.77 ± 6.86	42.65 ± 8.62	**＜0.001***
Cardiac index (L/min/m²)	2.06 ± 0.63	2.43 ± 0.55	0.078#
Strain LV (%)	-9.29 ± 3.52	-10.67 ± 6.63	0.412*
s` (cm/s)	4.55 ± 1.37	5.21 ± 2.02	0.159*
MAPSE sept (mm)	6.56 ± 1.34	8.33 ± 2.59	**0.003***
MAPSE lat (mm)	9.83 ± 2.55	11.33 ± 3.22	**0.042***
LVEDD (mm)	59.94 ± 6.9	56.83 ± 9.6	**0.025***
LVESD (mm)	50.72 ± 9.09	44.5 ± 10	**0.001***
LVEDV (ml)	160.06 ± 61.6	141.71 ± 49.11	0.052*
LVESV (ml)	110.39 ± 48.13	83.29 ± 39.64	**0.001#**
E (m/s)	0.74 ± 0.28	0.72 ± 0.3	0.810*
e' (cm/s)	6.71 ± 2.48	6.58 ± 2.87	0.865#
E/e'	11.87 ± 4.94	12.58 ± 7.77	0.594*
A (m/s)	0.66 ± 0.25	1.43 ± 1.82	0.072#
DT (ms)	243 ± 97.78	257.18 ± 146.07	0.623*
IVRT (cm/s)	125.53 ± 56.62	124.71 ± 60.74	0.712#
LA-Index (ml/m²)	55.07 ± 40.81	53.87 ± 46.42	0.379#
Sys PAP (mmHg)	25.75 ± 10.71	21.29 ± 12.86	0.623#
Vp (cm/s)	43.53 ± 11.35	39.5 ± 10.98	0.377*
RV-IVRT (cm/s)	66.44 ± 49.5	47.88 ± 28.04	0.167#
RV-AT (ms)	102.71 ± 34.54	126.27 ± 36.49	**0.015***
TAPSE (mm)	18.72 ± 4.23	19.67 ± 2.85	0.392#
RV-S` (cm/s)	8.94 ± 2.05	11.12 ± 2.76	**0.006***
RV-FAC (%)	29.47 ± 10.44	39.41 ± 9.27	**0.001***
NYHA class			**0.005**
II	9 (50)	6 (33.33)	
III	9 (50)	4 (22.22)	

P* stands for the paired T test. P# stands for Wilcoxon test. MAPSE: mitral annular plane systolic excursion; s`: systolic velocity in tissue doppler imaging; LA-Index: left atrial index; Sys PAP: systolic pulmonary artery pressure; Vp: velocity of flow progression.

Table 6 Changes in CPET (own representation).

	SV-pre (n=18)	SV-post (n=18)	P value
Max VE (l/min)	50.57 ± 13.79	47.14 ± 12.27	0.416#
Ref BF (l/min)	18 ± 5.03	19.57 ± 4.72	0.329*
Max BF (l/min)	27 ± 5.77	26 ± 5.42	0.643*
Max VO_2 (ml/min)	1157 ± 300	1097 ± 337	0.130*
Max O_2/HR (ml)	11.64 ± 3.96	11.97 ± 3.31	0.316*
FEV1 (L)	2.63 ± 0.8	2.85 ± 0.75	0.209*
NT-pro BNP (pg/ml)	1792 ± 1271	876 ± 984	**0.001#**

Data are presented as mean ± SD. BF: breathing frequency; Ref: reference; Max VO_2: maximal oxygen uptake; FEV1: forced expiratory volume for one second.

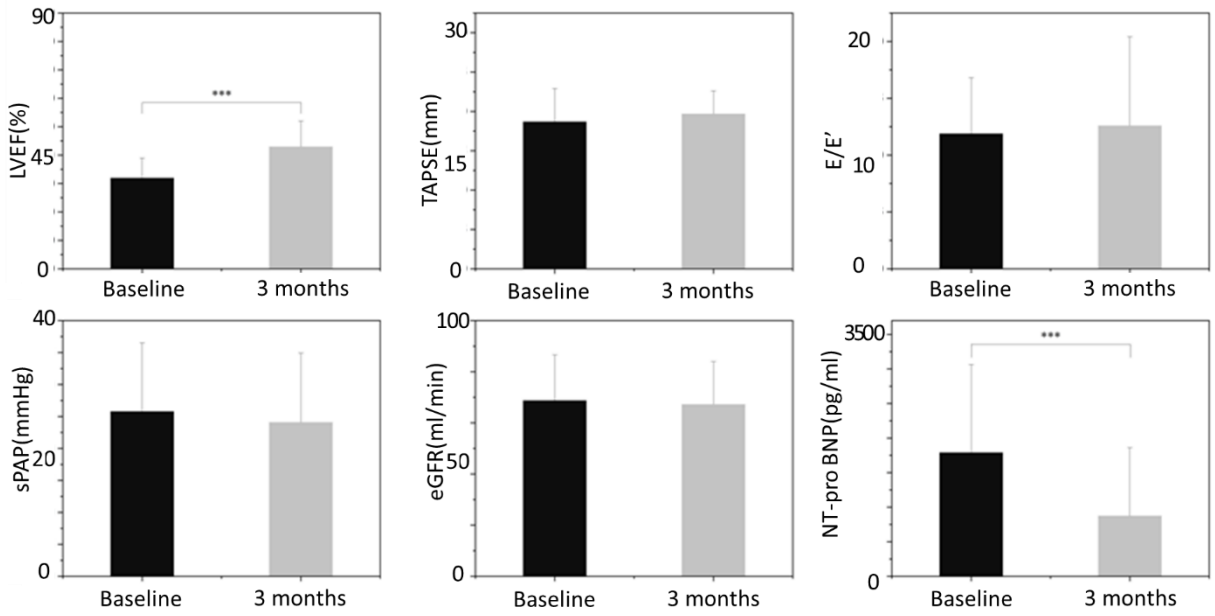

Figure 4 Changes in heart remodeling and blood examination (own representation). * = p < 0.05; ** = p < 0.01; *** = p < 0.001.

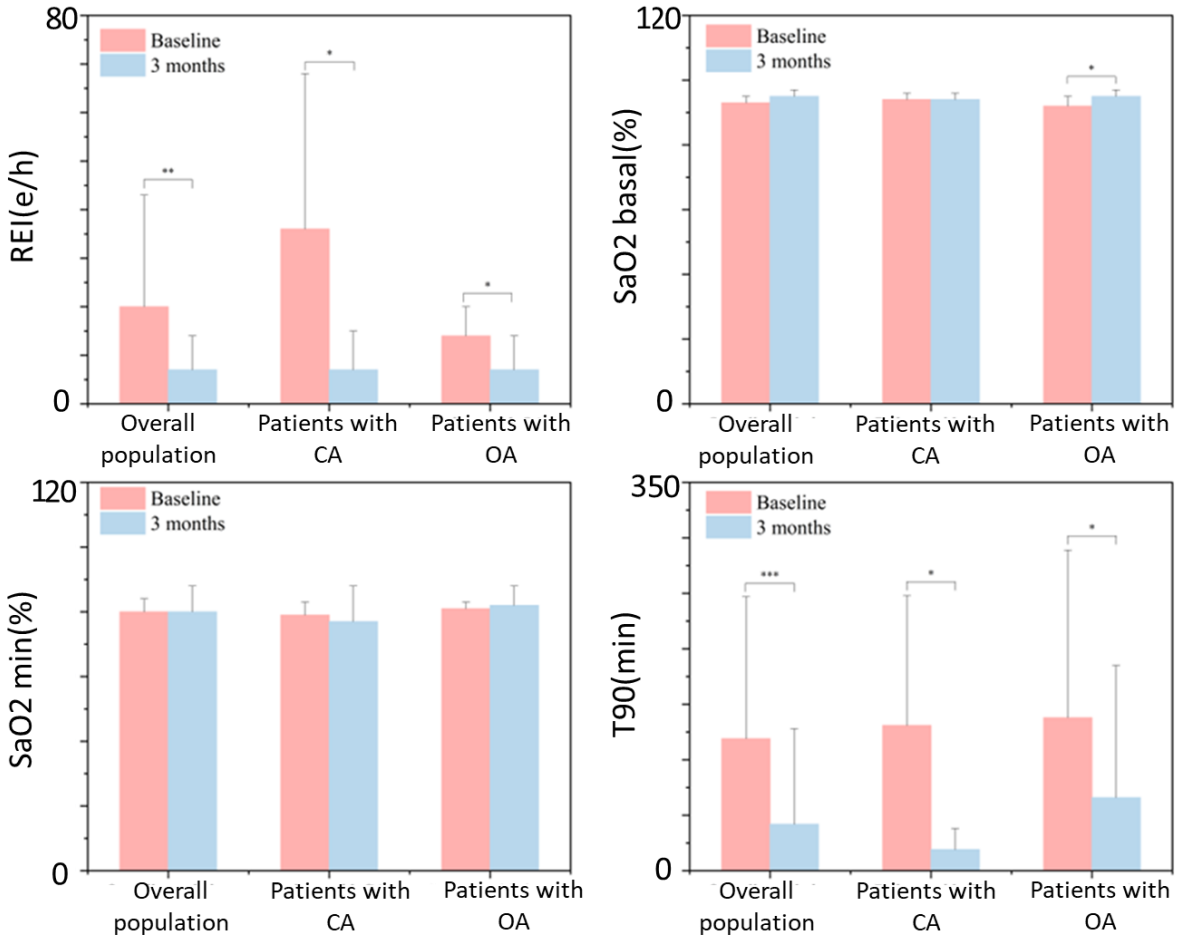

Figure 5 Changes of REI, oxygen saturation (SaO_2) and T90 after SV in subgroups (own representation). * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

Comparison of main findings between CAVI study and SV study.

SV treatment could affect sleep variables (AHI, ODI and T90), EKG parameters, NT-pro BNP, but CAVI could not change these parameters significantly Figure 6.

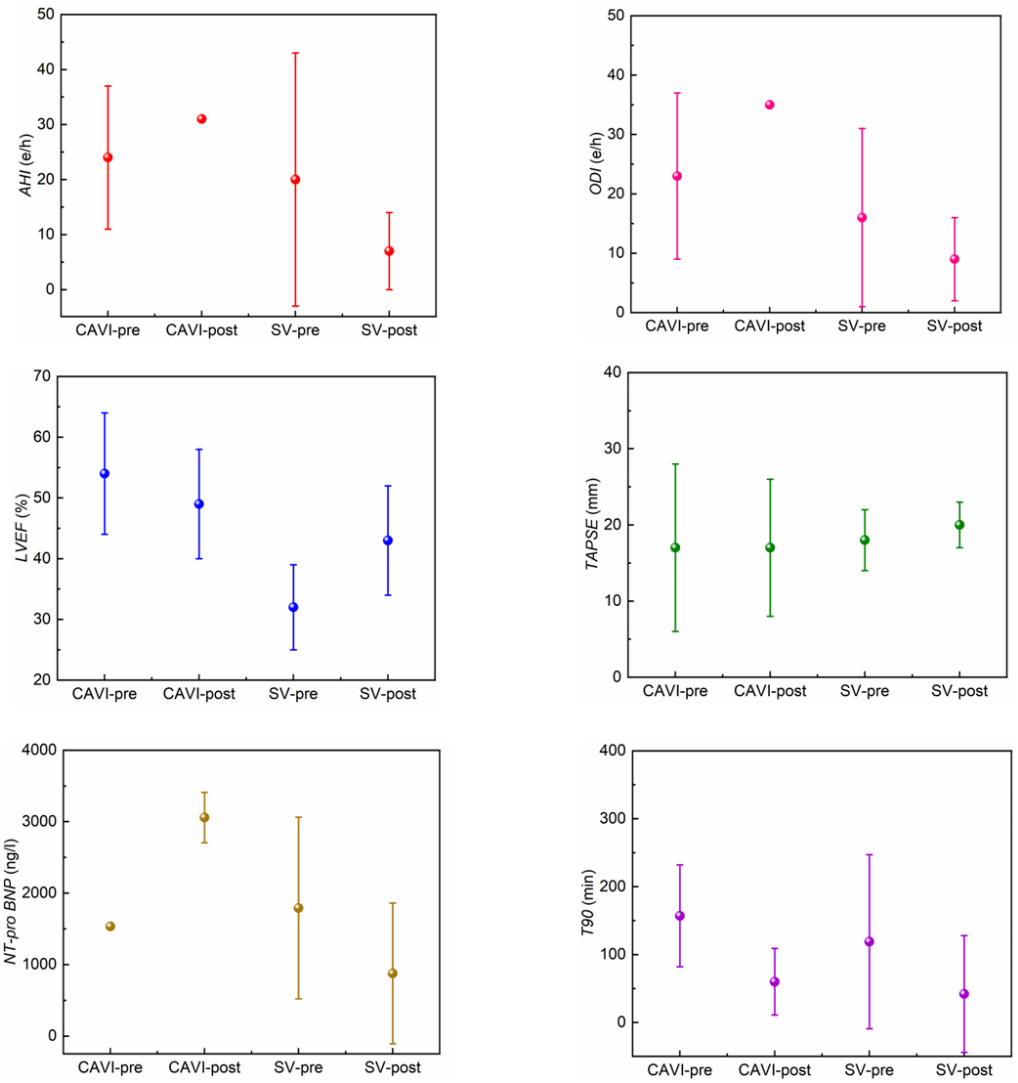

Figure 6 Comparison of main findings between CAVI study and SV study (own representation).

4. Discussion

In my doctoral thesis, I investigated multiple treatment options for sleep apnea patients with HF through two trials: CAVI and SV.

In Publication 1[36], we showed that CAVI had no significant impact on HF and SA patients. We also found no link between SA and poor outcomes after CAVI. This result is consistent with the previous study, they could not prove a relationship between SDB and postoperative outcomes in this cohort (107 patients) [38]. CAVI treatment is a newly designed valve replacement approach for participants with HF and severe TR who have high surgical risks [39]. Between CAVI-pre and CAVI-post groups, no significant changes were observed in sleep parameters. This result is contrary to past study that demonstrated improvement in SA patients with HF after heart valve surgery[40]. Although clinical data on the efficacy of transcatheter tricuspid valve interventions (TTVI) are scarce to date, the feasibility of using a variety of procedures has been demonstrated, including annular devices [41, 42] and leaflet and coaptation devices [43, 44], both in the orthotopic and heterotopic positions [45]. An earlier study revealed that CPAP could reduce AHI. Diastolic dysfunction can be alleviated with effective SA treatment[46]. Although there was no significant change in sleep parameters after the CAVI procedure, we could not prove that there was no association between the improvement in SA and CAVI procedure. The pathophysiology of SA in HF is complex but far less understood. It may be that SDB can predict the severity of HF, but this would require more studies with larger sample sizes.

In Publication 2[37], we have indicated that SV could improve SA in HFrEF patients. The use of SV along with optimal medical treatment could lead to a significant decrease in REI. When SV was compared with enalapril, the former was found to be more effective in reducing all-cause and sudden death mortality as well as reversing the course of HF [47]. Past study has found an association between SV and increased LVEF, with increased LVEF promoting reverse LV and improved REI. SV also increased the level of NT-pro BNP, a result consistent with previous studies [48, 49]. It should be noted that some patients converted from CA to OA during treatment with SV, and OA thus became the most prevalent respiratory disease. The initiating of SV reduced CA, validating the drug's previous claim of a beneficial effect on CA in a case study [50]. This result is also consistent with previous studies that increased cardiac efficiency leads to decreased CA [51, 52]. By inhibiting eprilysin, SV inhibits the degradation of natriuretic peptides, thereby

increasing their natriuretic and vasodilatory effects and reducing pulmonary congestion [53]. The beneficial effects of reverse cardiac remodeling associated with increased LVEF may lead to an increase in ventricular output[54, 55]. Overall, these attributes may contribute to gas exchange, as well as to chemical responses that enhance perfusion of peripheral chemoreceptors by inhibiting stimulation of pulmonary stretch receptors[56]. Finally, it has been demonstrated that the medication reduces the amount of fluid transferred from the rostrum while a person is lying down. In conclusion, our findings from HFrEF patients imply that SV is beneficial for both CA and OA. In comparison to CA, SV had a more restricted influence on OA. SV may be a viable therapy option for CA in patients with HFrEF.

5. Strengths and limitations

5.1 Strengths

In Publication 1[36], this is the first evaluation of the effect of CAVI on SA participants with HF and severe TR. Due to the severe complications of CAVI the number of patients is small, but we still collected these data for a preliminary study (Aplealink, echocardiography, spirometry, and laboratory blood tests) to describe in more detail the cardiovascular function of the patients. In Publication 2[37], We observed that SV had beneficial effects on SA and HFrEF patients. The use of SV to appropriate medical therapy resulted in a significant reduction in the REI.

5.2 Limitations

There are several limitations in Publication 1[36] that must be addressed. Our investigation was nonblinded and took place around 1 month. This is a relatively short period for the patients to adjust to their new hemodynamic situation. As a result, it is recommended that a double-blind trial be repeated with longer follow-up periods. Individual characteristics among individuals may also influence sleep patterns and quality. Furthermore, because our results are based on Apnealink, internight changes are unaccounted for. Finally, because of a significant complication following CAVI, this trial was halted early. It was conducted in a single center with a limited sample of older patients. To improve outcomes, multi-center research with high sample numbers is required.

Publication 2[37] has a few limitations as well. First, we note that this is a single-center study and that additional research is needed to establish the generalizability of the current findings. Furthermore, our study was limited to people over the age of 65 who had HFrEF. Another potential disadvantage is that the portable monitoring equipment does not record CO2 and sleep stages. Therefore, no inferences can be drawn about these elements, and events cannot be divided into separate sleep stages. Furthermore, no electroencephalograms were obtained in this investigation. ApneaLink may overstate the REI due to the fact that actual sleep time may be shorter than reported sleep time, indicating a greater prevalence and severity of apnea.

6. Conclusions and future directions

Patients with HF are often suffering from the influence of SA, If left untreated, the combination of these two diseases can lead to increased mortality. There is a correlation between HF and SA. It is hypothesized that the combination of multiple pathophysiological effects of HF and respiratory disorders lead to the development of SA. Given the increased mortality of untreated SA in subjects with HF, there is an urgent need to find safe and effective therapies. This study attempted to assess the impacts of CAVI and SV in subjects with HF and SA. The performed studies showed SV treatment was linked to a significant reduction in REI; SV could not affect spirometry parameters but can significantly improve heart function; NT-pro BNP has been decreased after SV treatment; SV could be a promising therapeutic option for CA. CAVI could not affect sleep variables, EKG, spirometry parameters and NT-pro BNP.

Given the small patient number of study, it is necessary to validate the results presented in our study. Polysomnography should be applied to record CO2 levels, sleep stages, and sleep position. Future multicenter studies should be conducted to investigate the positive effects of CAVI and SV on cardiovascular function and SA, as well as the interplay with HF medication / interventional therapy, is needed to extend the life of the patient.

References

[1] R.N. Khayat, D. Jarjoura, B. Patt, T. Yamokoski, W.T. Abraham, In-hospital testing for sleep-disordered breathing in hospitalized patients with decompensated heart failure: report of prevalence and patient characteristics, Journal of cardiac failure, 15 (2009) 739-746.
[2] A. Paulino, T. Damy, L. Margarit, M. Stoïca, G. Deswarte, L. Khouri, E. Vermes, A. Meizels, L. Hittinger, M.P. d'Ortho, Prevalence of sleep-disordered breathing in a 316-patient French cohort of stable congestive heart failure, Archives of cardiovascular diseases, 102 (2009) 169-175.
[3] M. Tsai, R. Khayat, Sleep Apnea in Heart Failure, Current Treat options cardiovasc medicine, 20 (2018) 33.
[4] Somnologie, 15 (2011).
[5] Y. Gerber, S.A. Weston, M.M. Redfield, A.M. Chamberlain, S.M. Manemann, R. Jiang, J.M. Killian, V.L. Roger, A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010, JAMA internal medicine, 175 (2015) 996-1004.
[6] B. Ziaeian, G.C. Fonarow, Epidemiology and aetiology of heart failure, Nature reviews Cardiology, 13 (2016) 368-378.
[7] S.M. Caples, Central sleep apnea and cardiovascular disease, Sleep medicine clinics, 9 (2014) 27-35.
[8] E. Watanabe, K. Kiyono, S. Matsui, V.K. Somers, K. Sano, J. Hayano, T. Ichikawa, M. Kawai, M. Harada, Y. Ozaki, Prognostic importance of novel oxygen desaturation metrics in patients with heart failure and central sleep apnea, Journal of cardiac failure, 23 (2017) 131-137.
[9] W. Randerath, O.C. Deleanu, S. Schiza, J.L. Pepin, Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options, European respiratory review, 28 (2019) 190084(1-10).
[10] M.R. Costanzo, Central sleep apnea in patients with heart failure—how to screen, how to treat, Current heart failure reports, 17 (2020) 277-287.
[11] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr, M.M. Colvin, M.H. Drazner, G.S. Filippatos, G.C. Fonarow, M.M. Givertz, 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Journal of the american college of cardiology, 70 (2017) 776-803.
[12] H. Yang, A.M. Sawyer, The effect of adaptive servo ventilation (ASV) on objective and subjective outcomes in Cheyne-Stokes respiration (CSR) with central sleep apnea (CSA) in heart failure (HF): A systematic review, Heart & Lung, 45 (2016) 199-211.
[13] R. Costanzo Maria, R. Khayat, P. Ponikowski, R. Augostini, C. Stellbrink, M. Mianulli, T. Abraham William, Mechanisms and Clinical Consequences of Untreated Central Sleep Apnea in Heart Failure, Journal of the american college of cardiology, 65 (2015) 72-84.
[14] P. Solin, P. Bergin, M. Richardson, D.M. Kaye, E.H. Walters, M.T. Naughton, Influence of pulmonary capillary wedge pressure on central apnea in heart failure, Circulation, 99 (1999) 1574-1579.
[15] J.W. Shepard, Jr, Pevernagie, D. A., Stanson, A. W., Daniels, B. K., & Sheedy, P. F, Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea, American journal of respiratory and critical care medicine, 153 (1996) 250-254.

[16] D. Yumino, S. Redolfi, P. Ruttanaumpawan, M.C. Su, S. Smith, G.E. Newton, S. Mak, T.D. Bradley, Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure, Circulation, 121 (2010) 1598-1605.
[17] Y. Peker, Glantz, H., Eulenburg, C., Wegscheider, K., Herlitz, J., & Thunström, E, Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea., The RICCADSA Randomized Controlled Trial. American journal of respiratory and critical care medicine, 194 (2016) 613-620.
[18] Y.M. Nakao, K. Ueshima, S. Yasuno, S. Sasayama, Effects of nocturnal oxygen therapy in patients with chronic heart failure and central sleep apnea: CHF-HOT study, Heart and vessels, 31 (2016) 165-172.
[19] J. Yu, Z. Zhou, R.D. McEvoy, C.S. Anderson, A. Rodgers, V. Perkovic, B. Neal, Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis, Jama, 318 (2017) 156-166.
[20] R. Mehra, Sleep apnea and the heart, Cleveland clinic journal of medicine, 86 (2019) 10-18.
[21] Y. Topilsky, V.T. Nkomo, O. Vatury, H.I. Michelena, T. Letourneau, R.M. Suri, S. Pislaru, S. Park, D.W. Mahoney, S. Biner, Clinical outcome of isolated tricuspid regurgitation, JACC: cardiovascular imaging, 7 (2014) 1185-1194.
[22] R.A. Nishimura, C.M. Otto, R.O. Bonow, B.A. Carabello, J.P. Erwin, R.A. Guyton, P.T. O'Gara, C.E. Ruiz, N.J. Skubas, P. Sorajja, 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the american college of cardiology/american heart association task force on practice guidelines, Journal of the american college of cardiology, 63 (2014) e57-e185.
[23] V. Falk, H. Baumgartner, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, B. Iung, P. Lancellotti, E. Lansac, D.R. Muñoz, 2017 ESC/EACTS Guidelines for the management of valvular heart disease, European Journal of cardio-thoracic surgery, 52 (2017) 616-664.
[24] K. Azarnoush, A.S. Nadeemy, B. Pereira, M.A. Leesar, C. Lambert, A. Azhari, V. Eljezi, N. Dauphin, E. Geoffroy, L. Camilleri, Clinical outcomes of tricuspid valve repair accompanying left-sided heart disease, World journal of cardiology, 9 (2017) 787.
[25] H. Kundi, J.J. Popma, D.J. Cohen, D.C. Liu, R.J. Laham, D.S. Pinto, L.M. Chu, J.B. Strom, C. Shen, R.W. Yeh, Prevalence and outcomes of isolated tricuspid valve surgery among Medicare beneficiaries, The american journal of cardiology, 123 (2019) 132-138.
[26] D.R. Mansfield, P. Solin, T. Roebuck, P. Bergin, D.M. Kaye, M.T. Naughton, The effect of successful heart transplant treatment of heart failure on central sleep apnea, Chest, 124 (2003) 1675-1681.
[27] A. Rubin, S. Gottlieb, A. Gold, A. Schwartz, P. Smith, Elimination of central sleep apnoea by mitral valvuloplasty: the role of feedback delay in periodic breathing, Thorax, 59 (2004) 174-176.
[28] J. Fan, X. Liu, L. Yu, Y. Sun, S. Jaiswal, Q. Zhu, H. Chen, Y. He, L. Wang, K. Ren, Impact of tricuspid regurgitation and right ventricular dysfunction on outcomes after transcatheter aortic valve replacement: a systematic review and meta-analysis, Clinical cardiology, 42 (2019) 206-212.
[29] H. Takagi, Y. Hari, N. Kawai, T. Ando, A. Group, Impact of concurrent tricuspid regurgitation on mortality after transcatheter aortic-valve implantation, Catheterization and cardiovascular interventions, 93 (2019) 946-953.
[30] S. von Haehling, M. Arzt, W. Doehner, F. Edelmann, R. Evertz, N. Ebner, C. Herrmann-Lingen, T. Garfias Macedo, M. Koziolek, M. Noutsias, Improving exercise

capacity and quality of life using non-invasive heart failure treatments: evidence from clinical trials, European journal of heart failure, 23 (2021) 92-113.
[31] A. Vazir, V. Sundaram, Management of sleep apnea in heart failure, Heart failure clinics, 14 (2018) 635-642.
[32] D. Jaffuel, N. Molinari, P. Berdague, A. Pathak, M. Galinier, M. Dupuis, J.E. Ricci, J.P. Mallet, A. Bourdin, F. Roubille, Impact of sacubitril–valsartan combination in patients with chronic heart failure and sleep apnoea syndrome: the ENTRESTO-SAS study design, ESC heart failure, 5 (2018) 222-230.
[33] C.H. Chen, Critical Questions about PARADIGM-HF and the Future, Acta cardiologica sinica, 32 (2016) 387.
[34] Y. Khariton, G.C. Fonarow, S.V. Arnold, A. Hellkamp, M.E. Nassif, P.P. Sharma, J. Butler, L. Thomas, C.I. Duffy, A.D. DeVore, Association between sacubitril/valsartan initiation and health status outcomes in heart failure with reduced ejection fraction, JACC: heart failure, 7 (2019) 933-941.
[35] C. Passino, P. Sciarrone, G. Vergaro, C. Borrelli, J. Spiesshoefer, F. Gentile, M. Emdin, A. Giannoni, Sacubitril–valsartan treatment is associated with decrease in central apneas in patients with heart failure with reduced ejection fraction, International journal of cardiology, 330 (2021) 112-119.
[36] Y. Wang, R. Fernandes Branco, A. Fietzeck, T. Penzel, C. Schöbel, Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients With Severe Tricuspid Regurgitation-A Pilot Study, Frontiers in cardiovascular medicine, 8 (2021) 673164.
[37] Y. Wang, R.F. Branco, M. Salanitro, T. Penzel, C. Schöbel, Effects of sacubitril-valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction, Sleep & breathing, (2022) First online: doi: 10.1007/s11325-022-02623-0.
[38] N. Foldvary-Schaefer, R. Kaw, N. Collop, N.D. Andrews, J. Bena, L. Wang, T. Stierer, M. Gillinov, M. Tarler, H. Kayyali, Prevalence of undetected sleep apnea in patients undergoing cardiovascular surgery and impact on postoperative outcomes, Journal of clinical sleep medicine, 11 (2015) 1083-1089.
[39] B. Del Forno, E. Lapenna, M. Dalrymple-Hay, M. Taramasso, A. Castiglioni, O. Alfieri, M. De Bonis, Recent advances in managing tricuspid regurgitation, F1000Research, 7 (2018) 355.
[40] S. Redline, E.F. Lewis, Gravitational influences and shifting propensity for sleep apnea: another source of heterogeneity or a new intervention target?, Circulation,121, 2010, 1583-1585.
[41] R.T. Hahn, C.U. Meduri, C.J. Davidson, S. Lim, T.M. Nazif, M.J. Ricciardi, V. Rajagopal, G. Ailawadi, M.A. Vannan, J.D. Thomas, Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results, Journal of the american college of cardiology, 69 (2017) 1795-1806.
[42] S. Kuwata, M. Taramasso, F. Nietlispach, F. Maisano, Transcatheter tricuspid valve repair toward a surgical standard: first-in-man report of direct annuloplasty with a cardioband device to treat severe functional tricuspid regurgitation, European heart journal, 38 (2017) 1261-1261.
[43] G. Nickenig, M. Kowalski, J. Hausleiter, D. Braun, J. Schofer, E. Yzeiraj, V. Rudolph, K. Friedrichs, F. Maisano, M. Taramasso, Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique, Circulation, 135 (2017) 1802-1814.
[44] N.P. Fam, E.C. Ho, M. Zahrani, S. Samargandy, K.A. Connelly, Transcatheter tricuspid valve repair with the PASCAL system, JACC: cardiovascular interventions, 11 (2018) 407-408.

[45] A. Lauten, T. Doenst, A. Hamadanchi, M. Franz, H.R. Figulla, Percutaneous bicaval valve implantation for transcatheter treatment of tricuspid regurgitation: clinical observations and 12-month follow-up, Circulation: cardiovascular interventions, 7 (2014) 268-272.
[46] N. Gupta, S. Agrawal, A.D. Goel, P. Ish, S. Chakrabarti, J. Suri, Profile of sleep disordered breathing in heart failure with preserved ejection fraction, Monaldi Archives for Chest Disease, 1329 (2020) 660-665.
[47] P. Martens, H. Beliën, M. Dupont, P. Vandervoort, W. Mullens, The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction, Cardiovascular therapeutics, 36 (2018) e12435.
[48] M.R. Zile, B.L. Claggett, M.F. Prescott, J.J. McMurray, M. Packer, J.L. Rouleau, K. Swedberg, A.S. Desai, J. Gong, V.C. Shi, Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure, Journal of the american college of cardiology, 68 (2016) 2425-2436.
[49] G. Vergaro, C. Passino, M. Emdin, No aldosterone breakthrough with the neprilysin inhibitor sacubitril, Journal of the american college of cardiology, 73 (2019) 3037-3038.
[50] N.E. Ibrahim, C.P. McCarthy, S. Shrestha, H.K. Gaggin, R. Mukai, J. Szymonifka, F.S. Apple, J.C. Burnett, S. Iyer, J.L. Januzzi, Effect of neprilysin inhibition on various natriuretic peptide assays, Journal of the american college of cardiology, 73 (2019) 1273-1284.
[51] H. Fox, T. Bitter, D. Horstkotte, O. Oldenburg, Cardioversion of atrial fibrillation or atrial flutter into sinus rhythm reduces nocturnal central respiratory events and unmasks obstructive sleep apnoea, Clinical research in cardiology, 105 (2016) 451-459.
[52] S. Selvaraj, B. Claggett, A. Pozzi, J.J. McMurray, P.S. Jhund, M. Packer, A.S. Desai, E.F. Lewis, M. Vaduganathan, M.P. Lefkowitz, Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF, Circulation, 140 (2019) 1369-1379.
[53] A. Giannoni, V. Raglianti, C. Taddei, C. Borrelli, V. Chubuchny, G. Vergaro, G. Mirizzi, A. Valleggi, M. Cameli, E. Pasanisi, Cheyne-Stokes respiration related oscillations in cardiopulmonary hemodynamics in patients with heart failure, International journal of cardiology, 289 (2019) 76-82.
[54] G. Bayard, A. Da Costa, R. Pierrard, C. Roméyer-Bouchard, J.B. Guichard, K. Isaaz, Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation, IJC heart & vasculature, 25 (2019) 100418.
[55] G. Romano, G. Vitale, L. Ajello, V. Agnese, D. Bellavia, G. Caccamo, E. Corrado, G. Di Gesaro, C. Falletta, E. La Franca, The effects of sacubitril/valsartan on clinical, biochemical and echocardiographic parameters in patients with heart failure with reduced ejection fraction: the “hemodynamic recovery”, Journal of clinical medicine, 8 (2019) 2165.
[56] A. Giannoni, V. Raglianti, G. Mirizzi, C. Taddei, A. Del Franco, G. Iudice, F. Bramanti, A. Aimo, E. Pasanisi, M. Emdin, Influence of central apneas and chemoreflex activation on pulmonary artery pressure in chronic heart failure, International journal of cardiology, 202 (2016) 200-206.

Statutory Declaration

“I, Youmeng Wang, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic: *Different Treatment Modalities of SA in Patients with Heart Failure / Unterschiedliche Behandlungsmodalitäten der Schlafapnoe bei Patienten mit Herzinsuffizienz* independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of my contribution to the publication

Youmeng Wang had the following share in the following publication:

Publication 1:

Youmeng Wang, Roberto Fernandes Branco, Andrea Fietzeck, Thomas Penzel and Christoph Schöbel. Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients with Severe Tricuspid Regurgitation-A Pilot Study. Frontiers in Cardiovascular Medicine. 2021; IF-6.05

Contribution in detail: I contributed to data collection and data analysis. I performed statistical analysis of the data using SPSS statistics software. I wrote the concept and the final version of the manuscript. I created all the tables and figures.

Publication 2:

Youmeng Wang, Roberto Fernandes Branco, Matthew Salanitro, Thomas Penzel, Christoph Schöbel. Effects of sacubitril‐valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction. Sleep and Breathing, 2022, IF-2.3

Contribution in detail:

I contributed to data collection and data analysis. I performed statistical analysis of the data using SPSS statistics software. I wrote the concept and the final version of the manuscript. I created Figure 1, Figure 2, Table 1, Table 2, and Table 3.

_____

Signature, date and stamp of first supervising university professor
(Prof. Dr. Thomas Penzel)

_____

Signature of doctoral candidate (Youmeng Wang)

Excerpt of Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"CARDIAC and CARDIOVASCULAR SYSTEMS"** Selected Category Scheme: WoS
Gesamtanzahl: 138 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CIRCULATION	158,218	23.603	0.205020
2	EUROPEAN HEART JOURNAL	59,968	22.673	0.140620
3	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	101,927	20.589	0.190280
4	Nature Reviews Cardiology	7,100	20.260	0.021130
5	CIRCULATION RESEARCH	51,539	14.467	0.071470
6	JAMA Cardiology	4,740	12.794	0.030110
7	JACC-Cardiovascular Imaging	10,110	12.740	0.027550
8	BASIC RESEARCH IN CARDIOLOGY	4,704	11.981	0.006380
9	EUROPEAN JOURNAL OF HEART FAILURE	12,784	11.627	0.028700
10	JACC-Heart Failure	4,117	8.750	0.019180
11	JACC-Cardiovascular Interventions	11,371	8.432	0.037330
12	CARDIOVASCULAR RESEARCH	21,526	8.168	0.019950
13	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,465	7.865	0.028140
14	Cardiovascular Diabetology	6,179	7.332	0.011390
15	PROGRESS IN CARDIOVASCULAR DISEASES	4,193	6.763	0.008340
16	European Heart Journal-Cardiovascular Pharmacotherapy	521	6.696	0.001640
17	Circulation-Heart Failure	6,773	6.033	0.018490
18	European Journal of Preventive Cardiology	5,589	5.864	0.015370
19	HEART RHYTHM	12,246	5.731	0.028620
20	Circulation-Cardiovascular Imaging	5,574	5.691	0.016320

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY	11,347	5.508	0.018230
22	Circulation-Cardiovascular Interventions	5,012	5.493	0.018140
23	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,205	5.361	0.011120
24	Clinical Research in Cardiology	3,321	5.268	0.007280
25	HEART	18,108	5.213	0.030140
26	Circulation-Cardiovascular Quality and Outcomes	4,728	5.071	0.014350
27	CANADIAN JOURNAL OF CARDIOLOGY	6,980	5.000	0.017630
28	European Heart Journal-Cardiovascular Imaging	6,359	4.841	0.023110
29	TRENDS IN CARDIOVASCULAR MEDICINE	2,695	4.755	0.003920
30	REVISTA ESPANOLA DE CARDIOLOGIA	3,672	4.642	0.004610
31	Journal of the American Heart Association	17,149	4.605	0.070620
32	Circulation-Cardiovascular Genetics	3,090	4.534	0.008600
33	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	28,491	4.451	0.034300
34	Circulation-Arrhythmia and Electrophysiology	6,344	4.393	0.016630
35	AMERICAN HEART JOURNAL	19,814	4.153	0.026810
36	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	14,031	4.133	0.017960
37	CARDIOVASCULAR DRUGS AND THERAPY	2,114	4.069	0.003340
38	Circulation-Genomic and Precision Medicine	375	4.063	0.002220
39	Hellenic Journal of Cardiology	987	4.047	0.001000
40	EUROPACE	9,973	4.045	0.024750

Selected JCR Year: 2019; Selected Categories: "CARDIAC and CARDIOVASCULAR SYSTEMS"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
41	EuroIntervention	5,542	3.993	0.016590
42	ATHEROSCLEROSIS	24,587	3.919	0.036590
43	Frontiers in Cardiovascular Medicine	1,303	3.915	0.004020
44	ESC Heart Failure	1,276	3.902	0.004120
45	AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY	26,114	3.864	0.020400
46	Global Heart	1,074	3.862	0.003180
47	European Heart Journal-Acute Cardiovascular Care	1,555	3.813	0.005430
48	NUTRITION METABOLISM AND CARDIOVASCULAR DISEASES	6,026	3.700	0.008820
49	ANNALS OF THORACIC SURGERY	35,221	3.639	0.040380
50	HEART FAILURE REVIEWS	2,697	3.538	0.005130
51	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	16,682	3.486	0.025820
52	JOURNAL OF CARDIAC FAILURE	4,983	3.435	0.008730
53	JOURNAL OF NUCLEAR CARDIOLOGY	3,600	3.366	0.004570
54	Journal of Cardiovascular Translational Research	1,656	3.312	0.003140
55	INTERNATIONAL JOURNAL OF CARDIOLOGY	31,193	3.229	0.068160
56	RESPIRATORY MEDICINE	11,934	3.095	0.013490
57	Annals of Cardiothoracic Surgery	1,828	3.058	0.005060
58	CURRENT PROBLEMS IN CARDIOLOGY	567	2.966	0.000740
59	Journal of Cardiovascular Computed Tomography	1,809	2.892	0.004850
60	American Journal of Cardiovascular Drugs	1,063	2.674	0.001580

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Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients With Severe Tricuspid Regurgitation—A Pilot Study

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Transcatheter caval valve implantation (CAVI) has been evaluated as a treatment option for inoperable patients with severe symptomatic tricuspid regurgitation (TR). We studied the effect of CAVI on sleep disorder breathing (SDB) in patients with right heart failure and TR. Twenty right heart failure patients with severe symptomatic TR who underwent portable monitoring of SDB (ApneaLink), echocardiography, cardiopulmonary exercise (CPET), and laboratory testing were enrolled. This was a single-center, nonblinded study. There were no significant changes in sleep variables, echocardiographic parameters, laboratory results, lung function, and CPET after CAVI. In conclusion, these data suggest that CAVI may not have an effect on SDB; however, additional follow-up fully powered studies with appropriate statistical analyses are needed.

Keywords: sleep-disordered breathing, tricuspid regurgitation, right heart failure, transcatheter caval valve implantation, ApneaLink

INTRODUCTION

Chronic heart failure (CHF) is an increasing health problem affecting more than 25 million people worldwide. The prevalence of heart failure in developed countries is about 1–2% in general and over 10% in patients above 70 years (1). Despite improvement in treatment, the prognosis of CHF is still poor, and more than 50% of hospitalized patients with CHF die within 5 years. Patients with CHF commonly suffer from breathing disorders during sleep (2, 3). Sleep disorder breathing (SDB) is a highly prevalent comorbidity in CHF patients, which has adverse effects on the prognosis of CHF. The presence of breathing disorders during sleep in patients with CHF is associated with increased risk of cardiovascular disease and mortality (4, 5). There are two different types of SDB in patients with HF: obstructive sleep apnea (OSA) and central sleep apnea (CSA) (6, 7).

Severe tricuspid regurgitation (TR) is a complex condition of the right ventricle (RV) and tricuspid valve apparatus and is frequently associated with symptomatic heart failure (8). The etiology of TR can be divided into primary and secondary causes. Primary TR may be caused by congenital, traumatic, rheumatic, and endomyocardial fibrosis. In these patients, left heart diseases could lead to chronic pressure overload of the RV, which eventually resulted in progressive RV expansion and functional TR. In patients with severe TR, medical therapy restricted to diuretics and heart failure medication is frequently infective, and surgical repair is associated with a high

risk of morbidity and mortality (9, 10). In addition, neither one of these treatment options has demonstrated beneficial long-term effects. Therefore, multiple innovative interventional treatment concepts to replace or repair tricuspid valve function are currently under investigation.

CAVI has been suggested as one of these interventional concepts. In the pathological cascade of tricuspid valve disease, CAVI aims at the caval backflow that occurs at a late stage of severe TR (11). One previous study showed a decrease in the apnea–hypopnea index (AHI) after heart transplantation and medical treatment in a population of CSA patients with congestive heart failure group ($n = 13$) (12). Another study showed that one 64-year-old male patient with CSA improved his sleep, daytime hypersommolence, dyspnea, and fatigue after mitral valve transplantation (13). There has only been one randomized controlled trial that showed that transcatheter aortic valve replacement in patients with CHF and TR did not show positive effects on SDB (8, 10). The aim of our study was to examine whether CAVI has an effect on SDB in patients with right heart failure and TR.

MATERIALS AND METHODS

Study Design and Collection of Data

Our investigation was added on top of a previous study (11). This was a single-center, nonblinded study. Between January 2015 and November 2019, 29 consecutive right heart failure patients with severe symptomatic TR were divided into the CAVI group ($n = 14$) and the control group ($n = 15$), treated with optimal medical therapy (OMT) alone. The CAVI procedures were successful in all patients. An indicator of success was that CAVI resulted in the full reduction of reverse caval flow as confirmed by a significant reduction in the inferior vena cava (IVC) v-wave in all patients; this is already known in a previous study (9). Four major complications in the CAVI group that occurred within 48 h after implantation and resulted in open-heart surgery (two cases of cardiac tamponade secondary to stent migration and two valve dislocations) were excluded. After the fourth major complication, recruitment was stopped for safety. Five patients in the control group did not receive portable monitoring results and were excluded from this study. Patients with severe symptomatic TR were screened for SDB using a three-channel screening system (ApneaLink, Resmed). Data were collected at baseline and at 1-month follow-up from medical records. Portable monitoring was performed in 20 patients for SDB assessment. To diagnose SDB, AHI had to be 10/h or above. According to the value of the AHI, we divided the patients into four groups: control-SDB ($n = 8$), CAVI-SDB ($n = 3$), CAVI-no-SDB ($n = 7$), and control-no-SDB ($n = 2$) (**Figure 1**). All patients provided informed consent, and treatment was performed after the approval of the local ethics committee (Landesamt fur Gesundheit und Soziales Berlin, Germany).

Patient Screening and Follow-Up

The inclusion criteria were the same as those defined by a previous study (11): (1) TR severity ≥ severe; (2) New York Heart Association (NYHA) functional class II or greater despite the established OMT; (3) age ≥ 50 years; and (4) high surgical risk. This study required that cardiac surgeons, interventional and non-interventional cardiologists, anesthesiologists, and imaging experts completed the evaluation and acceptance of CAVI patients. Routine preoperative examinations include transthoracic echocardiography, cardiopulmonary exercise, and laboratory examinations.

Exclusion criteria were as follows: (1) IVC diameter > 31 mm; (2) ongoing treatment of SDB; (3) inability to undergo portable monitoring; (4) serum creatinine concentration > 3.0 mg/dl; (5) patients for whom informed consent cannot be obtained; (6) chronic kidney disease undergoing regular dialysis; and (7) left ventricular ejection fraction < 30%. We offered CAVI to all severe symptomatic TR patients with SDB who met the inclusion criteria (11).

Portable Monitoring

ApneaLink (Resmed) is a three-channel, portable device that uses a nasal pressure transducer to derive the AHI, flow limitation, and snoring, in addition to monitoring oxygen saturation during sleep. The oxygen desaturation index (ODI) was measured with the AL during the simultaneous study. The AL device operates on battery power, with a sampling rate of 100 Hz, and has a 16-bit signal processor. The internal memory storage is 15 MB, which allows ∼10 h of data collection. The software analyzes the data generated by the flow signal, whereas full disclosure of data is available for review and rescoring by the clinician. AHI ≥ 10/h was defined as SDB in this study.

CAVI Procedure

All implantations were performed through transfemoral venous access under local anesthesia and transthoracic echocardiography. After preparing the landing area by implanting a self-expanding stent (Sinus-XL, Optimed, Ettlingen, Germany) to facilitate valve fixation, the Sapien XT transcatheter valve (Edwards Lifesciences, Irvine, CA) was implanted in the IVC at the level of the diaphragm and protruding ≈5 mm into the right atrium (RA) (11).

Laboratory Testing and Echocardiography

Blood sample collection: a nurse collected 2 ml venous blood, injected it into an anticoagulation tube, and fully blended it for later use. A biochemical auto-analyzer was applied to examine the eGFR. All patients underwent our standard 2-D and 3-D transthoracic and transesophageal echocardiography. Echocardiographic parameters included LVEF, RV-FAC, TAPSE, and the tissue Doppler E/E' ratio. All recordings were performed on ultrasound systems.

Lung Function and Cardiopulmonary Exercise Testing

Spirometry (FEV1, FVC; FEV1/FVC ratio), measurement of static lung volumes (total lung capacity (TLC) by body box plethysmography), and measurement of diffusing capacity of the lung for carbon monoxide (DLCO) by the single-breath technique were performed (Vmax22, SensorMedics, Yorba Linda, CA, USA) with the patient in the seated position. Testing

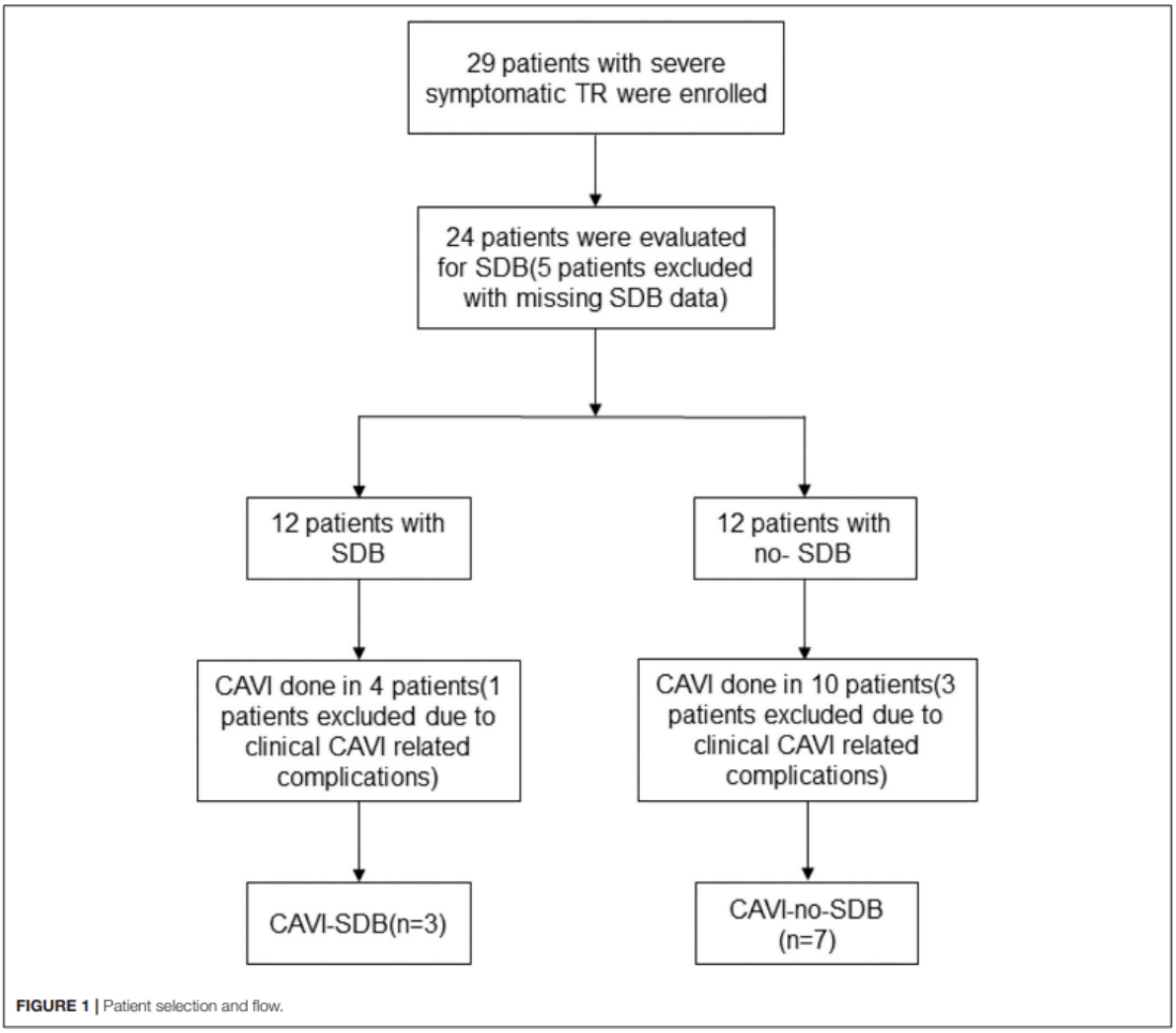

FIGURE 1 | Patient selection and flow.

protocols adhered to guidelines for calibration and testing recommended by the ATS/ERS standards. All patients performed a symptom-limited CPET by using a cycle ergometer protocol, which is cycling with a pedal speed of 60 rpm, starting at a workload of 20 W, followed by a stepwise 20-W increment every 2 min until exhaustion. AT was identified through a V-slope analysis of VO_2 and CO_2 production (VCO_2), and it was confirmed through the specific behavior of the ventilatory equivalents of O_2 (VE/VO_2) and CO_2 (VE/VCO_2), as well as through the end-tidal O_2 and CO_2 pressure. The relation between VE and VCO_2 was analyzed as the slope (VE/VCO_2 slope).

Statistical Analysis

Descriptive statistics (means and standard deviations) were used to describe baseline characteristics. Categorical variables are expressed as numbers (n) and percentages (%). Our data follow a normal distribution and were analyzed using a paired t-test and independent sample t-test for within-group and between-group comparisons, respectively. A value of $p < 0.05$ means statistically significant. All statistical data were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

RESULTS

The general characteristics of the participants at baseline are presented in **Table 1**. No significant differences in sex, age, body mass index (BMI), ejection fraction, NYHA functional class, and medications were observed between groups. All patients were taking loop diuretics, and they all had severe symptomatic TR. There were no changes in medication during the study.

Comparisons between CAVI -SDB and CAVI-no-SDB groups are displayed in **Table 2**. There were no significant changes of

TABLE 1 | Baseline clinical data comparisons.

Characteristic	CAVI-SDB ($n = 3$)	CAVI-no-SDB ($n = 7$)	*P*-value
Age, years	81 ± 3	69 ± 8	0.057
Female	2 (66.7%)	6 (85.7%)	1.000
Male	1 (33.3%)	1 (14.3%)	
BMI, kg/m^2	29 ± 7	25 ± 4	0.233
NYHA			1.000
II	0 (0%)	0 (0%)	
III	3 (100%)	7 (100%)	
IV	0 (0%)	0 (0%)	
PAP mean, mmHg	26 ± 5	29 ± 18	0.814
PCWP mean, mmHg	16 ± 6	16 ± 9	0.975
Arterial hypertension	3 (100%)	7 (100%)	–
Nicotine abuse	1 (33.3%)	1 (14.3%)	1.000
COPD	1 (33.3%)	4 (57.1%)	1.000
GFR, ml/min	35 ± 16	49 ± 23	0.365
Diabetes mellitus			1.000
No diabetes	2 (66.7%)	5 (71.4%)	
Type 1	0 (0%)	1 (14.3%)	
Type 2	1 (33.3%)	1 (14.3%)	
LVEF, %	54 ± 10	61 ± 2	0.360
Medication			
Beta blocker	3 (100%)	7 (100%)	–
Loop diuretics	3 (100%)	7 (100%)	–
Aldosterone antagonist	1 (33.3%)	3 (42.9%)	1.000
Statin	2 (66.7%)	3 (42.9%)	1.000
ACE	2 (66.7%)	6 (85.7%)	1.000
Antiplatelet	2 (66.7%)	3 (42.9%)	1.000
Oral anticoagulant	2 (66.7%)	1 (14.3%)	0.183
Calcium antagonist	1 (33.3%)	2 (28.6%)	1.000
Antiarrhythmic	0 (0%)	0 (0%)	–

BMI, body mass index; ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; COPD, Chronic Obstructive Pulmonary Disease; PAP, Pulmonary Artery Pressure; PCWP, Pulmonary Capillary Wedge Pressure; GFR, Glomerular filtration rate. Data were presented as mean ± SD or n (%). None of the variables is statistically significant.

all parameters before and after treatment in both groups ($p > 0.05$). By design, significant differences of tissue Doppler E/E, FVC % pred, FEV1, and FEV1 % pred were observed before the treatment between groups ($p < 0.05$). There were significant differences of LVEF, RVFAC, AHI, and ODI after the treatment between groups ($p < 0.05$).

DISCUSSION

To the best of our knowledge, this is the first time to investigate the effect of CAVI on SDB in patients with right heart failure and severe symptomatic TR. The main finding from this investigation showed that CAVI had no obvious effect on SDB in patients with HF and TR.

Previous studies have indicated that SDB is associated with postoperative complications after general and cardiac surgery (14–16). In another study, they found SDB to be associated with a higher rate of long-term cardiovascular events after coronary artery bypass grafting (17). A study found that SDB is highly prevalent in patients undergoing cardiovascular surgery. However, in this population, the authors did not find an association between SDB and adverse postoperative outcomes due to a relatively small sample size (107 patients) (18). In our study, we also did not find any association between SDB and adverse outcome after CAVI.

SDB is known to be associated with heart disease, e.g., heart failure, coronary artery disease, and atrial fibrillation (19), but less is known about its prevalence in valve diseases. Past studies indicated a high prevalence of SDB in patients with severe aortic stenosis. Printz et al. (20) reported SDB in 15 out of 42 individuals (36%) with high-grade aortic stenosis. In our study cohort of patients with severe symptomatic tricuspid regurgitation before CAVI, the prevalence of SDB was as high as 50%. Although the total number of subjects is very small, these findings should increase the awareness of existence of SDB in patients with severe symptomatic tricuspid regurgitation.

The relation of subclinical lung function impairment with cardiovascular diseases in the absence of diagnosed pulmonary diseases has recently drawn more attention. In a cohort with long-term follow-up, low FEV1 was strongly and independently associated with incident CHF (21). A population-based study of middle-aged men observed the association between moderately reduced FEV1 and FVC and incident heart failure hospitalization (22). In our population based on relatively older subjects and limited patients sample, we demonstrated that there were no significant differences between FEV1, FEV1/FVC, and TLC after CAVI ($p > 0.05$; **Table 2**).

A previous study showed that an increasing VE/VCO_2 slope was a potential negative sign (23). As presented in **Table 2,** the VE/VCO_2 slope showed no obvious changes post-CAVI probably due to our very small sample size. The past study showed that the VE/VCO_2 slope was insignificantly correlated with the AHI, and patients with CHF-SDB have hyperpnea not only during sleep but also during exercise (24). However, the correlation coefficient between the VE/VCO_2 slope and the AHI was less than between chemosensitivity and the AHI. Chemosensitivity could not be observed, and it was speculated that the steeper VE/VCO_2 slope was caused by augmented chemosensitivity (25). The VE/VCO_2 slope of CHF-SDB patients increases due to increased abnormal ventilation and perfusion and physiological lung dead space.

In a mixed sample of patients with HF and mitral or aortic valve disease, they showed an improvement of SDB after heart valve surgery (26). The CAVI procedure is a recently developed method of valve replacement for use in patients with severe tricuspid regurgitation, who cannot undergo surgery or who have a high perioperative risk (27). There were no significant differences for sleep variables between pre- and post-CAVI. This could not support that SDB is another manifestation of cardiac dysfunction. Additionally, the risk for four patients experiencing severe clinical issues after CAVI in our study was 28%. Although, to date, only limited clinical data are available regarding the efficacy of transcatheter tricuspid valve intervention (TTVI), feasibility has been shown with different techniques, including annuloplasty devices (28–30) and

TABLE 2 | Comparisons between CAVI-SDB and CAVI-no-SDB group.

Variables	CAVI-SDB			CAVI-no-SDB				
	Pre	Post	*P*	Pre	Post	*P*	*P**	*P*#
LVEF, %	54 ± 10	49 ± 9	0.383	61 ± 2	63 ± 6	0.321	0.360	**0.021**
RVFAC, %	12 ± 0	30 ± 2	–	44 ± 13	48 ± 10	0.211	0.062	**0.043**
TAPSE, mm	17 ± 11	17 ± 9	0.853	16 ± 3	18 ± 2	0.253	0.974	0.947
Tissue Doppler E/E	48 ± 0	12 ± 8	–	15 ± 8	16 ± 9	0.258	**0.014**	0.541
FVC (L)	3 ± 1	3 ± 1	0.595	2 ± 1	1	(a)	0.053	0.452
FVC % pred	96 ± 18	104 ± 16	0.691	58 ± 19	57	(a)	**0.017**	0.255
FEV1, L	2 ± 0	2 ± 0	0.874	1 ± 0	1	(a)	**0.025**	0.263
FEV1, %	92 ± 28	103 ± 24	0.795	51 ± 16	38	(a)	**0.017**	0.273
FEV1/FVC, %	74 ± 11	76 ± 10	0.805	74 ± 7	56	(a)	0.976	0.350
TLC, L	5 ± 1	6 ± 1	0.772	5 ± 1	5	(a)	0.701	0.744
TLC % pred	91 ± 15	102 ± 9	0.677	90 ± 21	105	(a)	0.955	0.854
DLCO, mmol/min/kPa	5 ± 0	5 ± 1	0.670	4 ± 1	1	(a)	0.105	0.123
DLCO, %	74 ± 14	76 ± 9	0.726	51 ± 14	18	(a)	0.125	0.116
VO_2AT, ml/min/kg	8 ± 5	6 ± 3	0.425	8 ± 2	8 ± 1	0.612	0.900	0.289
VE/VCO_2 slope	41 ± 3	47 ± 1	0.205	41 ± 5	44 ± 10	0.600	0.960	0.777
eGFR, ml/min	35 ± 16	31 ± 9	0.594	49 ± 23	42 ± 18	0.295	0.365	0.386
AHI, events/h	24 ± 13	31 ± 0	0.674	3 ± 3	2 ± 2	0.701	0.098	**<0.001**
ODI, events/h	23 ± 14	35 ± 0	0.272	3 ± 4	3 ± 3	0.162	0.130	**<0.001**
MeanSPO_2, %	92 ± 2	94 ± 1	0.205	94 ± 3	92 ± 3	0.342	0.236	0.634
MinSPO_2, %	70 ± 18	81 ± 2	0.874	80 ± 11	72 ± 13	0.089	0.311	0.415
*t*90 (SaO_2 < 90% min)	157 ± 75	60 ± 49	0.137	68 ± 132	170 ± 194	0.598	0.333	0.483

Data were presented as mean ± SD; AHI, apnea/hypopnea index; AI, apnea index; ODI, Oxygen Desaturation Index; minSPO_2, minimal pulse oxyhemoglobin saturation; t90, oxygen saturation (SaO_2) < 90%; mean SPO_2, mean pulse oxyhemoglobin saturation; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change; TAPSE. tricuspid annular plane systolic excursion; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; VE/VCO2 slope, rate of increase in ventilation per unit increase in carbon dioxide; TLC, total lung capacity.

P, Paired sample test.

P and P#: Independent sample t-test; P* means the comparisons between groups for the pre time point; P# means the comparisons between groups for the post time point.*

(a) means no testing only 1 subject for the post time point of the control-SDB group; The bold values show significant difference.

leaflet and coaptation devices (31, 32), both in the heterotopic (CAVI; to reduce the backflow in the venous system) and the orthotopic positions. Despite the increased risk of the patients, the current report confirms the safety and feasibility of TTVI: intraprocedural mortality was 0%, 30-day mortality and periprocedural adverse events did not change, and procedural success improved significantly, from 62 to 72.8%. Clinical experience started in 2011, when CAVI was first reported for compassionate treatment of patients with severe TR using investigational self-expandable valves. Since then, compassionate clinical use has confirmed the technical feasibility of CAVI (33). Improved procedural success is likely multifactorial and related to the following: the early learning curve effect in CAVI, which is common and universal for new devices and techniques; a better understanding of TV anatomy and disease pathophysiology; and improved and more standardized intraprocedural guidance (34).

A previous study suggested that perioperative continuous positive airway pressure (CPAP) treatment could improve the AHI. Effective treatment of SDB can alleviate diastolic dysfunction (35). Whereas SDB did not improve significantly after CAVI, in this small patient cohort, we were unable to demonstrate a direct correlation between SDB improvement and CAVI procedure. The pathogenesis of SDB in HF is complex and remains to be incompletely understood. It is unclear whether SDB directly affects chronic HF pathophysiology. Therefore, the causal link to the prognosis of HF is not clear. Possibly SDB is rather an index for the severity of HF. Further studies with larger sample sizes and with pre- and post-operative evaluations are necessary.

STUDY LIMITATIONS

There are many limitations of the current pilot study that need to be addressed. Our study was nonblinded and conducted about 30 days after the intervention. This is a fairly short interval for the patients to adapt to the new hemodynamic condition. Therefore, it is recommended to repeat a double-blinded study with longer periods for follow-up. The individual differences of the participants, such as their gender, age, and psychological condition, might also influence the pattern and quality of sleep. Moreover, our results are based on single-night portable monitoring; therefore, internight variations remain to be unaccounted for. Finally, this study was stopped early because of a major complication after CAVI, carried out in a single center and on a small sample of elderly people.

Multicenter studies with large sample sizes are needed for improving outcomes.

CONCLUSION

In summary, these data suggest that CAVI may not have an effect on SDB; however, additional follow-up fully powered studies with appropriate statistical analyses are needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Landesamt fur Gesundheit und Soziales Berlin, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW, RB, and RF contributed to the data collection and analysis. CS planed the study, is the guarantor of the manuscript, and assumes responsibility for the integrity of the data. TP contributed to coordinating this project. All authors contributed to drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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REFERENCES

1. Mosterd A, Hoes AW. (2007). Clinical epidemiology of heart failure. *Heart.* 93, 1137–46. doi: 10.1136/hrt.2003.025270
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* (2013) 177:1006–14. doi: 10.1093/aje/kws342
3. Sánchez-De-La-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med.* (2013) 1:61–72. doi: 10.1016/S2213-2600(12)70051-6
4. Farrell PC, Richards G. Recognition and treatment of sleep-disordered breathing: an important component of chronic disease management. *J Transl Med.* (2017) 15:114. doi: 10.1186/s12967-017-1211-y
5. Vazir A, Sundaram V. Management of sleep apnea in heart failure. *Heart Fail Clin.* (2018) 14:635–42. doi: 10.1016/j.hfc.2018.06.008
6. Yoshihisa A, Suzuki S, Yamauchi H, Sato T, Oikawa M, Kobayashi A, et al. Beneficial effects of positive airway pressure therapy for sleep-disordered breathing in heart failure patients with preserved left ventricular ejection fraction. *Clin Cardiol.* (2015) 38:413–21. doi: 10.1002/clc.22412
7. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. *Respirology.* (2017) 22:43–52. doi: 10.1111/resp.12927
8. Takagi H, Hari Y, Kawai N, Ando T, Group A. Impact of concurrent tricuspid regurgitation on mortality after transcatheter aortic-valve implantation. *Catheter Cardiovasc Interv.* (2019) 93:946–53. doi: 10.1002/ccd.27948
9. Lauten A, Dreger H, Schofer J, Grube E, Beckhoff F, Jakob P, et al. Caval valve implantation for treatment of severe tricuspid regurgitation. *J Am Coll Cardiol.* (2018) 71:1183–4. doi: 10.1016/j.jacc.2017.12.056
10. Fan J, Liu X, Yu L, Sun Y, Jaiswal S, Zhu Q, et al. Impact of tricuspid regurgitation and right ventricular dysfunction on outcomes after transcatheter aortic valve replacement: a systematic review and meta-analysis. *Clin Cardiol.* (2019) 42:206–12. doi: 10.1002/clc.23126
11. Laule M, Mattig I, Schobel C, Knebel F, Lauten A, Lembcke A, et al. Inferior caval valve implantation versus optimal medical therapy for severe tricuspid regurgitation. *J Am Coll Cardiol.* (2019) 74:473–5. doi: 10.1016/j.jacc.2019.05.019
12. Mansfield DR, Solin P, Roebuck T, Bergin P, Kaye DM, Naughton MT. The effect of successful heart transplant treatment of heart failure on central sleep apnea. *Chest.* (2003) 124:1675–81. doi: 10.1378/chest.124.5.1675
13. Rubin AE, Gottlieb SH, Gold AR, Schwartz AR, Smith PL. Elimination of central sleep apnoea by mitral valvuloplasty: the role of feedback delay in periodic breathing. *Thorax.* (2004) 59:174–6. doi: 10.1136/thorax.2003.007799
14. Abdelsattar ZM, Hendren S, Wong SL, Campbell DAJr, Ramachandran SK. The impact of untreated obstructive sleep apnea on cardiopulmonary complications in general and vascular surgery: a cohort study. *Sleep.* (2015) 38:1205–10. doi: 10.5665/sleep.4892
15. Wong JK, Maxwell BG, Kushida CA, Sainani KL, Lobato RL, Woo YJ, et al. Obstructive sleep apnea is an independent predictor of postoperative atrial fibrillation in cardiac surgery. *J Cardiothorac Vasc Anesth.* (2015) 29:1140–7. doi: 10.1053/j.jvca.2015.03.024
16. De Raaff CA, Bindt DM, De Vries N, Van Wagensveld BA. Positional obstructive sleep apnea in bariatric surgery patients: risk factor for postoperative cardiopulmonary complications? *Sleep Breath.* (2016) 20:113–9. doi: 10.1007/s11325-015-1192-0
17. Uchôa CHG, Danzi-Soares NJ, Nunes FS, de Souza AAL, Nerbass FB, Pedrosa RP. Impact of OSA on cardiovascular events after coronary artery bypass surgery. *Chest.* (2015) 147:1352–60. doi: 10.1378/chest.14-2152
18. Foldvary-Schaefer N, Kaw R, Collop N, Andrews ND, Bena J, Wang L, et al. Prevalence of undetected sleep apnea in patients undergoing cardiovascular surgery and impact on postoperative outcomes. *J Clin Sleep Med.* (2015) 11:1083–9. doi: 10.5664/jcsm.5076
19. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet.* (2009) 373:82–93. doi: 10.1016/S0140-6736(08)61622-0
20. Prinz C, Bitter T, Oldenburg O, Faber L, Horstkotte D, Piper C. Sleep apnoea in severe aortic stenosis. *Postgrad Med J.* (2011) 87:458–62. doi: 10.1136/pgmj.2010.112052
21. Agarwal SK, Heiss G, Barr RG, Chang PP, Loehr LR, Chambless LE, et al. Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Heart Fail.* (2012) 14:414–22. doi: 10.1093/eurjhf/hfs016
22. Engstrom G, Melander O, Hedblad B. Population-based study of lung function and incidence of heart failure hospitalisations. *Thorax.* (2010) 65:633–8. doi: 10.1136/thx.2010.135392

23. Servantes DM, Javaheri S, Kravchychyn ACP, Storti LJ, Almeida DR, De Mello MT, et al. Effects of exercise training and CPAP in patients with heart failure and OSA: a preliminary study. *Chest.* (2018) 154:808–17. doi: 10.1016/j.chest.2018.05.011
24. Meguro K, Adachi H, Oshima S, Taniguchi K, Nagai R. Exercise tolerance, exercise hyperpnea and central chemosensitivity to carbon dioxide in sleep apnea syndrome in heart failure patients. *Circ J.* (2005) 69:695–9. doi: 10.1253/circj.69.695
25. Arzt M, Harth M, Luchner A, Muders F, Holmer SR, Blumberg FC, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and central sleep apnea. *Circulation.* (2003) 107:1998–2003. doi: 10.1161/01.CIR.0000065227.04025.C2
26. Redline S, Lewis EF. Gravitational influences and shifting propensity for sleep apnea: another source of heterogeneity or a new intervention target? *Circulation.* (2010) 121:1583–5. doi: 10.1161/CIR.0b013e3181dd3e5f
27. Del Forno B, Lapenna E, Dalrymple-Hay M, Taramasso M, Castiglioni A, Alfieri O, et al. Recent advances in managing tricuspid regurgitation. *F1000Res.* (2018) 7:355. doi: 10.12688/f1000research.13328.1
28. Lin G, Nishimura RA, Connolly HM, Dearani JA, Sundt TM 3rd, Hayes DL. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J Am Coll Cardiol.* (2005) 45:1672–5. doi: 10.1016/j.jacc.2005.02.037
29. Hahn RT, Meduri CU, Davidson CJ, Lim S, Nazif TM, Ricciardi MJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. *J Am Coll Cardiol.* (2017) 69:1795–806. doi: 10.1016/j.jacc.2017.01.054
30. Kuwata S, Taramasso M, Nietlispach F, Maisano F. Transcatheter tricuspid valve repair toward a surgical standard: first-in-man report of direct annuloplasty with a cardioband device to treat severe functional tricuspid regurgitation. *Eur Heart J.* (2017) 38:1261. doi: 10.1093/eurheartj/ehw660
31. Nickenig G, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, et al. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. *Circulation.* (2017) 135:1802–14. doi: 10.1161/CIRCULATIONAHA.116.024848
32. Fam NP, Ho EC, Zahrani M, Samargandy S, Connelly KA. Transcatheter tricuspid valve repair with the PASCAL system. *JACC Cardiovasc Interv.* (2018) 11:407–8. doi: 10.1016/j.jcin.2017.12.004
33. Lauten A, Doenst T, Hamadanchi A, Franz M, Figulla HR. Percutaneous bicaval valve implantation for transcatheter treatment of tricuspid regurgitation: clinical observations and 12-month follow-up. *Circ Cardiovasc Interv.* (2014) 7:268–72. doi: 10.1161/CIRCINTERVENTIONS.113.001033
34. Taramasso M, Zuber M, Kuwata S, Nietlispach F, Maisano F. Clipping of the tricuspid valve: proposal of a "Rosetta Stone" nomenclature for procedural 3D transoesophageal guidance. *Eurointervention.* (2017) 12:e1825–e7. doi: 10.4244/EIJ-D-16-00307
35. Gupta N, Agrawal S, Goel AD, Ish P, Chakrabarti S, Suri JC. Profile of sleep disordered breathing in heart failure with preserved ejection fraction. *Monaldi Arch Chest Dis.* (2020) 90:660–5. doi: 10.4081/monaldi.2020.1329

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
Selected Categories: **"CLINICAL NEUROLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 208 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET NEUROLOGY	43,457	44.182	0.059560
2	Nature Reviews Neurology	15,738	42.937	0.029580
3	Alzheimers & Dementia	21,824	21.566	0.045940
4	JAMA Neurology	17,086	18.302	0.043360
5	ACTA NEUROPATHOLOGICA	28,031	17.088	0.036970
6	BRAIN	64,627	13.501	0.061550
7	NEURO-ONCOLOGY	17,812	12.300	0.029210
8	SLEEP MEDICINE REVIEWS	11,218	11.609	0.014840
9	ANNALS OF NEUROLOGY	43,728	10.422	0.039960
10	MOVEMENT DISORDERS	35,072	10.338	0.030790
11	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	37,094	10.154	0.026380
12	NEUROLOGY	109,905	9.910	0.097500
13	Brain Stimulation	9,206	8.955	0.015960
14	Neurology-Neuroimmunology & Neuroinflammation	3,863	8.485	0.008390
15	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	4,791	8.090	0.004640
16	STROKE	78,912	7.914	0.068320
17	Neurotherapeutics	6,764	7.620	0.009400
18	NEUROSCIENTIST	5,949	7.519	0.005010
19	Epilepsy Currents	1,246	7.500	0.001750
20	JOURNAL OF HEADACHE AND PAIN	5,400	7.277	0.008140

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	Alzheimers Research & Therapy	5,593	6.982	0.011680
22	Journal of Stroke	1,692	6.967	0.003950
23	PAIN	45,325	6.961	0.031030
24	Translational Stroke Research	3,377	6.829	0.003920
25	BIPOLAR DISORDERS	6,185	6.744	0.007510
26	Therapeutic Advances in Neurological Disorders	2,328	6.570	0.004000
27	BRAIN PATHOLOGY	6,559	6.508	0.006220
28	Multiple Sclerosis Journal	15,551	6.312	0.016680
29	CEPHALALGIA	12,756	6.292	0.011940
30	EUROPEAN JOURNAL OF NEUROLOGY	14,490	6.089	0.016730
31	HEADACHE	10,445	5.887	0.009580
32	EPILEPSIA	33,890	5.864	0.026030
33	SLEEP	28,688	5.849	0.023920
34	JOURNAL OF PAIN	13,655	5.820	0.014690
35	Neurology and Therapy	711	5.814	0.001590
36	CNS DRUGS	5,948	5.749	0.007070
37	Pain and Therapy	620	5.725	0.001240
38	CURRENT OPINION IN NEUROLOGY	6,723	5.710	0.008480
39	DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY	16,571	5.449	0.011470
40	Nature and Science of Sleep	1,240	5.346	0.002290
41	EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE	5,451	5.270	0.005150
42	JOURNAL OF NEUROTRAUMA	19,004	5.269	0.018210

Selected JCR Year: 2020; Selected Categories: "CLINICAL NEUROLOGY"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
43	International Journal of Stroke	6,321	5.266	0.014130
44	PSYCHIATRY AND CLINICAL NEUROSCIENCES	5,454	5.188	0.004700
45	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	7,865	5.176	0.008440
46	JOURNAL OF NEUROSURGERY	43,275	5.115	0.027680
47	Current Neurology and Neuroscience Reports	4,549	5.081	0.007300
48	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	13,777	5.067	0.013440
49	Pain Physician	6,424	4.965	0.006760
50	Journal of Neurogastroenterology and Motility	2,217	4.924	0.003800
51	PARKINSONISM & RELATED DISORDERS	13,674	4.891	0.018700
52	JOURNAL OF NEUROLOGY	21,116	4.849	0.021660
53	JOURNAL OF AFFECTIVE DISORDERS	46,992	4.839	0.062720
54	NEUROMODULATION	4,447	4.722	0.005540
55	JPAD-Journal of Prevention of Alzheimers Disease	649	4.671	0.001470
56	NEUROSURGERY	34,635	4.654	0.022250
57	Expert Review of Neurotherapeutics	5,314	4.618	0.005630
58	EUROPEAN NEUROPSYCHOPHARMACOLOGY	8,999	4.600	0.011190
59	Annals of Clinical and Translational Neurology	4,188	4.511	0.012270
60	Sleep Health	2,255	4.450	0.006090
61	CLINICAL AUTONOMIC RESEARCH	2,164	4.435	0.002530
62	Multiple Sclerosis and Related Disorders	5,292	4.339	0.008880
63	NEUROMUSCULAR DISORDERS	6,588	4.296	0.007410
64	Spine Journal	12,504	4.166	0.016130

Selected JCR Year: 2020; Selected Categories: "CLINICAL NEUROLOGY"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
65	JOURNAL OF PSYCHOPHARMACOLOGY	8,158	4.153	0.010010
66	JOURNAL OF NEURO-ONCOLOGY	15,608	4.130	0.016390
67	Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration	4,709	4.092	0.005160
68	Stroke and Vascular Neurology	1,005	4.081	0.002390
69	Journal of Clinical Sleep Medicine	9,720	4.062	0.013760
70	Neurosurgical Focus	9,818	4.047	0.011120
71	Journal of Neurodevelopmental Disorders	1,819	4.025	0.002850
72	Frontiers in Neurology	18,626	4.003	0.040660
73	JOURNAL OF SLEEP RESEARCH	8,023	3.981	0.007750
74	JOURNAL OF NEUROSURGICAL ANESTHESIOLOGY	1,988	3.956	0.001470
75	EUROPEAN JOURNAL OF PAIN	9,204	3.931	0.009110
76	NEUROREHABILITATION AND NEURAL REPAIR	6,710	3.919	0.006880
77	AMERICAN JOURNAL OF NEURORADIOLOGY	27,423	3.825	0.024030
78	NEUROLOGIC CLINICS	3,097	3.806	0.003060
79	CNS SPECTRUMS	3,177	3.790	0.003600
80	NEUROPHYSIOLOGIE CLINIQUE-CLINICAL NEUROPHYSIOLOGY	1,825	3.734	0.001950
81	CLINICAL NEUROPHYSIOLOGY	23,593	3.708	0.018330
82	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	11,189	3.685	0.006630
83	Clinical Neuroradiology	1,298	3.649	0.002610
83	Journal of Neurologic Physical Therapy	1,491	3.649	0.001510
85	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	15,063	3.612	0.015920
86	JOURNAL OF NEUROSURGERY-SPINE	10,175	3.602	0.011700

Selected JCR Year: 2020; Selected Categories: "CLINICAL NEUROLOGY"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
87	Current Treatment Options in Neurology	1,809	3.598	0.002790
87	NEUROGASTROENTEROLOGY AND MOTILITY	10,724	3.598	0.013180
89	JOURNAL OF NEURAL TRANSMISSION	8,972	3.575	0.007300
90	CLINICAL NEUROPSYCHOLOGIST	5,144	3.535	0.003220
91	Current Alzheimer Research	5,357	3.498	0.005380
92	Current Pain and Headache Reports	3,117	3.494	0.003550
92	JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM	2,264	3.494	0.001980
94	Neurospine	498	3.492	0.000920
94	SLEEP MEDICINE	14,810	3.492	0.016190
96	Neurology-Genetics	1,218	3.485	0.003910
97	SPINE	53,384	3.468	0.024770
98	JOURNAL OF NEURORADIOLOGY	1,475	3.447	0.001920
99	CLINICAL JOURNAL OF PAIN	8,589	3.442	0.007510
100	SEMINARS IN NEUROLOGY	2,594	3.420	0.003420
101	PEDIATRIC NEUROLOGY	7,192	3.372	0.007700
102	BEHAVIOURAL NEUROLOGY	2,030	3.342	0.002390
103	NEUROLOGICAL SCIENCES	8,857	3.307	0.009240
104	Brain Tumor Pathology	866	3.298	0.001020
105	NEUROEPIDEMIOLOGY	4,484	3.282	0.004260
106	MUSCLE & NERVE	15,760	3.217	0.012520
107	Neurocritical Care	5,603	3.210	0.006420
108	ACTA NEUROLOGICA SCANDINAVICA	8,457	3.209	0.006230

Selected JCR Year: 2020; Selected Categories: "CLINICAL NEUROLOGY"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
109	SEIZURE-EUROPEAN JOURNAL OF EPILEPSY	8,044	3.184	0.010950
110	Pain Practice	3,187	3.183	0.003750
111	JOURNAL OF THE NEUROLOGICAL SCIENCES	22,390	3.181	0.018500
112	EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY	3,856	3.140	0.005240
113	EUROPEAN SPINE JOURNAL	20,361	3.134	0.018870
114	Journal of Pain Research	5,058	3.133	0.010270
115	NEUROLOGIA	1,877	3.109	0.002140
116	Journal of Clinical Neurology	2,091	3.077	0.003400
117	EPILEPSY RESEARCH	8,587	3.045	0.007730
118	JOURNAL OF NEURO-OPHTHALMOLOGY	2,206	3.042	0.002660
118	NEUROSURGICAL REVIEW	3,616	3.042	0.003650
120	Pain Research & Management	2,523	3.037	0.002830
121	BRAIN TOPOGRAPHY	3,130	3.020	0.003750
122	Korean Journal of Pain	792	3.016	0.000970
123	Neurodegenerative Diseases	1,798	2.977	0.001400
124	Behavioral Sleep Medicine	2,032	2.964	0.002610
125	DEMENTIA AND GERIATRIC COGNITIVE DISORDERS	5,326	2.959	0.003020
126	EPILEPSY & BEHAVIOR	14,990	2.937	0.016830
127	Global Spine Journal	2,389	2.915	0.005530
128	JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY	8,866	2.892	0.005620
129	Sleep and Breathing	4,728	2.816	0.005870
130	NEURORADIOLOGY	6,702	2.804	0.005900

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Sleep and Breathing
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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Effects of sacubitril-valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction

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Abstract

Objective This study aimed to evaluate the effect of sacubitril-valsartan (SV) on central apneas (CA) and obstructive apneas (OA) in patients with heart failure with reduced ejection fraction (HFrEF).

Methods In patients with HFrEF, SV initiation was titrated to the highest tolerable dosage. Patients were evaluated with portable apnea monitoring, echocardiography, and cardiopulmonary exercise testing at baseline and 3 months later.

Results Of a total of 18 patients, 9 (50%) had OA, 7 (39%) had CA, and 2 (11%) had normal breathing. SV therapy was related to a reduction in NT-pro BNP and an improvement in LV function after 3 months. Portable apnea monitoring revealed a significant decrease of the respiratory event index (REI) after treatment with SV (20 ± 23 events/h to 7 ± 7 events/h, $p = 0.003$). When subgrouping according to type of apneas, REI, and time spent below 90% saturation (T90) decreased in patients with CA and OA (all $p < 0.05$).

Conclusion In this prospective study, SV treatment for 3 months in patients with CA and OA is associated with a significant decrease in REI.

Keywords Heart failure · Sacubitril-valsartan · ARNI · Central apneas · Obstructive apneas

Introduction

Heart failure (HF) is now recognized as a severe health issue affecting almost 65 million people of all ages worldwide. The prevalence of HF is 1–2% in patients over 65 years old, and it appears to be increasing in developed countries [1]. Despite substantial breakthroughs in medical and surgical treatment of HF, approximately 30% of patients are admitted annually for HF exacerbation [2]. Central apneas (CA) and obstructive apneas (OA) are increasingly recognized comorbidity in subjects with HF and may affect the prognosis of HF [3]. To date, there is consensus that the initial step in managing patients with CA/OA and HF should be optimizing HF treatment [4]. Indeed, past research has shown that optimizing pharmacological therapy [5, 6] and utilizing non-pharmacological ways to treat HF can improve CA/OA [7]. However, the best way to manage CA/OA in HF is still being debated, owing to the fact that the therapeutic benefit of additional respiration treatment for patients with HFrEF has been questioned following the SERVE-HF trial's results and ongoing findings of the ADVENT-HF research, respectively. The results showed that not only was adaptive servo-ventilation (ASV) ineffective, but also a post hoc analysis found excessive cardiovascular mortality in patients who received the treatment [8].

Sacubitril-valsartan (SV) is a first-in-class angiotensin-receptor neprilysin inhibitor used to treat HFrEF (New York Heart Association [NYHA] functional class II–IV) [9]. Therapy with SV decreased cardiovascular death, overall mortality, and HF-related hospitalizations in the PARADIGM-HF study compared to treatment with enalapril [10]. In preliminary investigations, angiotensin-converting enzyme

Youmeng Wang and Fernandes Branco Roberto contributed equally to the paper as first authors.

Thomas Penzel—although the co-author is the Editor of the journal, there was no involvement with the peer review process for this article.

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(ACE) inhibitors have been shown to ameliorate CA/OA in patients with HF [11]. Despite the fact that the combination therapy can improve apneas in patients with HF, there is little research on the effect of SV on CA/OA [12]. In this study, we investigated the effect of initiating SV on apneas and hypothesized that CA/OA would improve when using treatment with SV.

Methods

Study population

This trial was a 3-month, single-center, open-label, prospective study from January 2019 to July 2021. Inclusion criteria were as follows: non-childbearing female and male patients age 60 + with HF (NYHA class II–IV); LVEF ≤ 40%; patients had to receive stable doses (at least 1 month) standard-of-care HF medication before the study; a blood test result of serum potassium ≤ 5.2 mmol/L, estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2, and systolic blood pressure (SBP) ≥ 100 mmHg. Exclusion criteria were as follows: severe valvular disease, isolated right HF, secondary cardiomyopathy, hypertrophic obstructive cardiomyopathy, previous or upcoming heart transplantation, and unstable angina within half a year before the study; patients treated with a history of angioedema or significantly increased liver enzymes (at least three times higher than the upper threshold), or with combination drugs such as ACE inhibitors and angiotensin-receptor blockers (ARBs). To participate in this study, the subjects were required to provide written informed permission. Our study was registered with ClinicalTrials.gov, number NCT02768298, and the EU Clinical Trials Register, number CLCZ696BDE01.

Study drug

According to the dosage approved by European Union, patients took SV twice a day and adjusted it for renal function and hemodynamic tolerance. Patients were advised to take the study drug simultaneously every day, according to the approved instructions that follow the current European HF guidelines' best medical treatment recommendations.

Home portable apnea monitoring

The ApneaLink device (ResMed Inc., Martinsried, Germany) was used to measure nasal flow and pulse oximetry in this study [13]. Participants were instructed to use the device in a standardized manner by study personnel who had undergone extensive training. Adults with apnea can be assessed using portable apnea monitoring devices instead of overnight polysomnography [14, 15]. Apnea was defined as a reduction in airflow of more than 90% from baseline for more than 10 s. Apneas were further classified as OA if there was any evidence of respiratory effort, CA if there was no evidence of respiratory effort, and mixed apnea if features of both CA and OA were present. For the purposes of this study, hypopnea was described as a 30% decrease in airflow

Table 1 Baseline characteristics of patients

HF patients treated with SV ($n = 18$)	
Age (years)	66.7 ± 10.7
Gender (male/female, *n*)	15/3
BMI (kg/m^2)	43.8 ± 50.2
NYHA class (%)	
Class II	50
Class III	50
Atrial fibrillation (%)	22
CKD (%)	39
Diabetes (%)	17
Hypertension (%)	78
COPD (%)	28
Cardiac infarction (%)	22
Beta-blocker (%)	89
Loop diuretics (%)	72
ICD (%)	72
CRT (%)	17

BMI body mass index; *COPD* chronic obstructive pulmonary disease; *CKD* chronic kidney disease; *CRT* cardiac resynchronization therapy; *ICD* implantable cardioverter defibrillator; *NYHA* New York Heart Association

Table 2 Relation between SV treatment and heart remodeling, CPT, and blood examination

	Baseline	3 months	*p*-value
LVEF (%)	32 ± 7	43 ± 9	< 0.001a
LVEDD (mm)	59.9 ± 6.9	56.8 ± 9.6	0.025a
LVESD (mm)	50.7 ± 9.1	44.5 ± 10	0.001a
LVESV (ml)	110.4 ± 48.1	83.3 ± 39.7	0.001b
TAPSE (mm)	18.7 ± 4.2	19.7 ± 2.9	0.392b
E/E'	11.9 ± 4.9	12.6 ± 7.8	0.594a
sPAP (mmHg)	25.8 ± 10.7	24.1 ± 10.8	0.623b
FEV_1 (L)	2.6 ± 1	2.9 ± 0.8	0.209a
Max VO_2 (ml/min/kg)	14.4 ± 2.3	13.8 ± 2.4	0.296a
eGFR (ml/min/1.73 m^2)	68.8 ± 17.8	67.3 ± 16.6	0.576a
NT-pro BNP (pg/ml)	1792.1 ± 1271.3	876.9 ± 984.2	0.001b

eGFR estimated glomerular filtration rate; FEV_1 forced expiratory volume for one second; *LVEF* left ventricular ejection fraction; *LVEDD* left ventricular end-diastolic diameter; *LVESD* left ventricular end-systolic diameter; *LVESV* left ventricular end-systolic volume; *NT-proBNP* pro-B-type natriuretic peptide; *RV-FAC* right-ventricular fractional area change; *sPAP* systolic pulmonary artery pressure; *TAPSE* tricuspid annular plane systolic excursion; VO_2 oxygen consumption; P^a represents the paired *T*-test; P^b represents Wilcoxon test

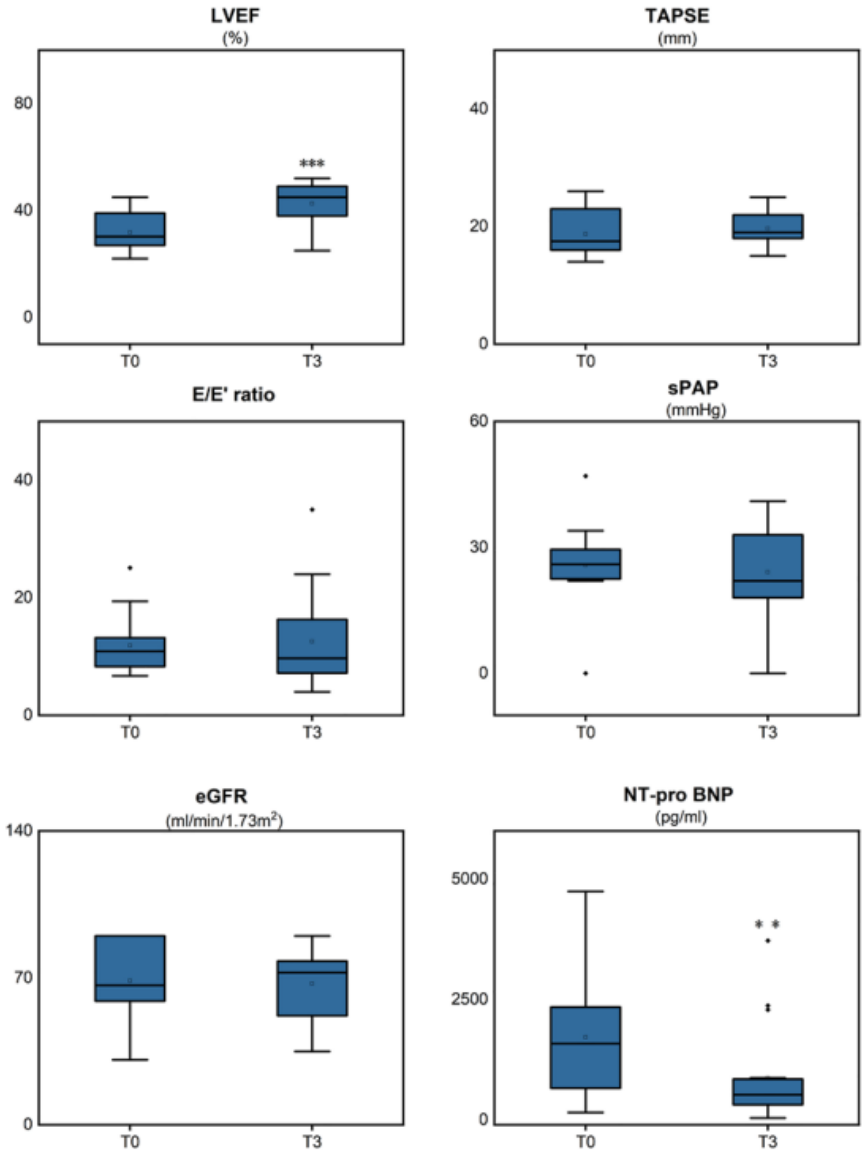

Fig. 1 Changes in echocardiographic measures and blood examination after 3 months of treatment with SV. $*p<0.05$; $**p<0.01$; $***p<0.001$. eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; NT-proBNP pro-B-type natriuretic peptide; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion

lasting for more than than 10 s, followed by a 3% reduction in oxygen saturation. The number of apnea and hypopnea events per hour of monitoring during a certain period was described as the respiratory event index (REI). The REI is used as a surrogate for the apnea–hypopnea index (AHI) because it measures time spent monitoring rather than total sleep time [16].

The changes in echocardiographic parameters from baseline were examined in patients with HF who had a baseline LVEF of less than 40%. A ramp technique was used following calibration on a treadmill, and a cardiopulmonary exercise test (CPET) was performed on the patients after taking their age and gender into consideration [17]. Normative clinical chemistry tests were performed which included a full blood count and the N-terminal segment of the pro-brain natriuretic peptide (NT-pro BNP). These procedures were supervised and managed by a clinically experienced cardiologist and nurse.

Statistical analysis

Descriptive data are presented as means ± standard deviation (SD) or as numbers and percentages of each category unless otherwise indicated. Paired *t*-tests (for data with normal

Table 3 Relation between SV treatment and apneas

	Baseline	3 months	p-value
Overall population ($n=18$)			
REI (e/h)	20±23	7±7	0.003[b]
SaO_2 basal (%)	93±2	95±2	0.053[a]
SaO_2 min (%)	80±4	80±8	0.812[a]
T90 (min)	119±128	42±86	0.001[b]
Patients with CA ($n=7$)			
REI (e/h)	36±32	7±8	0.018[b]
SaO_2 basal (%)	94±2	94±2	0.876[a]
SaO_2 min (%)	79±4	77±11	0.598[a]
T90 (min)	131±117	19±19	0.028[b]
Patients with OA ($n=9$)			
REI (e/h)	14±6	7±7	0.039[a]
SaO_2 basal (%)	92±3	95±2	0.025[a]
SaO_2 min (%)	81±2	82±6	0.404[b]
T90 (min)	138±151	66±119	0.038[b]

CA central apnea; *OA* obstructive apnea; *REI* respiratory event index; *SaO_2* oxygen saturation; *T90* time spent with oxygen saturation < 90%; *P^a* represent the paired *T* test; *P^b* represent Wilcoxon test

distribution) and Wilcoxon tests (for data with abnormal distribution) were used due to the reliance of both populations before and after. The level of statistical significance was established at $p<0.05$. All statistical data were performed using SPSS version 25.0 (IBM SPSS Statistics, Armonk, NY, USA).

Results

A total of eighteen eligible patients were enrolled in the study. Table 1 summarizes the clinical, demographic, and medications data. Despite being given optimal medical treatment, most subjects had apneas at baseline. Only 2 patients (11%) had normal breathing, 9 had OA (50%), and 7 had CA (39%). Among subjects with OA, 4 (23%), 5 (27%), and 0 (0%) had mild ($5 \leq REI < 15$), moderate ($15 \leq REI < 30$), and severe ($REI \geq 30$) apnea, respectively, while among subjects with CA, 4 (22%), 0 (0%), and 3 (17%) had mild, moderate, and severe apnea, respectively. Before using the ApneaLink monitoring, the patients were requested to stop taking any medications that had a direct impact on ventilatory control.

Results of SV on cardiac function, CPET, and blood testing in the overall population are presented in Table 2 and Fig. 1. SV has been shown to be associated with a statistically significant decrease in NT-pro BNP. The administration of the drug was also associated with improved left ventricular (LV) systolic and diastolic function, as indicated by an increase in LV end-diastolic diameter, as well as with improvement in LV reverse remodeling, as indicated by increased LVEF. No statistically significant changes were noted in tricuspid annular plane systolic excursion (TAPSE) and systolic pulmonary artery pressure (sPAP). There were no differences in peak oxygen consumption or FEV_1 (both $p>0.05$) after therapy at CPET compared to baseline.

SV treatment was found to be associated with a significant reduction in REI in the general population (Table 3 and Fig. 2). The effect of SV administration was significantly associated with a decrease in REI in the subgroup of subjects with OA (by 47%). In the subgroup of subjects with CA, SV was also associated with a decrease in REI (by 81%). SV had a decreasing effect on the minimal oxygen saturation and T90% (all $p<0.05$).

Discussion

SV has been shown to benefit both CA and OA in patients with HFrEF. The administration of SV to optimal medical therapy was associated with a significant decrease in the REI.

A comparison of SV and enalapril has shown that the former was more effective at decreasing all-cause and sudden-death mortality, as well as limiting the progression of HF [18]. This study shows that SV is associated with an increase in LVEF, which in turn promotes LV and left atrial reverse remodeling and an improvement in REI [12]. As expected, SV also had a positive effect on NT-pro BNP [19, 20]. It is worth noting that some participants transitioned from CA to OA following therapy with SV, which consequently became the most common respiratory disorder. The administration of SV reduced CA, confirming the beneficial effect of the medication on CA stated previously in a previous case study [21]. In this study, successful cardiac function optimization by SV was related to a shift in the apnea phenotype from CA to OA. This finding is consistent with earlier studies, which have shown that improvements in cardiac performance lead to reduced CA, consequently unmasking previously undiagnosed OA [22–25]. Fox et al. found a 71-year-old man who suffered from HF and sleep-disordered breathing (SDB). Treatment with SV was associated with improved cardiac function, as measured by a decrease in NT-pro BNP and an increase in LVEF. This was associated with a significant decrease in the AHI. This is the first case to demonstrate improvement in HF and SDB following the start of SV treatment [26].

SV, by inhibition of neprilysin, prevents the degradation of natriuretic peptides, hence enhancing their natriuretic and vasodilatory actions and lowering pulmonary congestion, respectively [27, 28]. Additionally, the beneficial effects on cardiac reverse remodeling,

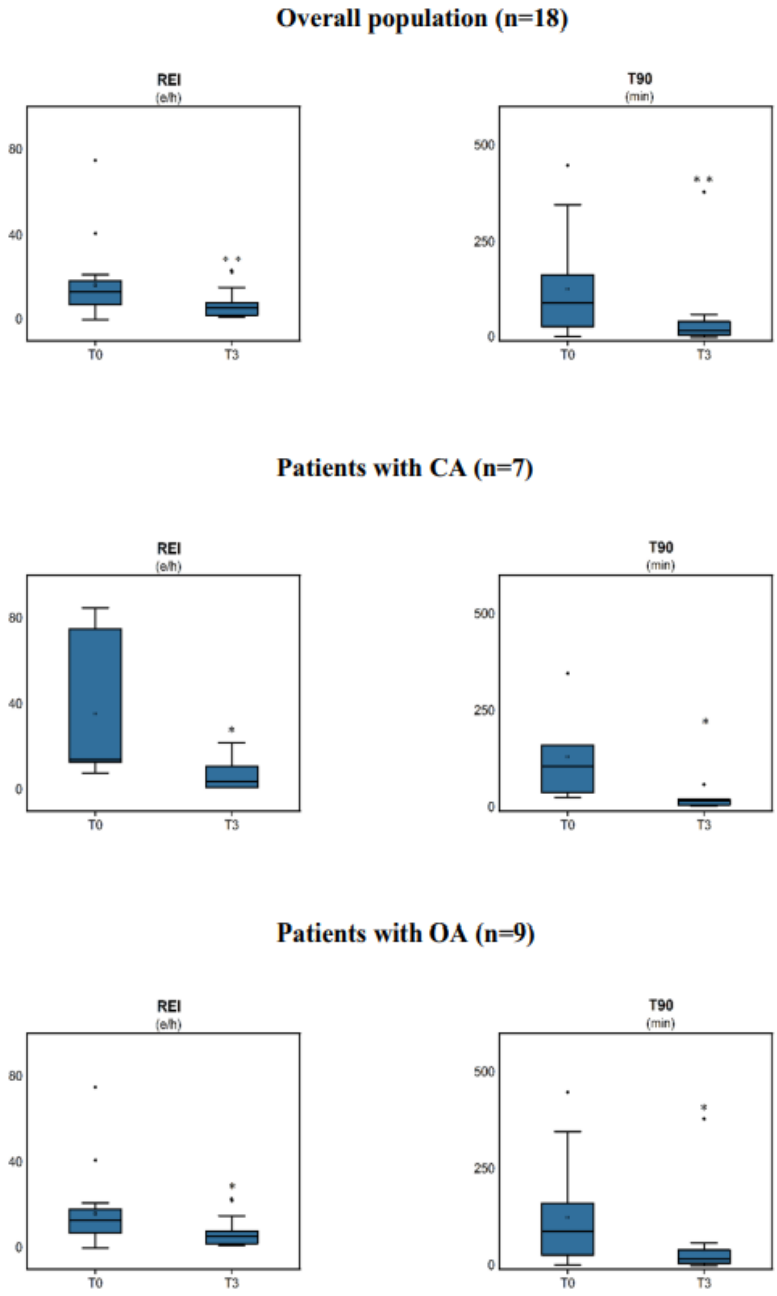

Fig. 2 Changes of REI and T90 after 3-month SV treatment in the overall population and in the subgroups with OA and with CA. $*p<0.05$; $**p<0.01$; $***p<0.001$. CA central apnea; OA obstructive apnea; REI respiratory event index; T90 time spent with oxygen saturation < 90%

which are associated with enhanced LVEF, may increase cardiac output [29, 30]. Overall, those effects may promote effective ventilation and gas exchange, and the chemoreflex, which reduces pulmonary stretch receptor stimulation while increasing the perfusion of peripheral chemoreceptors [31]. Furthermore, an increase in cardiac output may decrease circulation time, reducing the amount of time available for the chemoreflex system to detect and respond to changes in CO_2 [32]. Finally, the medication has been shown to reduce the amount of rostral fluid shift that occurs when a person is in a reclined position. Although the PARADIGM-HF trial made a small but significant contribution to improving survival, it is tempting to conclude that this can be

attributed to the reduced apneic burden. It is equally tempting to consider SV as an alternative first-line therapeutic strategy for apneas and, specifically, CA in HF [10]. Additionally, there are more alternative therapeutic approaches for hypoxemic burden. Olaf et al. discovered that transvenous phrenic nerve stimulation (TPNS) could significantly reduce nocturnal hypoxemic load. Hypoxemic burden is more predictive of mortality than AHI and should be a primary indicator for CSA treatments [33]. However, to address these intriguing challenges precisely, larger cohorts with definitive outcomes followed for longer periods of time would be required.

Limitations

This study has several limitations. First, we acknowledge this is a single-center study and requires further studies to support the generalizability of the findings presented. In addition, our study was limited to the older population with HFrEF. Another possible limitation is that portable monitoring devices do not record CO_2 levels, sleep stages, and sleep position. As a result, conclusions concerning these factors cannot be drawn and events cannot be classified into different sleep stages. In addition, no electroencephalograms were recorded in this study. Thus, it was impossible to determine if patients were asleep during the assessment, which could underestimate the severity of OA and CA. Importantly, the ApneaLink may overestimate the REI, as actual sleep time may be shorter than recorded time, implying a higher prevalence and severity of apnea.

Conclusion

In summary, our findings obtained from patients with HFrEF show that SV had positive effects on both CA and OA. The effects of SV are more limited on OA than CA. SV may become a promising therapeutic option for CA in HFrEF.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval The study was conducted according to the ethical principles laid down in the Declaration of Helsinki. The study was reviewed and approved by the ethics committee of Charité University Hospital.

Informed consent The research involved human participants. Written informed consent was provided from each participant. The work of this research was carried out at Charité Hospital.

Conflict of interest The authors declare no competing interests.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW (2020) Epidemiology of heart failure. Eur J Heart Fail 22:1342–1356
2. Sangaralingham LR, Sangaralingham SJ, Shah ND et al (2018) Adoption of sacubitril/valsartan for the management of patients with heart failure. Circ Heart Fail 11:e004302
3. Oldenburg O, Wellmann B, Buchholz A et al (2016) Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J 37:1695–1703
4. Jaffuel D, Nogue E, Berdague P et al (2021) Sacubitril-valsartan initiation in chronic heart failure patients impacts sleep apnea: the ENTRESTO-SAS study. ESC Heart Fail 8:2513–2526
5. Bucca CB, Brussino L, Battisti A et al (2007) Diuretics in obstructive sleep apnea with diastolic heart failure. Chest 132:440–446
6. Tamura A, Kawano Y, Kadota J (2009) Carvedilol reduces the severity of central sleep apnea in chronic heart failure. Circ J:Official J Japanese Circ Soc 73:295–298
7. Kara T, Novak M, Nykodym J et al (2008) Short-term effects of cardiac resynchronization therapy on sleep-disordered breathing in patients with systolic heart failure. Chest 134:87–93
8. Javaheri S, Brown LK, Randerath W, Khayat R (2016) SERVE-HF: more questions than answers. Chest 149:900–904
9. von Haehling S, Arzt M, Doehner W et al (2021) Improving exercise capacity and quality of life using non-invasive heart failure treatments: evidence from clinical trials. Eur J Heart Fail 23:92–113
10. McMurray JJ, Packer M, Desai AS et al (2014) Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371:993–1004
11. Vazir A, Sundaram V (2018) Management of sleep apnea in heart failure. Heart Fail Clin 14:635–642
12. Passino C, Sciarrone P, Vergaro G et al (2021) Sacubitril–valsartan treatment is associated with decrease in central apneas in patients with heart failure with reduced ejection fraction. Int J Cardiol 330:112–119

13. Stadler S, Zimmermann T, Franke F et al (2017) Association of sleep-disordered breathing with diabetes-associated kidney disease. Ann Med 49:487–495
14. Arzt M, Woehrle H, Oldenburg O et al (2016) Prevalence and predictors of sleep-disordered breathing in patients with stable chronic heart failure: the SchlaHF registry. JACC Heart Fail 4:116–125
15. Chen H, Lowe AA, Bai Y et al (2009) Evaluation of a portable recording device (ApneaLink™) for case selection of obstructive sleep apnea. Sleep Breath 13:213–219
16. Lin SH, Branson C, Park L et al (2018) Oximetry as an accurate tool for identifying moderate to severe sleep apnea in patients with acute stroke. J Clin Sleep Med 14:2065–2073
17. Fox H, Bitter T, Sauzet O et al (2021) Automatic positive airway pressure for obstructive sleep apnea in heart failure with reduced ejection fraction. Clin Res Cardiol 110:983–992
18. Martens P, Beliën H, Dupont M et al (2018) The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovasc Ther 36:e12435
19. Zile MR, Claggett BL, Prescott MF et al (2016) Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 68:2425–2436
20. Vergaro G, Passino C, Emdin M (2019) No aldosterone breakthrough with the neprilysin inhibitor sacubitril. J Am Coll Cardiol 73:3037–3038
21. Ibrahim NE, McCarthy CP, Shrestha S (2019) Effect of neprilysin inhibition on various natriuretic peptide assays. J Am Coll Cardiol 73:1273–1284
22. Fox H, Bitter T, Horstkotte D, Oldenburg O (2016) Cardioversion of atrial fibrillation or atrial flutter into sinus rhythm reduces nocturnal central respiratory events and unmasks obstructive sleep apnoea. Clin Res Cardiol 105:451–459
23. Vardeny O, Claggett B, Kachadourian J et al (2019) Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail 21:337–341
24. Spiesshoefer J, Spieker M, Klose S et al (2019) Reduction of sleep-disordered breathing following effective percutaneous mitral valve repair with the MitraClip system. Sleep Breath 23:815–824
25. Fox H, Puehler T, Schulz U et al (2014) Delayed recovery from Cheyne-Stokes respiration in heart failure after successful cardiac transplantation: a case report. In Transplantation Proceedings 46:2462–2463
26. Fox H, Bitter T, Horstkotte D, Oldenburg O (2017) Resolution of Cheyne-Stokes respiration after treatment of heart failure with sacubitril/valsartan: a first case report. Cardiology 137:96–99
27. Selvaraj S, Claggett B, Pozzi A et al (2019) Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. Circulation 140:1369–1379
28. Giannoni A, Raglianti V, Taddei C et al (2019) Cheyne-Stokes respiration related oscillations in cardiopulmonary hemodynamics in patients with heart failure. Int J Cardiol 289:76–82
29. Bayard G, Da Costa A, Pierrard R et al (2019) Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. IJC Heart Vasc 25:100418
30. Romano G, Vitale G, Ajello L et al (2019) The effects of sacubitril/valsartan on clinical, biochemical and echocardiographic parameters in patients with heart failure with reduced ejection fraction: the "hemodynamic recovery." J Clin Med 8:2165
31. Giannoni A, Raglianti V, Mirizzi G et al (2016) Influence of central apneas and chemoreflex activation on pulmonary artery pressure in chronic heart failure. Int J Cardiol 202:200–206
32. Spiesshoefer J, Aries J, Giannoni A et al (2020) APAP therapy does not improve impaired sleep quality and sympatho-vagal balance: a randomized trial in patients with obstructive sleep apnea and systolic heart failure. Sleep Breath 24:211–219
33. Oldenburg O, Costanzo MR, Germany R et al (2021) Improving nocturnal hypoxemic burden with transvenous phrenic nerve stimulation for the treatment of central sleep apnea. J Cardiovasc Transl Res 14:377–385

Printed Publications

Publication 1: Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients with Severe Tricuspid Regurgitation-A Pilot Study.

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Impact Factor: 6.050

Publication 2: Effects of sacubitril-valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction.

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Publications list

Wang Y, Fernandes Branco R, Fietzeck A, Penzel T, Schöbel C. Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients With Severe Tricuspid Regurgitation-A Pilot Study. Front Cardiovasc Med. 2021 Jul 19;8:673164. (IF: 6.050)

Wang Y, Schöbel C, Penzel T. Management of Obstructive SA in Patients With Heart Failure. Front Med (Lausanne). 2022 Feb 18;9:803388. (IF: 5.091)

Wang Y, Branco RF, Salanitro M, Penzel T, Schöbel C. Effects of sacubitril-valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction. Sleep Breath. 2022 Apr 29. doi: 10.1007/s11325-022-02623-0. (IF: 2.816)

Youmeng Wang, Ying Huang, Mengdi Xia, Theresa Toncar, Christoph Schöbel, Thomas Penzel. Effect of phrenic nerve stimulation on patients with central SA: a meta-analysis. (Submitted)

Youmeng Wang, Juliane Schoebela, Matthew Salanitroa, Jan Kraemera, Theresa Toncara, Jacob Siegerta, Thomas Penzel, Christoph Schöbel. Feasibility of phrenic nerve stimulation for treatment of central SA in heart failure patients. (In preparation)

Published contributions to academic conferences – Posters

Wang Y, Penzel T, Schöbel C. Feasibility of Transcatheter Caval Valve Implantation to Improve Sleep-Disordered Breathing in Patients With Severe Tricuspid Regurgitation-A Pilot Study. World Sleep 2022. Rome, Italy. March 11-16, 2022.

Youmeng Wang, Roberto Fernandes Branco, Thomas Penzel, Chris-toph Schöbel. Effects of sacubitril‑valsartan on central and obstructive apneas in heart failure patients with reduced ejection fraction. World Sleep 2022. Rome, Italy. March 11-16, 2022.

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