Cardiovascular Diabetology



# Early hemodynamic impact of SGLT2 inhibitors in overweight cardiometabolic heart failure: beyond fluid offloading to vascular adaptation– a preliminary report



Nadia Salerno<sup>1</sup>, Jessica Ielapi<sup>1</sup>, Angelica Cersosimo<sup>1</sup>, Isabella Leo<sup>1</sup>, Assunta Di Costanzo<sup>2</sup>, Giuseppe Armentaro<sup>2</sup>, Salvatore De Rosa<sup>2</sup>, Angela Sciacqua<sup>2</sup>, Sabato Sorrentino<sup>2\*</sup> and Daniele Torella<sup>1\*</sup>

#### Abstract

**Background** Heart failure (HF) is increasingly recognized as a heterogeneous cardiometabolic disorder, often in the context of overweight/obesity independently from diabetes. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce HF hospitalizations and cardiovascular mortality across ejection fraction (EF) categories, yet their early hemodynamic effects in cardiometabolic HF, and with preserved ejection fraction (HFpEF) in particular, remain underexplored.

**Methods** A prospective, single-center study included 20 consecutive HF patients receiving SGLT2i alongside optimized therapy. Transthoracic echocardiography and non-invasive bioimpedance assessments (NICaS system) were performed at baseline and after 4 weeks.

**Results** The median patient age was 75 years [58–84], with 14 patients (70%) being overweight/obese, and only 4 patients with diabetes. The majority (65%) had HF with preserved EF (HFpEF), 25% with mildly reduced EF (HFmrEF), and 10% with reduced EF (HFrEF). At a median follow-up of 33 days [30–68], significant reductions were observed in body weight (67.65 kg [46-99.20] to 65.50 kg [46.30–97], p = 0.027) and systolic blood pressure (130 mmHg [100–150] to 116.50 mmHg [100–141], p = 0.015). Hemodynamic assessments revealed a significant decrease in total peripheral resistance index (TPRi, 3616.50 dynes·sec·cm3 [1600–5024] to 3098.50 dynes·sec·cm3 [1608–4684], p = 0.002). The left atrial volume index decreased significantly (42.84 ml/m<sup>2</sup> [27-69.40] to 41.15 ml/m<sup>2</sup> [26-62.60], p < 0.001); a significant decrease in peak tricuspid regurgitation velocity [2.52 m/Sect. (1.30–3.20]), vs. 2.21 m/Sect. (1.44–2.92), p = 0.023] and in pulmonary artery systolic pressure (PASP) [31.0 mmHg (15.0–40.0) vs. 25.50 mmHg (15.0–38.0-), p = 0.010] was observed. Patients with HFrEF or HFmrEF showed significant reduction in total body water (66.33 [51.45–74.45] vs. 58.68 [55.13–66.50]), while HFpEF patients (overweight/obese, n = 11, 79%) had a significant reduction in TPRi (3681 dynes·sec·cm3 [1600–5024] vs. 3085 dynes·sec·cm3 [1608–4684] p = 0.005).

\*Correspondence: Sabato Sorrentino sorrentino@unicz.it Daniele Torella dtorella@unicz.it

Full list of author information is available at the end of the article



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**Conclusions** Early hemodynamic responses to SGLT2i may differ across HF subtypes. In overweight patients with cardiometabolic HFpEF, our preliminary findings suggest an association with reduced vascular resistance, while in HFrEF/HFmrEF, the primary benefit appears to be volume unloading. However, the vascular effects of SGLT2i remain uncertain, and given the small sample size, these results should be interpreted as hypothesis-generating. Our findings also highlight the potential role of non-invasive hemodynamic monitoring in guiding therapy in HF.

Keywords Heart failure, Sodium-glucose cotransporter 2 inhibitors, Hemodynamics, Non-invasive monitoring

#### Introduction

Heart failure (HF) remains a significant global health challenge, associated with substantial morbidity and mortality despite advances in prevention, diagnosis, and treatment strategies [1, 2]. Among the various HF subtypes, HF with preserved ejection fraction (HFpEF) now accounts for approximately 50% of all HF cases [3, 4]. Unlike HF with reduced ejection fraction (HFrEF), therapeutic options for HFpEF are limited, as recommended treatments effective for HFrEF have not demonstrated similar efficacy in improving primary outcomes for HFpEF patients [5-7]. This divergence underscores the distinct pathophysiological mechanisms underlying these two conditions. Recently, landmark clinical trials, including DELIVER [8] and EMPEROR-Preserved [9], have demonstrated significant reductions in HF hospitalizations and cardiovascular mortality with sodium-glucose cotransporter-2 inhibitors (SGLT2i) in HFpEF patients, establishing this class of drugs as the only therapy with a Class I recommendation for HFpEF management [7].

The precise mechanisms by which SGLT2i confer these clinical benefits are not yet fully understood and may vary according to the HF phenotype. Notably, a pooled analysis of over 21,000 patients from five randomized controlled trials revealed that SGLT2i significantly reduced cardiovascular death and HF hospitalizations, with benefits emerging within the first month and being sustained from four months onward [10]. These effects may be partly attributed to the short-term blood pressure-lowering properties of SGLT2i, which reduce cardiac afterload and enhance ventricular-arterial coupling [11]. This hemodynamic improvement increases cardiac efficiency and promotes reverse cardiac remodeling, as consistently demonstrated by imaging studies [12–15]. Moreover, emerging evidence suggests that the cardioprotective benefits provided by SGLT2 inhibitors are mediated through mechanisms reminiscent of calorie restriction, including weight loss, ketogenesis, and nutrient-deprivation signaling [16].

The quantification of hemodynamic parameters (i.e. cardiac output, cardiac index, stroke volume, cardiac power, and peripheral resistance), may offer unique insights in this context [17]. Although thermodilution via right heart catheterization remains the gold standard for measuring these parameters [18], techniques based on bioimpedance analysis have proven to be an accurate,

non-invasive alternative [19]. For instance, the integration of the total-body impedance cardiography-based Non-Invasive Cardiac System (NICaS) into routine clinical evaluation has already been demonstrated to offer a reliable method for monitoring the hemodynamic status of HF patients and assessing improvements following therapy [20].

Despite the known benefits of SGLT2i, the early hemodynamic effects and cardiac remodeling induced by SGLT2i across different HF phenotypes remain insufficiently characterized. Understanding these short-term impacts could provide deeper insights into the mechanisms of SGLT2i and optimize their therapeutic use in HF management [16]. Accordingly, this study aimed to investigate the early effects of SGLT2i on hemodynamic parameters and cardiac remodeling, stratified by the HF phenotype.

#### Methods

#### Study design

This prospective, single-center observational study was conducted at "Renato Dulbecco" University Hospital in Catanzaro, Italy. Patients enrolled in the study underwent clinical examination, six-minute walking test (6MWT), echocardiographic and non-invasive hemodynamic evaluation at baseline and 1 month after starting SGLT2i therapy, on top of optimal medical therapy (OMT). Laboratory data were collected for all patients both at baseline and at 1-month follow-up. All patients provided written informed consent. All study procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the Calabria Region Local Ethics Committee (Protocol Register No. 170, May 30, 2024).

#### Study population

Consecutive patients diagnosed with HF and naïve to SGLT2i were enrolled in the study between June 2024 and December 2024. A baseline visit and a 1-month follow-up in-person visit were conducted to collect data on clinical status, echocardiographic and non-invasive hemodynamic parameters, which were included in a prespecified dataset. The key exclusion criteria were: [1] patients with severe renal impairment (stage IV or V); [2] patients with congenital heart disease [3], patient with previous acute coronary syndrome in the past three months, and [4] patients aged  $\leq$ 18 years.

#### **Echocardiographic assessment**

At baseline and 4-weeks after initiating SGLT2i therapy, comprehensive transthoracic echocardiography was performed using Philips EPIQ 7 ultrasound system (Philips Healthcare, Amsterdam, Netherlands), equipped with an X5-1 xMatrix array transducer. Data acquisition and interpretation adhered to the 2015 American Society of Echocardiography (ASE) guidelines for chamber guantification [22]. Briefly, left ventricular (LV) structure and function were assessed using LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) via the biplane Simpson method. The LV mass index was calculated by incorporating LV end-diastolic diameter (LVEDD), posterior wall thickness (PWED), and interventricular septal thickness (IVSED). Diastolic function was evaluated through transmitral flow (E/A ratio) and tissue Doppler imaging (TDI) of lateral and septal mitral annulus velocities, with E/e' ratio and left atrial volume index (LAVi) values [23].

Right ventricular (RV) function was assessed via the tricuspid annular plane systolic excursion (TAPSE) and the systolic velocity (S'). Systolic pulmonary artery pressure (PASP) was calculated using the peak tricuspid regurgitant velocity (TRVmax) and the estimated right atrial pressure (RAP), with TAPSE/PASP used to evaluate RV-pulmonary artery coupling [24].

Speckle-tracking echocardiography (STE) was performed per EACVI/ASE recommendations, analyzing LV global longitudinal strain (GLS), left atrial strain (reservoir, conduit, and contraction phases), and RV strain (free wall and global) [25, 26].

#### Non-invasive hemodynamic assessment

Non-invasive hemodynamic assessment was conducted using the FDA-approved total-body impedance cardiography-based Non-Invasive Cardiac System (NICaS) (NI Medical Ltd, Ra'anana, Israel). The device detects bioimpedance changes in peripheral tissues by applying a low-intensity electrical current through the body via two pairs of tetrapolar sensors positioned in a wrist-to-ankle configuration. Before initiating the analysis, patientspecific information, including sex, age, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), hematocrit, sodium levels, peripheral oxygen saturation, and electrode positioning, was entered into the system.

Measurements were performed with patients in the supine position after a 5-minute rest period to ensure hemodynamic stability. The NICaS system collects a minimum of five measurements per patient to enhance reliability, providing the average of these readings as the final result. The parameters provided include stroke volume (SV), cardiac output (CO), cardiac index (CI), mean arterial pressure (MAP), cardiac power (CP), total peripheral resistance (TPR) and its indexed value (TPRi), total body water (TBW), and the Granov-Goor Index (GGI) [27–30].

#### Statistical analysis

Continuous variables are presented as median [minmax], categorical variables are reported as frequencies and percentages. Comparisons were made using either the paired Student's t-test or the appropriate nonparametric tests. All tests were conducted at a two-sided alpha level of 0.05, which was deemed statistically significant. Statistical analysis was performed using GraphPad Prism version 6.00 for Macintosh (GraphPad Software, La Jolla, CA, USA).

#### Results

#### **Baseline characteristics**

A total of 20 patients naïve for treatment with SGLT2i (either empagliflozin, n = 11 or dapagliflozin, n = 9) were enrolled from June 2024 to December 2024. The median age of the population enrolled was 75 years [58-84], and 12 (60%) of patients were male. Table 1 summarizes baseline clinical characteristics. Briefly, typical cardiovascular risk factors were largely prevalent, including 18 (90%) patients with hypertension, 18 (90%) with dyslipidaemia, 9 (45%) reporting previous smoking habit, and 4 (20%) treated for diabetes mellitus. Furthermore, 8 (40%) patients had history of previous myocardial infarction, 10 (50%) received percutaneous coronary interventions, and 5 (25%) surgical revascularizations. Atrial fibrillation was present in 9 (45%) patients, 4 (20%) in a permanent form. Furthermore, about a quarter of patients presented chronic kidney disease (CKD) and the median value of glomerular filtrate was 62.90 [30-91.50] mL/min/1.73m<sup>2</sup>. Importantly, two-thirds of the patients were overweight  $(BMI \ge 25 \text{ kg/m}^2)$  or obese  $(BMI \ge 30 \text{ kg/m}^2)$  (total of *n* = 14, 70%) (Table 1).

Finally, among the enrolled patients 65% presented with HFpEF, 25% with HFmrEF and 10% with HFrEF (baseline clinical characteristics across HF groups are summarized in **Supplementary Table 1**).

## Changes in clinical, echocardiographic and non-invasive hemodynamic parameters and fluid indices

Table 2 summarizes the echocardiographic and hemodynamic parameters at baseline and follow-up. The median follow-up was 33 days [30–68]. Significant reductions in both body weight (kg) (67.65 [46-99.20] vs. 65.50 [46.30–97]; p=0.027) and SBP (mmHg) (130 [100–150] vs. 116.50 [100–141]; p=0.015) were observed. No significant differences were found in biochemical parameters, except for a significant increase in haemoglobin level (g/ dl) (12.90 [9.60–15.50] vs. 13.20 [9.70–15.40] p=0.034). All patients had elevated NT-proBNP values (pg/mL) at

 Table 1
 Baseline characteristics

General characteristics	
Age (years)	75 [58–84]
Male sex	12 (60)
Weight (kg)	68 [46-99.20]
BMI (kg/m <sup>2</sup> )	26.40 [20.40-37.70]
<25	6 (30)
≥25 to < 30	9 (45)
≥30	5 (25)
Smoker	9 (45)
Dyslipidemia	18 (90)
Diabetes	4 (20)
Hypertension	18 (90)
Prior Myocardial infarction	8 (40)
Prior PCI	10 (50)
Prior CABG	5 (25)
CIED	3 (15)
CKD	5 (25)
COPD	4 (20)
OSAS	1 (5)
Atrial Fibrillation	9 (45)
paroxysmal	5 (25)
persistent	0 (0)
permanent	4 (20)
HF type	20 (100)
HFpEF	13 (65)
HFMTEF	5 (25)
	2 (10)
Drugs therapy	10 (00)
Beld-Diocker	18 (90)
Calcium channel blockers	I (5)
ACEI	11 (55)
ARB	3 (15)
ARNI	2 (10)
MRA	4 (20)
Loop Diuretic	12 (60)
Thiazide Diuretic	1 (5)
SGLT2i	20 (100)
Empaglifozin	11 (55)
Dapaglitozin	9 (45)

Values are expressed as median [min-max] or n (%)

BMI- Body mass index; HF-Heart failure; HFpEF-Heart failure with preserved ejection fraction; HFmrEF- Heart failure with mildly reduced ejection fraction; HFrEF- Heart failure with reduced ejection fraction; PCI- Percutaneous coronary intervention; CABG- Coronary artery bypass graft surgery; CIED- Cardiac implantable electronic device; CKD– Chronic kidney disease; COPD- Chronic obstructive pulmonary disease; OSAS- Obstructive sleep apnea syndrome; ACEi- ACEi nhibitor; ARB– Angiotensin receptor blocker; ARNI– Angiotensin receptor neprilisin inhibitor; MRA– Mineralocorticoids receptor antagonists; SGLT2i- Sodium-glucose co-transporter 2 inhibitors

baseline (906.50 [231–7287]), with no statistically significant trend toward reduction at follow-up (505 [146.60–8927], p = 0.328).

At echocardiographic evaluation there was a significant decrease in LAVi (ml/m<sup>2</sup>) (42.84 [27-69.40] vs. 41.15 [26-62.60], p < 0.001), in peak TR velocity (m/sec) (2.52 [1.30–3.20] vs. 2.21 [1.44–2.92], p = 0.023) and in PASP (mmHg) (31 [15–40] vs. 25.50 [15–38], p = 0.010). Assessing

the hemodynamic effects of SGLT2i initiation, a slight reduced MAP was observed (mmHg) (91.50 [74–109] vs. 83.50 [63–106], p=0.015). Furthermore, SGLT2i also favourably influenced the TPR (dn\*s/cm<sup>5</sup>), both as absolute values (2048.50 [1082–2767] vs. 1776 [1061–2863] p=0.004) and as indexed values (dn\*s/cm<sup>3</sup>) (3616.50 [1600–5024] vs. 3098.50 [1608–4684], p=0.002). Finally, no differences were observed in the 6MWT (m) at follow-up (390 [120–480] vs. 390 [120–540], p=0.231).

At follow-up, when considering only the overweight and obese patients (n = 14), these patients exhibited a significant reduction in body weight (77.25 kg [57.80-99.20] vs. 74.05 kg [57.60–97], p = 0.031) and SBP (132.50 mmHg [110–150] vs. 122 mmHg [104–141], *p* = 0.039). Although NT-proBNP levels were not significantly lower (609.5 pg/ mL [231–1759] vs. 381 pg/mL [146.60–1803], p=0.322), significant reductions were observed in EDV (105.05 mL [62.60–240] vs. 93.45 mL [60–236], p=0.036), ESV (45.40 mL [27.60–173] vs. 39.40 mL [26–169], p=0.009), LAVi (44.70 mL/m<sup>2</sup> [30-69.40] vs. 40.50 mL/m<sup>2</sup> [29-62.6], p = 0.008), and PASP (27 mmHg [15-40] vs. 24.5 mmHg [15-35], p=0.036). Moreover, NICaS measurements revealed a significant decrease in MAP (95.5 mmHg [78-109] vs. 87.5 mmHg [63–106], p = 0.043), TPR (2048.5 dns/cm<sup>5</sup> [1577–2767] vs. 1657.5 dns/cm<sup>5</sup> [1259–2863], p = 0.002), and TPRi (3616.5 dns/cm<sup>3</sup> [2911-5024] vs.  $3098.5 \text{ dns/cm}^3$  [2400–4684], p = 0.001) (Table 3). Notably, in patients with a  $BMI < 25 \text{ kg/m}^2(n=6)$ , no significant changes were observed in any parameter at follow-up.

#### Changes in echocardiographic and non-invasive hemodynamic parameters and fluid indices across HF phenotypes

Table 4 summarizes the clinical, echocardiographic, noninvasive hemodynamic parameters and fluid indices of patients with HFrEF and HFmrEF. In these subsets of patients, a significant reduction in weight was observed. NT-proBNP values were not significantly lower at follow-up (1759 pg/mL [296–7287] vs. 1326 [237–8927] p=0.594). Additionally, notable decreases were recorded in LAVi (ml/m<sup>2</sup>) (45.50 [38-58.60] vs. 41 [32-44.90], p<0.03), and in PASP (mmHg) (30 [23–38] vs. 25 [15– 33], p=0.013) (Fig. 1).

Regarding hemodynamic parameters and fluid indices, no substantial differences were found, except for a reduction in TBW (% weight): 66.33 [51.45–74.45] vs. 58.68 [55.13–66.50], p = 0.047) (Fig. 2).

In patients with HFpEF, the majority of which were overweight (n = 8) or obese (n = 3) (total 85%) (Supplementary Table 1), no significant changes in morphometric variables were observed (Table 5). NT-proBNP values were not significantly lower (870 pg/mL [231–6631], vs. 384 [146.60–1803], p = 0.219). However, a significant

#### Table 2 Difference between baseline and after 1 mo of treatment with SGLT2i

	Baseline characteristics	30-days post SGLT2i therapy	<i>p</i> -value
General characteristics		50 ad/5 post 502121 (11c1ap)	p vulue
Weight (kg)	67.65 [46-99.20]	65.50 [46.30-97]	0.027
SBP (mmHq)	130 [100–150]	116.50 [100–141]	0.015
DBP (mmHg)	69.50 [55–90]	70 [45–90]	0.097
HR (bpm)	62.50 [54–90]	65 [47–99]	0.567
6MWT (m)	390 [120–480]	390 [120–540]	0.231
Sat% O <sub>2</sub> at basal time	97 [94–100]	97 [94–100]	0.878
Sat% $O_2$ at 6 min	97 [88–99]	97 [94–99]	0.335
Biochemical parameters		[]	
Hb (a/dl )	12.90 [9.60-15.50]	13.20 [9.70-15.40]	0.034
HCT (%)	39.90 [30.30–44.50]	40 40 [29 80-47 90]	0.293
Creatinine (mg/dL)	0.95 [0.68–2.04]	1 05 [0 77–1 68]	0.484
eGER (ml /min/1 $73m^2$ )	62 90 [30-91 50]	58 50 [37 30–88 30]	0.589
NT-proBNP (pg/ml)	906 50 [231–7287]	505 [146 60–8927]	0.328
Easting blood alucose (mg/dL)	89 [76-133]	88 [65–143]	0.889
Clucated homoglobin (%)	5 95 [5 12 6 40]	5 73 [4 00 6 70]	0.742
Echocardiography parameters	5.55 [5.12-0.40]	5.75 [4.90-0.70]	0.742
	97 10 [62 60_155]	94.05 [60_150]	0.102
	45 40 [26 60 71 20]	41 50 [26 77 00]	0.102
$L_{\rm V}$ (IIIL)			0.042
	90.44 [49-157] 53.90 [10.60, 65.20]	99.00 [40-120] 54.20 [22,62.90]	0.159
	55.60 [19.00-05.20] 16 75 [4 90, 22.00]	54.50 [22-02.60]	0.045
	77.55 [4.60-22.90]	17.10 [4.70-25.20]	0.655
E wave (cm/sec)	//.55 [3/.20-130]	80.40 [33-121]	0.760
A wave (cm/sec)	82.40 [34.60–135]	/5.50 [35.60–135]	0.955
	0.80 [0.40-2.30]	0.80 [0.40–1.90]	0.095
Sept E'(cm/sec)	/.14 [3.10–17.70]	6.85 [3.26–12.60]	0.361
Lat E'(cm/sec)	8.71 [3.92–13.10]	/./3 [4.13–14.50]	0.938
	9.42 [4.50–18.80]	9.03 [5.30–21.50]	0.866
	42.84 [27-69.40]	41.15 [26-62.60]	< 0.001
PALS (%)	19.75 [4.60–46.50]	20.20 [4.30–60.50]	0.171
LACD(%)	9.60 [1.90–25.10]	9.35 [2.40-41.60]	0.821
LACT(%)	8.80 [2.10-21.40]	10.25 [1.60–21.60]	0.597
RAVi (ml/m <sup>2</sup> )	22.50 [13-44.30]	21 [15–45]	0.867
RVLS free wall (%)	21.6 [7.20–27.7]	21.90 [9.70–27.70]	0.250
RVLS Global (%)	17.90 [5.80–22.90]	18.20 [7.50–27.70]	0.072
TAPSE (mm)	22.20 [18–29]	22 [11–28]	0.739
RV S' (cm/s)	12.80 [9.20–25]	12.35 [6.70–24.50]	0.822
peak TR vel (m/sec)	2.52 [1.30–3.20]	2.21 [1.44–2.92]	0.023
PASP (mmHg)	31 [15–40]	25.50 [15–38]	0.010
TAPSE/PASP (mm/mmHg)	0.73 [0.53–1.49]	0.85 [0.33–1.73]	0.059
NICaS parameters			
MAP (mmHg)	91.50 [74–109]	83.50 [63–106]	0.015
CI (I/min/m <sup>2</sup> )	2.07 [1.46–3.70]	2.09 [1.32–3.68]	0.089
CO (l/min)	3.77 [2.54–5.47]	3.72 [2.14–5.58]	0.108
Stroke volume (ml)	55.59 [32.94–76.08]	56.52 [36.88–93.13]	0.303
Stroke volume index (ml/m <sup>2</sup> )	31.75 [18.95–48.69]	31.82 [23.24–49.34]	0.359
CPi (w/m²)	0.41 [0.25–0.61]	0.40 [0.20-0.62]	0.902
TPR (dn*s/cm <sup>5</sup> )	2048.50 [1082–2767]	1776 [1061–2863]	0.004
TPRi (dn*s/cm <sup>3</sup> )	3616.50 [1600–5024]	3098.50 [1608–4684]	0.002
GGI	9.25 [5.83–17.70]	10.02 [7.70–18.90]	0.162
RR (l/min)	17 [11–21]	16 [11–24]	0.934
TBW (kg)	44.17 [31.80–65]	42 [30.60–55.70]	0.081

#### Table 2 (continued)

	Baseline characteristics	30-days post SGLT2i therapy	<i>p</i> -value
General characteristics			
TBW (% weight),	63.44 [49.40-77.50]	59.55 [49.80–73.40]	0.268
Basal impedence (ohm)	311.50 [226–391]	317 [244–410]	0.074
Values and announced as modiling fusion of			

Values are expressed as median [min-max] or n (%)

SPB- Systolic blood pressure; DPB- Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV- End-diastolic volume; ESV- End-systolic volume; EF- Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMI- Left Ventricular Mass Index; LAVi- Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi- Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP-Pulmonary artery systolic pressure; TAPSE- Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

reduction in LAVi (ml/m<sup>2</sup>) (41.37 [26.15-63] vs. 40.32 [23.29–62.25], p = 0.005), and a reduction, even if not statistically significant, in right ventricular parameters, including peak TR velocity (m/sec) (2.61 [1.30–3.20] vs. 2.21 [1.67–2.92], p = 0.108), PASP (mmHg) (32 [15–40] vs. 26 [16–38], p = 0.134), and TAPSE/PASP ratio (0.73 [0.53–1.49] vs. 0.87 [0.60–1.25], p = 0.154) were detected (Fig. 3). Interestingly, NICaS measurements revealed a significant reduction in TPR (dn\*s/cm<sup>5</sup>) (2073 [1082–2767] vs. 1676 [1061–2863], p = 0.009) and indexed TPR (dn\*s/cm<sup>3</sup>) (TPRI: 3681 [1600–5024] vs. 3085 [1608–4684], p = 0.005) (Fig. 4). The above data were practically undistinguishable when considering only the overweight/ obese HFpEF patients.

#### Discussion

SGLT2i significantly reduce the risk of cardiovascular death and hospitalization for HF, regardless of EF or glycemic status [6, 7]. These benefits often manifest within the first month of therapy initiation [31]. Several mechanisms have been proposed for the early effects of SGLT2i. The weight loss observed with these drugs is primarily due to reduced extracellular water levels, driven by glycosuric and natriuretic effects during the first days of treatment [32, 33]. Furthermore, SGLT2i modulate the renin-angiotensin-aldosterone system, yielding modest but clinically significant reductions in SBP and DBP of approximately 2.46 mmHg and 1.46 mmHg, respectively [29]. Notably, findings from the DAPASALT study demonstrated a reduction in blood pressure within 24 h of initiating dapagliflozin, without concurrent increases in sodium or fluid excretion, suggesting alternative non-diuretic mechanisms [35]. In our population, we observed a significant decline in blood pressure, demonstrated by a reduction in SBP, and a slight increase in hemoglobin levels and a modest haematocrit elevation. This elevation may be related to the SGLT2i diuresisdriven plasma concentration of red blood cells and to the direct erythropoiesis stimulation via early increases in erythropoietin levels [36-38].

Furthermore, echocardiographic changes underscore the early decongestive effects of SGLT2i, evidenced by a reduction in cardiac preload markers, such as LAVi, and PASP values.

Interestingly, we also observed a reduction in systemic resistance by the NICaS non-invasive hemodynamic assessment in our study population, suggesting that SGLT2 inhibition exerts its protective effects on renal and cardiac properties by negatively regulating the sympathetic nervous system [39–41].

Interestingly, subgroup analyses further revealed phenotype-specific responses. In patients with HFrEF and HFmrEF, significant reductions in preload markers (e.g., LAVi and PASP) and TBW suggest a pronounced natriuretic effect. Conversely, in patients with HFpEF, reduction in SBP was accompanied by significant decreases in TPR. These findings highlight SGLT2i's role in reducing vascular stiffness, enhancing ventricular-arterial coupling, and improving cardiac efficiency—key therapeutic targets in HFpEF. This analysis reinforces previous evidence showing reductions in blood pressure and systemic vascular resistance with dapagliflozin and canagliflozin, likely mediated by improved endothelial function, increased nitric oxide bioavailability, and reduced inflammation and oxidative stress [42–44].

Our data do not challenge the role of SGLT2i in modulating intravascular volume in HF but rather propose that their primary acute mechanism extends beyond fluid modulation. The impact of SGLT2i on fluid volume regulation in patients with type 2 diabetes and cardiovascular disease remains significant. Indeed, Tanaka et al. demonstrated that empagliflozin reduced estimated plasma volume (ePV) and extracellular volume (eEV) over 24 weeks, suggesting a mechanistic link between volume reduction and cardiac stress relief [45]. Similarly, luseogliflozin led to a sustained reduction in ePV over 24 weeks in HFpEF patients, with significant associations between ePV changes and lLAVi, reinforcing its potential hemodynamic benefits [46]. In a longer-term analysis, tofogliflozin reduced body weight, ePV, and BNP levels over 52 weeks, but after withdrawal, these parameters rebounded above baseline, highlighting the transient nature of its volume-modulating effects [47]. Finally, in HFrEF patients, empagliflozin reduced stressed blood volume

### **Table 3** Difference between baseline and after 1 mo of treatment in patients with $BMI \ge 25 \text{ kg/m}^2$

General characteristics         V           Weight (dg)         72.25 [57.80–92.0]         74.05 [57.60–97]         0.031           SBP (nmitig)         132.50 [110–150]         122 [104–141]         0.039           DBP (nmitig)         77.30 [55–90]         72 (15–90]         0.084           DBP (nmitig)         77.50 [55–90]         72 (15–90]         0.083           SRM Or, at basal time         97 [95–100]         97 [94–100]         0.825           SAMK Or, at basal time         97 [96–98]         97 (94–90]         0.522           Bichemical parameters         13 [020–1550]         13.00 [270–1540]         0.009           Hit (H)         13 [020–1550]         13.01 [270–1540]         0.009           Certainine (mg/d1)         0.97 [07–57.04]         1 [0.77–148]         0.974           Certainine (mg/d1)         0.97 [07–57.04]         1 [0.77–148]         0.932           Fasting Blood glucose (mg/d1)         99.50 [81–108]         94.50 [82–10]         0.322           Fasting Blood glucose (mg/d1)         99.50 [81–108]         94.50 [82–87]         0.332           For composition (%)         55 [5.27–401         9.45 [92–87]         0.332           For composition (%)         55 [5.27–412.34]         97.24 [5.343–12.92.07]         0.155		Baseline	Follow-up	<i>p</i> -value
Weight (bg)         72.5 [57.8-92.0]         74.6 [57.80-97]         0.031           SBP from (bg)         122.20 [10-150]         122 [04-14]         0.039           SBP from (bg)         77.50 [55-90]         66 [(7-99]         0.018           MMT (m)         37.51 [20-480]         46 [12-540]         0.018           Sark O, at basil time         97 [55-100]         97 [64-50]         0.025           Sark O, at basil time         97 [55-100]         97 [64-50]         0.232           Bicchernical parameters         97 [64-50]         15.60 [97.0-500]         0.039           Creattrinic (mg/d1)         0.02 [0.7-2.04]         1 [12/-1.60]         0.039           Creattrinic (mg/d1)         0.02 [0.7-2.04]         1 [12/-1.60]         0.039           Creattrinic (mg/d1)         0.02 [0.1-0.8]         94.50 [0.5-10]         0.039           Creattrinic (mg/d1)         0.05 [0.260-240]         93.45 [0.2-36]         0.036           Creattrinic (mg/d1)         0.05 [0.260-240]         93.45 [0.2-36]         0.036           Creattrinic (mg/d1)         0.50 [0.260-240]         93.45 [0.2-36]         0.036           Creattrinic (mg/d1)         0.50 [0.260-240]         93.45 [0.2-36]         0.036           Divid (g/m)         95.2 [0.2-1.42]	General characteristics			
ShP [mm/ap]12.20 (110-150)12.101-141)0.039DSP [mm/ap]75.0 (SS-00)72 (45-00)0.058DSP [mm/ap]2.30 (SS-30)66 [47-30]1.31AWW (m)3.7 (12-480)40 (120-340)0.12SAWO (J tabail time)97 (80-08)97 [84-100]0.256Sawo (J tabail time)97 (80-08)97 [84-100]0.256Sawo (J tabail time)97 (80-08)1.500 (90-15-40]0.006Inf (m)40.7 (50.00 44-50)4.500 (92-15-40]0.006Inf (m)0.250 (92-15-204)1.500 (92-15-40]0.006Inf (m)0.250 (92-15-204)1.500 (92-16-10)0.024Cotathine (mg/d)0.250 (92-17-27)850 (92-10)0.252Parting block glucose (mg/d)9.505 (82-0-201)9.345 (60-230)0.252Parting block glucose (mg/d)0.505 (82-0-201)9.345 (60-230)0.009I/Mit (g/m)9.505 (82-0-201)9.345 (60-230)0.009I/Mit (g/m)9.505 (82-0-201)9.345 (90-231)0.15I/Mit (g/m)9.505 (82-0-201)9.345 (90-231)0.15I/Mit (g/m)9.505 (82-0-201)9.345 (90-231)0.15I/Mit (g/m)9.505 (82-0-201)9.345 (90-230)0.57I/Mit (g/m)9.505 (82-0-201)9.345 (90-230)0.57I/Mit (g/m)9.505 (82-0-201)9.35 (92-131)0.15I/Mit (g/m)9.35 (92-130)0.570.57I/Mit (g/m)9.35 (92-130)0.570.57I/Mit (g/m)9.35 (92-130)0.570	Weight (kg)	77.25 [57.80–99.20;]	74.05 [57.60–97]	0.031
DPP (nmmping)75 0155-90172 (47-90)088HR (bpm)62.50 (55-90166 (47-90)0.371Safk O <sub>2</sub> at basal time97 (152-1001)97 (94-10010.856Safk O <sub>2</sub> at basal time97 (195-1001)97 (94-10010.532Bichemaci parameters77 (96-98)97 (94-97)0.153Ha (gdt1)13 (96-015.501)13.50 (29.50-47.90)0.039HT (%)40.75 (83.30-44.50)11.50 (29.80-47.90)0.039Creatinine (mg/d1)0.07 (0.75-704)11.07-1.48]0.94Creatinine (mg/d1)0.950 (53.1-179)38 (1/4.00-1803)0.371Easting blood glucose (mg/d1)0.505 (81-108)94.50 (65-110)0.951Garaca chemagibbin (%)5.85 (52.62-2401)92.45 (60-236)0.036Cardwing (mg/d1)0.505 (22.62-2401)92.45 (60-236)0.036Cardwing (mg/d1)0.505 (22.62-241)92.45 (60-236)0.036Cardwing (mg/d1)0.505 (22.62-241)92.45 (50.23.51)0.036Cardwing (mg/d1)0.505 (22.62-241)92.45 (50.23.51)0.036Cardwing (mg/d1)0.505 (22.52-241)92.45 (50.23.51)0.036Cardwing (mg/d1)0.505 (22.52-12.51)0.0360.036Cardwing (mg/d1)0.505 (22.52-12.61)0.0360.036Cardwing (mg/d1)0.505 (22.52-12.61)0.0360.036Cardwing (mg/d1)0.505 (22.62-13.51)0.611Cardwing (mg/d1)0.31 (22.70-1001)0.3510.351Cardwing (mg/d1)0.31 (22.70-1001)0.3510.	SBP (mmHg)	132.50 [110–150]	122 [104–141]	0.039
He (bgn)62:0 (5-00)66 (47-09)0.216MWT (m)375 (120-480)405 (120-400)0.3536MWT (m)97 (96-08)97 (94-09)0.35360 chemical parameters13 (96-1550)1360 (570-1540)0.036He (gdu)13 (96-1550)1450 (920-4200)0.039Creatrinie (mg/d1)0.92 (0.2-204)1 (0.77-1548)0.939Creatrinie (mg/d1)0.92 (0.2-204)1 (0.77-1548)0.939Creatrinie (mg/d1)0.950 (31-1259)381 (1466-1803)0.322Creatrinie (mg/d1)0.950 (31-103)9.518 (1-00)0.939Creatrinie (mg/d1)9.50 (81-108)9.50 (81-00)0.939Creatrinie (mg/d1)9.50 (81-010)9.50 (81-00)0.939Creatrinie (mg/d1)9.50 (81-010)9.50 (81-00)0.939Creatrinie (mg/d1)9.50 (81-010)9.50 (81-00)0.939Creatrinie (mg/d1)9.50 (81-010)9.50 (81-010)0.939Creatrinie (mg/d1)9.50 (81-012)9.50 (81-010)0.939Creatrinie (mg/d1)9.50 (81-010)0.9390.939Creatrinie (mg/d1)9.50 (81-010)0.9390.931Creatrinie (mg/d1)9.50 (81-010)0.9310.931Creatrinie (mg/d1)9.50 (81-010)0.9310.931Creatrinie (mg/d1)9.50 (81-010)0.9310.931Creatrinie (mg/d1)9.50 (81-010)0.9310.931Creatrinie (mg/d1)9.51 (81-012)0.9310.931Creatrinie (mg/d1)9.71 (83-1720)0.931 <t< td=""><td>DBP (mmHg)</td><td>77.50 [55–90]</td><td>72 [45–90]</td><td>0.088</td></t<>	DBP (mmHg)	77.50 [55–90]	72 [45–90]	0.088
dMM1 (m)375 (120-400)405 (120-540)6132Satk O, at basal time97 (95-100)97 (94-90)0.856Satk O, at time97 (96-90)97 (94-90)0.852Bichemical parameters97 (94-90)0.000Ho (M)130 (92-01-540)0.0090.009Creatinine (mg/d1)0.02 (0.2-520)150 (92-01-360)0.039Creatinine (mg/d1)0.050 (91-108)0.001 (91-08)0.021Creatinine (mg/d1)0.050 (91-108)0.001 (91-08)0.021Creatinine (mg/d1)0.050 (91-108)0.001 (91-08)0.021Creatinine (mg/d1)0.050 (91-108)0.001 (91-08)0.001 (91-08)Creating Mod glucose (mg/d1)0.050 (91-108)0.001 (91-08)0.001 (91-08)Creating Mod glucose (mg/d1)0.050 (92-06)0.013 (92-010)0.013 (92-010)0.013 (92-010)Creating Mod glucose (mg/d1)0.050 (92-06)9.044 (92-100)0.013 (92-010)	HR (bpm)	62.50 [55–90]	66 [47–99]	0.371
Saft8 Q, at basil timeP (95-100)97 (94-90)0.836Saft8 Q, at G min97 (96-98)97 (94-99)0.532Bicchemical parameters13 (96-15.00)13.00 (970-15.40)0.006H (G/GL)13 (96-05.50)41.50 (920-47.40)0.039Creatnine (mg/dL)0.92 (075-2.04)11 (077-1.68)0.92166 (31-08)0.50 (51.71-57)381 (146-60-1.03)0.321PhrpoRNP (grymL)0.905 (121-125)381 (146-61-103)0.322Fasting blood glucose (mg/dL)0.905 (121-125)381 (146-61-103)0.321Cycated hemoglobin (%)555 (12-6.40)560 (890-6.70)0.036Cycated hemoglobin (%)555 (12-6.40)9345 (02-236)0.036Cycated hemoglobin (%)100.05 (50.0-240)9344 (50.2-230)0.036Cycated hemoglobin (%)100.05 (50.0-240)9344 (50.2-130)0.036Cycated hemoglobin (%)100.05 (50.0-240)9344 (50.2-130)0.036Cycated hemoglobin (%)100.05 (50.0-240)9344 (50.2-130)0.036Cycated hemoglobin (%)100.05 (50.0-240)934 (50.2-130)0.036Cycated hemoglobin (%)100.05 (50.0-240)100.050.036Cycate (ms/cc)935 (52.2-14.2.2.4)934 (50.2-201)0.036Cycate (ms/cc)17.10 (15.0-2.201)17.55 (50.2-2.01)0.036Cycate (ms/cc)17.10 (15.0-2.201)17.55 (50.2-2.02)0.036Cycate (ms/cc)17.10 (15.0-2.102)10.25 (16.0-2.102)0.051Cycate (ms/cc)103 (15.0-2.102)10.25 (16.0-2	6MWT (m)	375 [120–480]	405 [120–540]	0.132
Sarts O, at 6 min         97 (96-98)         97 (94-99)         0532           Biochemical parameters	Sat% $O_2$ at basal time	97 [95–100]	97 [94–100]	0.836
Biochemical parameters         13.60 [870-15.40]         0.006           Hb (g/dL)         13 [9.60-15.50]         13.60 [870-15.40]         0.039           Creatinine (mg/dL)         0.92 [0.75-2.04]         1 [0.77-1.68]         0.924           OER (m.//m./17am2)         05 [38-90]         0.57 [37.37-98.30]         0.391           NF-proBNP (pg/m.)         609.50 [231-17.59]         381 [146.60-1803]         0.322           Fasting blood glucose (mg/dL)         90.50 [81-08]         94.50 [65-110]         0.894           Cycated hemoglobin (%)         5.85 [51.2-6.40]         5.60 [4.90-6.70]         0.036           Echocatolog aphy parameters         200.00         0.0199         0.0099         0.0199           LVM (g/m)         95.50 [52.52-142.24]         97.44 [53.43-12.907]         0.155           Echocatolog aphy parameters         200.00         0.059         0.036           EV (mL)         45.00 [27.40-173]         39.40 [24-0-8.90]         0.059           VM (m/h)         95.25 [25.21-12.24]         97.41 [53.43-12.907]         0.155           EV (mL)         45.00 [27.40-173]         39.40 [24-0-2.80]         0.059           VM (m/m)         94.95 [37.20-130]         83.5 [31-2-13]         0.611           EV (mL)         45.00 [27.0-130] </td <td>Sat% <math>O_2</math> at 6 min</td> <td>97 [96–98]</td> <td>97 [94–99]</td> <td>0.532</td>	Sat% $O_2$ at 6 min	97 [96–98]	97 [94–99]	0.532
Hb (g/dL)         13 (360-1550)         13 (360 (970-1540)         0.006           HCT (%)         4075 (30.30-44.50)         41,50 (2980-47.90)         0.039           Catatinic (mg/dL)         0.02 (0.75-2.04)         10,77-1.69         0.924           eGFR (m/mir/L 73m2)         65 (30-90)         65,70 (37.30-88.30)         0.332           Stafing blod glucose (mg/dL)         90.50 (231-17.59)         83 (16.60-1803)         0.322           Stafing blod glucose (mg/dL)         90.50 (251-6.40)         56.0 (490-6.70)         0.834           Ghyata themaglibin (%)         55.5 (52.6-240)         93.45 (60-236)         0.036           ESV (mL)         155.05 (62.60-240)         93.45 (60-236)         0.036           ESV (mL)         45.00 (27.00-17.3)         93.40 (20-10)         0.125           EF (%)         45.80 (27.90-60)         56 (28.40-62.80)         0.069           LVMI (g/m <sup>2</sup> )         95.9 (25.22.142.24)         97.44 (53.43-12.90.7)         0.437           A wase (cm/sec)         84.95 (27.20-17.3)         83.45 (33-12.90.7)         0.457           A wase (cm/sec)         84.95 (27.20-17.0)         83.53 (33-12.1)         0.437           A wase (cm/sec)         84.95 (27.20-17.0)         7.64 (555-12.60)         0.053           LAC (m/sec)	Biochemical parameters			
HCT (%)         40.75 [0.3.044.50]         41.50 [0.9.8047.50]         0.039           Creatinine (mg/dL)         0.92 [0.75-204]         100.77-168]         0.924           CPR (mL/min/L7am2)         65 [00-90]         65.70 [37.30-88.30]         0.331           NT-proBNP (pg/mL)         6005 0 [211-759]         811 [146.60-1803]         0.322           Fasting blood glucose (mg/dL)         0.903 (B1-08]         56.06 [4.90-6.70]         0.751           Echocardiography parameters         U         0.036         0.036           EV/ (mL)         165.05 [62.60-240]         9.45 [60-236]         0.036           EV/ (mL)         15.05 [62.60-240]         9.45 [60-236]         0.036           EV/ (mL)         15.05 [62.60-240]         9.73 [53.41-150.01         0.73           EV/ (mL)         17.01 [55.0-21.60]         13.53         0.351           EV/ (mL)         17.01 [55.0-21.60]         0.53         0.55 <td>Hb (g/dL)</td> <td>13 [9.60–15.50]</td> <td>13.60 [9.70–15.40]</td> <td>0.006</td>	Hb (g/dL)	13 [9.60–15.50]	13.60 [9.70–15.40]	0.006
Creatinine (mg/dL)         0.92 (0.75–2.04)         10.07–1.68)         0.924           cGFR (mL/min/L73m2)         65 (08–00)         65.70 (173.0-88.00)         0.331           Fatting blood glucose (mg/dL)         0.05 (02.11-759)         381 (146-06–1803)         0.332           Fatting blood glucose (mg/dL)         0.05 (02.11-759)         381 (146-06–1803)         0.834           Glycated hemoglobin (%)         5.85 [5.12-6.40)         5.60 (4.90-6.70)         0.751           EDV (mL)         105.05 [62.60-240]         93.45 [60-26]         0.036           EV (mL)         95.52 [52.52-142.24]         97.34 [53.43-129.07]         0.125           EV (mg)         94.52 [62.20-10]         5.62 [840-62.80]         0.069           LVMI (g/m <sup>2</sup> )         95.2 [52.52-142.24]         97.34 [53.43-129.07]         0.447           EV (mg)         94.52 [62.20-31]         0.457         0.4487           EV (ms)         94.59 [37.20-130]         83.35 [33-121]         0.447           EV (ms)         87.4450-135         7.50 [58.20-135]         0.611           EV (ms)         87.4450-130         0.751 [44-1450]         0.753           LAC (ms/sec)         87.4450-130         7.96 [53-0-7.90]         0.457           LAV (m(m/m)         47.30 [63-644]	HCT (%)	40.75 [30.30-44.50]	41.50 [29.80-47.90]	0.039
eGFR (mL/min/1.73m2)         65 (30-90]         65 70 (37.30-88.30)         0.3391           NT:proRNP (bg/mL)         6905 (231-1759)         381 [1466.1903]         0.332           Stating blood glucose (mg/dL)         9505 [61-108]         9505 [65-110]         0.894           Glycated hemoglobin (%)         585 [5.12-6.40]         560 [4.90-6.70]         0.751           Echocardiography parameters         U         0.036         0.036           EV (mL)         105.05 [62.60-240]         95.45 [60-236]         0.036           EV (mL)         45.40 [27.00-62]         95.45 [63.2-131]         0.437           King/m <sup>2</sup> 9.952 [52.52 +12.24]         97.44 [53.43-129.07]         0.125           E(%)         84.80 [27.00-62]         83.25 [33-121]         0.437           A wave (mr/sec)         87 [64.50-135]         7.55 [53.0-213]         0.611           E/A         0.70 [0.40-130]         0.70 [0.40-110]         0.188           Sept E/(mr/sec)         87 [64.50-17.60]         7.86 [5.50-12.60]         0.573           E/A         0.70 [0.40-130]         0.70 [0.40-130]         0.70 [0.40-130]         0.726           E/F         9.33 [32-11.70]         7.86 [5.50-12.60]         0.573           E/A (mr/sec)         83.5 [32-12.73]	Creatinine (mg/dL)	0.92 [0.75–2.04]	1 [0.77–1.68]	0.924
NF-pro8NP (pg/mL)         609.50 [231–17.59]         381 [14.660–1803]         0.322           Fasting blood glucose (my/dL)         90.50 [81–108]         94.50 [65–110]         0.884           Glycated hemoglobin (%)         5.65 [51.2-6.40]         5.60 [4.90.6-70]         0.751           Echocardiography parameters          94.5 [60-236]         94.5 [60-236]         0.0099           IVMI (g/m <sup>2</sup> )         95.5 [52.52-142.24]         97.34 [53.43-129.07]         0.125           Ef (%)         54.60 [27.50-60]         155 [63.20-210]         17.55 [0.30-21]         0.457           E wave (cm/sec)         84.95 [37.20-130]         83.35 [33-12]         0.457           E wave (cm/sec)         87 [44.50-135]         7.50 [58.20-135]         0.611           E/A         07 [0.40-1.01]         0.750 [0.82-0.13]         0.457           A wave (cm/sec)         80.3 [3.29-11.70]         7.64 [5.55-12.60]         0.753           LAV( m/m <sup>2</sup> )         44.70 [0.669.40]         7.05 [58.20-13.0]         0.751           LAV( m/m <sup>2</sup> )         44.70 [0.669.40]         7.05 [58.20-13.0]         0.751           LAV( m/m <sup>2</sup> )         44.70 [0.669.40]         10.25 [1.60-21.60]         0.058           PALS (%)         18.45 [1.0-28.30]         19.25 [4.30-3.20]         0.573	eGFR (mL/min/1.73m2)	65 [30–90]	65.70 [37.30–88.30]	0.391
Fasting blood glucose (mg/dL)         9050 [81-108]         9450 [65-110]         02894           Giycated hemoglobin (%)         555 [51-2-640]         500 [43-6-70]         0.751           Ebchacardiography parameters         10505 [62.60-240]         9345 [60-236]         0.036           ESV (mL)         4540 [27.60-173]         9440 [26-16]         0.009           LWM (g/m)         9592 [52.52-412.24]         97.45 [53.41-129.07]         0.059           LWM (g/m)         9459 [27.02-112]         97.45 [53.41-129.07]         0.059           LWM (g/m)         9459 [27.02-112]         87.55 [38.20-113]         0.451           E wave (mr/sec)         87 [44.50-135]         7.50 [82.0-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 (0.40-1.10]         0.148           ExatP (mr/sec)         87 [44.50-135]         7.50 [82.0-135]         0.611           E/A         0.70 [0.40-1.30]         7.83 [5.4-14.50]         0.726           E/F         9.43 [45.0-17.01]         7.83 [5.4-14.50]         0.726           E/F         9.43 [4.50-17.01]         7.83 [5.4-14.50]         0.721           E/E (M/m)         9.15 [1.90-2.110]         9.35 [2.0-23.10]         0.573           LAX (m/m)         9.45 [1.0-2.770]         9.25 [1.0-2.1	NT-proBNP (pg/mL)	609.50 [231–1759]	381 [146.60–1803]	0.322
Glycated hemoglobin (%)         5.85 [5,12-6.40]         5.60 [4.90-6.70]         0.751           Echocardiography parameters               EVV (mL)         105.05 [52.60-240]         93.45 [60-236]             EVV (mL)         45.40 [27.60-173]         39.40 [26-169]	Fasting blood glucose (mg/dL)	90.50 [81–108]	94.50 [65–110]	0.894
Echocardiography parameters         Instrumentation           EDV (mL)         105.05 [62.60–240]         93.45 [60–236]         0.036           ESV (mL)         45.00 [27.60–173]         39.40 [26–169]         0.009           LWMI (g/m <sup>2</sup> )         99.52 [52.52-142.24]         97.34 [53.43+129.07]         0.125           EF (%)         54.80 [27.90–60]         56 [28.40–62.80]         0.069           LVGLS (%)         17.10 [950–22.90]         17.55 [93.0–21]         0.487           A wave (cm/sec)         84.95 [37.20–130]         83.35 [33–121]         0.487           A wave (cm/sec)         87 [44.50–135]         75.50 [58.20–135]         0.611           E/A         0.70 [0.40–130]         0.70 [0.40–1.01]         0.148           Sept E/cm/sec)         803 [3.92–11.70]         7.64 [5.55–12.60]         0.573           LAU (m/m <sup>2</sup> )         44.70 (3.649-40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [8.10–28.30]         19.25 [4.30–39.20]         0.351           LAU (m/m <sup>2</sup> )         14.55 [1.90–21.10]         9.35 [2.90–23.10]         0.573           LACT(%)         84.5 [2.10–19.20]         10.25 [1.60–21.60]         0.418           RAV (m/m <sup>2</sup> )         15 [1.90–21.10]         9.35 [2.90–23.10]         0.571 <td>Glycated hemoglobin (%)</td> <td>5.85 [5.12-6.40]</td> <td>5.60 [4.90–6.70]</td> <td>0.751</td>	Glycated hemoglobin (%)	5.85 [5.12-6.40]	5.60 [4.90–6.70]	0.751
EDV (mL)         105.05 [62.60-240]         93.45 [60-236]         0.036           ESV (mL)         45.40 [27.60-173]         39.40 [52-163]         0.009           LWM (g/m)         9952 [52.21.42.24]         97.34 [53.43-129.07]         0.125           EF (%)         54.80 [27.90-60]         7.65 [28.40-62.80]         0.669           LVGLS (%)         17.10 [95.0-22.90]         7.55 [58.20-13]         0.611           E wave (cm/sec)         87 [44.50-135]         7.55 [58.20-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept E/(cm/sec)         7.91 [5.3-17.70]         7.64 [5.5-1.260]         0.573           Lat E/(cm/sec)         8.03 [3.92-11.70]         7.68 [5.44-14.50]         0.726           E/E'         9.43 [4.50-17.60]         7.98 [5.30-17.90]         0.487           LAV (m/m <sup>2</sup> )         4.470 [30.694.01]         4.05 [2.90-23.10]         0.573           LAV (m/m <sup>2</sup> )         4.470 [30.694.01]         4.05 [2.90-23.10]         0.573           LAC (%)         18.45 [8.10-28.30]         19.25 [4.30-32.01]         0.351           LAV (m/m <sup>2</sup> )         1.55 [5.70-27.70]         1.05 [1.50-21.60]         0.618           RAV (m/m <sup>2</sup> )         2.15 [1.32-61.01]         2.10 [1.30-2	Echocardiography parameters			
ESV (mL)         45.40 (27.60–173]         39.40 (26–169)         0.009           LVM (g/m)         99.52 (52.52–14.24)         97.44 (53.43–129.07)         0.125           F (%)         54.80 (27.90–60)         56 (28.40–62.80)         0.069           LVM (s) (%)         17.01 (9.50–22.90)         17.55 (9.30–21)         0.447           Ewave (cm/sec)         84.95 (37.20–130)         83.35 (33–121)         0.437           A wave (cm/sec)         87.445.0–135]         75.05 (82.0–135)         0.611           E/A         0.70 (0.40–1.00)         0.148         55.07 (3.40–1.30)         0.73 (3.41–1.450)         0.730           Sept F(cm/sec)         7.91 (5.33–17.70)         7.64 (5.55–1.260)         0.738         1.41 (5.70–2.70)         0.730           LAT (MM/m <sup>2</sup> )         44.70 (30-69.40)         40.50 (29-62.60)         0.008         1.45 (8.10–28.30)         9.25 (4.30–39.20)         0.351           LACD(%)         184.5 (8.10–28.30)         19.25 (4.30–39.20)         0.531         1.42 (1.01–1.20)         0.573           LACD(%)         18.45 (8.10–28.30)         19.25 (1.40–3.20.0)         0.573         0.744           RVL (m/m <sup>2</sup> )         21.15 (1.30–21.70)         10.25 (1.60–21.60)         0.618         0.744           RVL (m/m <sup>2</sup> )         21.55 (1.	EDV (mL)	105.05 [62.60–240]	93.45 [60–236]	0.036
LVM (g/m²)         9952 [5252-142.24]         97.34 [53.33-129.07]         0.125           F(%)         5480 [27,90-60]         56 [24.04-2.80]         0.069           LVGLS (%)         17.10 [950-22.90]         17.55 [930-21]         0.437           Awave (mr/sec)         8495 [37.20-130]         83.35 [33-121]         0.437           Awave (mr/sec)         87 [44.50-135]         75.05 [58.20-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept F(mr/sec)         80.31 [3.92-117.0]         7.64 [5.55-1.26.0]         0.573           LatE(mr/sec)         80.31 [3.92-117.0]         7.63 [5.44-14.50]         0.361           LAV (m/m²)         447.01 [3.69,40]         40.50 [26.06.0]         0.0081           LAV (m/m²)         18.45 [8.10-28.30]         1.925 [4.30-32.0]         0.351           LAV (m/m²)         18.45 [8.10-28.0]         1.925 [4.30-32.0]         0.351           LAV (m/m²)         18.55 [5.20-27.70]         1.925 [4.30-32.0]         0.372           LACT(%)         18.45 [2.40-19.20]         1.90 [13.0-27.70]         0.972           RAV (m/m²)         12.65 [1.30-3.20]         1.90 [13.0-27.70]         0.972           RAS (m/m²)         12.66 [1.2-21]         0.935	ESV (mL)	45.40 [27.60–173]	39.40 [26–169]	0.009
EF (%)         54.80 (27.90-60)         56 [24.0-62.80]         0.069           LVGLS (%)         17.10 [950-22.90]         17.55 [9.30-21]         0.487           E wave (cm/sec)         84.95 [37.20-130]         83.35 [33-12]         0.437           A wave (cm/sec)         87 [44.50-135]         75.50 [58.20-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept E/(cm/sec)         8.73 [45.0-17.60]         7.98 [5.30-17.90]         0.487           LAV (m/m²)         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [8.10-28.30]         19.25 [4.30-39.20]         0.351           LACC (%)         9.15 [1.90-21.10]         2.95 [2.40-28.30]         0.273           LACC (%)         9.15 [1.90-21.10]         2.91 [1.70]         0.74           RAVE (m/m²)         2.165 [7.20-27.70]         2.190 [13.90-29.80]         0.271           RAVE (m/m²)         2.165 [7.20-27.70]         2.190 [13.90-29.80]         0.272           TAPSE (mm)         2.160 [18-28]         2.21 [17-26]         0.904           RV S (mem/mmHg)         0.73 [5.3-1.49]         0.81 [6.0-1.73]         0.956           PASE (mm/msc)         2.750 [5.3-1.49]         3.91 [2.8-5.37]	$LVMi (a/m^2)$	99.52 [52.52-142.24]	97.34 [53.43-129.07]	0.125
LVGLS (%)         17.10 [9.50–22.90]         17.55 [9.30–21]         0.487           Ewave (cm/sec)         84.95 [37.20–130]         83.35 [33–121]         0.437           A wave (cm/sec)         87 [44.50–135]         75.05 [82.0–135]         0.611           E/A         0.70 [0.40–1.30]         0.70 [0.40–1.10]         0.148           Sept E/(cm/sec)         7.91 [5.33–17.70]         7.64 [5.55–12.60]         0.733           Lat E/(cm/sec)         803 [3.92–11.70]         7.63 [5.44–14.50]         0.726           E/E'         9.43 [4.50–17.60]         7.98 [5.30–17.90]         0.487           LAV((m/m <sup>2</sup> )         44.70 (50-69.40)         40.50 [2.96-2.60]         0.008           PALS (%)         18.45 [8.10–28.30]         19.25 [4.30–39.20]         0.351           LAC(%)         8.45 [2.10–19.20]         0.201 [16–2.23]         0.744           RVLS fice wall (%)         21.15 [13-26.10]         2.010 [15–2.23]         0.741           RVLS fice wall (%)         21.65 [7.20–27.70]         21.90 [13.00–29.80]         0.271           RVLS fice wall (%)         21.65 [13-26.10]         2.01 [15–23]         0.742           RVS (cm/s)         12.60 [18–28]         22.10 [13.0–27.70]         0.72           RVS (cmm/s)         12.60 [17.0–27.70]	EF (%)	54.80 [27.90–60]	56 [28.40-62.80]	0.069
E wave (cm/sec)         8495 [37.20-130]         83.35 [33-121]         0.437           A wave (cm/sec)         87 [44 50-135]         7550 [58.20-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept E'(cm/sec)         791 [53.3-17.70]         746 [55.7-12.60]         0.753           Lat E'(cm/sec)         803 [3.92-11.70]         763 [5.44-14.50]         0.726           E/F         9.43 [4.50-17.60]         7.88 [5.30-17.90]         0.487           LAV (m/m <sup>2</sup> )         9.43 [4.50-17.60]         7.88 [5.30-17.90]         0.487           LAV (m/m <sup>2</sup> )         9.43 [4.50-17.60]         7.88 [5.30-17.90]         0.487           LAV (m/m <sup>2</sup> )         9.43 [4.50-17.60]         7.88 [5.30-17.90]         0.487           LAV (m/m <sup>2</sup> )         9.43 [4.50-17.60]         1.925 [1.30-32.00]         0.573           LACT(%)         8.45 [2.10-19.20]         1.025 [1.60-21.60]         0.618           RAV (m/m <sup>2</sup> )         21.15 [1.3-26.10]         21.90 [13.0-29.80]         0.271           RVLS Global (%)         1.815 [5.80-22.90]         1.90 [11.30-27.70]         0.072           RVLS fee wall (%)         21.60 [11.20-25]         1.245 [10-24.50]         0.995           PASE (mm/lg)         2.60 [11.20-25]	LVGLS (%)	17.10 [9.50–22.90]	17.55 [9.30–21]	0.487
A wave (cm/sec)         87 [44.50-135]         75.50 [58.20-135]         0.611           E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept E/(cm/sec)         7.91 [53.3-17.70]         7.44 [55.5-12.60]         0.573           Lat E/(cm/sec)         8.03 [3.92-11.70]         7.46 [55.5-12.60]         0.726           E/E'         9.43 [45.0-17.60]         7.98 [53.0-17.90]         0.487           LAV/ (m/m <sup>*</sup> )         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         1845 [8.10-28.30]         19.25 [4.30-39.20]         0.351           LAV/ (m/m <sup>*</sup> )         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         1845 [8.10-28.30]         19.25 [4.30-39.20]         0.351           LAV/ (m/m <sup>*</sup> )         44.70 [30-69.40]         40.50 [29-62.60]         0.008           RAUS (%)         18.45 [8.10-28.30]         19.25 [4.30-39.20]         0.573           LACT(%)         8.45 [2.10-19.20]         10.25 [1.60-21.60]         0.618           RAV (m/m <sup>*</sup> )         21.15 [1.326.10]         20.10 [15-23]         0.744           RVLS Global (%)         18.15 [50.02.200]         12.90 [11.30-27.70]         0.972           TAPSE (mm)         12.60 [11.20-25]         12	E wave (cm/sec)	84.95 [37.20–130]	83.35 [33–121]	0.437
E/A         0.70 [0.40-1.30]         0.70 [0.40-1.10]         0.148           Sept E'(cm/sec)         7.91 [5.33-17.70]         7.64 [5.55-12.60]         0.573           Lat E'(cm/sec)         8.03 [3.92-11.70]         7.63 [5.44-14.50]         0.726           E/E'         9.43 [4.50-17.60]         9.85 [5.0-17.90]         0.487           LAV (m/m²)         4470 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [8.10-28.30]         19.25 [4.30-39.20]         0.573           LACD(%)         9.15 [1.90-21.10]         9.35 [2.90-23.10]         0.573           LACT(%)         8.45 [2.10-9.20]         10.25 [1.60-21.60]         0.618           RAV (m/m²)         21.15 [1.3-26.10]         0.21 [1.30-27.70]         0.794           RVLS fee wall (%)         18.15 [5.80-22.90]         1.920 [11.30-27.70]         0.972           RVLS fee wall (%)         12.60 [18-28]         22 [17-26]         0.904           RV S (cm/s)         12.60 [18-28]         22 [17-26]         0.905	A wave (cm/sec)	87 [44.50–135]	75.50 [58.20–135]	0.611
Sept E'(cm/sec)         7.91 [5.33-17.70]         7.64 [5.55-12.60]         0.573           Lat E'(cm/sec)         8.03 [3.92-11.70]         7.64 [5.55-12.60]         0.726           E/E'         9.43 [4.50-17.60]         7.98 [5.30-17.90]         0.487           LAV (m/m²)         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [8.10-28.30]         19.25 [4.30-39.20]         0.573           LAV(m/m²)         9.15 [1.90-21.10]         9.35 [2.90-23.10]         0.573           LACT(%)         8.45 [2.10-19.20]         10.25 [1.60-21.60]         0.618           RAV (m/m²)         21.15 [1.3-26.10]         20.10 [15-23]         0.744           Stock wall (%)         18.15 [5.80-22.90]         19.20 [11.30-27.70]         0.072           TAPSE (mm)         21.60 [18-28]         22 [17-26]         0.904           RV S (rem/s)         12.60 [11.20-25]         12.45 [10-24.50]         0.959           peak TR vel (m/sec)         2.36 [1.30-3.20]         2.15 [1.44-2.90]         0.056           NC4S parameters          0.73 [5.54-1.49]         0.88 [6.60-1.73]         0.096           NC4S parameters           0.71 [5.3-2.25]         0.201 [4.2-2.77]         0.892           C0 (/mi	F/A	0.70 [0.40–1.30]	0.70 [0.40–1.10]	0.148
Lat E(cm/sec)         B03 [392-11.70]         7.63 [5.44-14.50]         0.726           E/E'         9.43 [4.50-17.60]         7.98 [5.30-17.90]         0.487           LAVI (ml/m <sup>2</sup> )         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [81.0-28.30]         9.25 [4.30-39.20]         0.351           LACD(%)         9.15 [1.90-21.10]         9.35 [2.90-23.10]         0.573           LACT(%)         8.45 [2.10-19.20]         10.25 [1.60-21.60]         0.618           RAV (ml/m <sup>2</sup> )         21.15 [13-26.10]         20.10 [15-23]         0.744           RVLS free wall (%)         21.65 [7.20-27.70]         21.90 [13.90-29.80]         0.271           RVLS free wall (%)         18.15 [58-22.90]         19.20 [11.30-27.70]         0.072           TAPSE (mm)         21.66 [18-28]         22 [17-26]         0.904           RV S (cm/s)         12.60 [11.20-25]         12.45 [10-24.50]         0.959           peak TR vel (m/sec)         2.36 [1.30-3.20]         2.15 [1.44-2.90]         0.056           PASP (mmHg)         0.73 [0.53-1.49]         0.88 [0.60-1.73]         0.82           CO (/min/m <sup>2</sup> )         0.77 [1.53-2.25]         2.20 [1.42-2.77]         0.82           CO (/min/m <sup>2</sup> )         9.55 [7.8-109]	Sept F'(cm/sec)	7.91 [5.33–17.70]	7.64 [5.55–12.60]	0.573
EF         943 [430-17.60]         788 [530-17.90]         0.487           LAVi (m/m <sup>2</sup> )         447.0 [30-6940]         40.50 [29-62.60]         0.008           PALS (%)         1845 [8.10-28.30]         1925 [4.30-39.20]         0.351           LACD(%)         9.15 [1.90-21.10]         9.35 [2.90-23.10]         0.573           LACT(%)         8.45 [2.10-19.20]         10.25 [1.60-21.60]         0.618           RAVi (m/m <sup>2</sup> )         21.15 [13-26.10]         20.10 [15-23]         0.744           RVLS free wall (%)         18.15 [5.80-22.90]         19.20 [11.30-27.70]         0.72           RVLS Global (%)         18.15 [5.80-22.90]         19.20 [11.30-27.70]         0.72           TAPSE (mm)         21.60 [12.0-25]         12.45 [10-24.50]         0.904           RV 5 (cm/s)         12.60 [11.20-25]         12.45 [1.60-21.60]         0.959           peak TR vel (m/sec)         2.36 [1.30-3.20]         2.15 [1.44-2.90]         0.956           PASP (mmHg)         0.73 [0.53-1.49]         0.88 [0.60-1.73]         0.966           NICAS parameters          0.445         0.944           CI (/min/m <sup>2</sup> )         2.07 [1.53-225]         2.20 [1.42-2.77]         0.882           CO (/min/m <sup>2</sup> )         3.77 [2.306-40.97]         31.43 [2.24-49.3.	Lat F'(cm/sec)	8.03 [3.92–11.70]	7.63 [5.44–14.50]	0.726
LAV: (m/m <sup>2</sup> )         44.70 [30-69.40]         40.50 [29-62.60]         0.008           PALS (%)         18.45 [8.10-28.30]         19.25 [4.30-39.20]         0.351           LACD(%)         9.15 [1.90-21.10]         9.35 [2.90-23.10]         0.573           LACT(%)         8.45 [2.10-19.20]         10.25 [1.60-21.60]         0.618           RAV (m/m <sup>2</sup> )         21.15 [13-26.10]         20.10 [15-23]         0.744           RVLS free wall (%)         16.5 [7.20-27.70]         19.90 [13.90-29.80]         0.271           RVLS Global (%)         18.15 [5.80-22.90]         19.20 [11.30-27.70]         0.072           TAPSE (mm)         21.60 [18-28]         22 [17-26]         0.904           RV S (cm/s)         12.60 [11.20-25]         12.45 [10-24.50]         0.955           PASP (mmHg)         27 [15-40]         24.50 [15-35]         0.036           TAPSE/pASP (mm/mHg)         0.50 [78-109]         87.50 [63-106]         0.043           CI (/min/m <sup>2</sup> )         2.07 [1.53-225]         2.20 [1.42-2.77]         0.882           CO (/min)         3.77 [2.59-4.48]         3.91 [2.68-5.37]         1.120           Stroke volume (ml)         5.55 [3.68-93.13]         0.276           Stroke volume (ml)         3.77 [2.30-6-40.97]         3.143 [2.32-4-49.34]	F/F'	9.43 [4.50–17.60]	7.98 [5.30–17.90]	0.487
PALS (%)         18.45 [8.10–28.30]         19.25 [4.30–39.20]         0.351           LACD(%)         9.15 [1.90–21.10]         9.35 [2.90–23.10]         0.573           LACT(%)         8.45 [2.10–19.20]         10.25 [1.60–21.60]         0.618           RAV. (m/m²)         21.15 [13-26.10]         20.10 [15–23]         0.744           RVLS free wall (%)         21.65 [7.20–27.70]         21.90 [13.90–29.80]         0.271           RVLS folobal (%)         18.15 [5.80–22.90]         19.20 [11.30–27.70]         0.072           TAPSE (mm)         21.60 [18–28]         22 [17–26]         0.904           RV S (cm/s)         12.60 [11.20–25]         12.45 [10-24.50]         0.959           peak TR vel (m/sec)         2.36 [1.30–3.20]         2.15 [1.44–2.90]         0.056           PASP (mmHg)         0.73 [0.53–1.49]         0.88 [0.60–1.73]         0.904           NICaS parameters           0.91         0.925           VC (min/m²)         0.71 [0.53–2.5]         2.02 [1.42–2.77]         0.082         0.043           C0 (/min/m²)         2.07 [1.53–2.56]         2.02 [1.42–2.77]         0.82         0.076           Stroke volume (ml)         5558 [41.05–76.08]         5.502 [36.88–93.13]         0.276         0.926	L = 1 AVi (ml/m <sup>2</sup> )	44.70 [30-69.40]	40.50 [29-62.60]	0.008
LACD(%)9.15 [1,90–21.10]9.35 [2,90–23.10]0.573LACT(%)8.45 [2.10–19.20]10.25 [1.60–21.60]0.618RAV. (m/m²)21.15 [13-26.10]20.10 [15–23]0.744RVLS free wall (%)21.65 [7,20–27.70]21.90 [13.90–29.80]0.271RVLS Global (%)18.15 [5.80–22.90]19.20 [11.30–27.70]0.072TAPSE (mm)21.60 [18–28]22 [17–26]0.904RV S (cm/s)12.60 [11.20–25]12.45 [10-24.50]0.956PASP (mm/g)2.70 [1.30–3.20]2.15 [1.44–2.90]0.056PASP (mmHg)0.73 [0.53–1.49]0.88 [0.60–1.73]0.096NICaS parameters0.944C1 (/min/m²)0.77 [1.53–2.25]2.20 [1.42–2.77]0.882C0 (/min/m²)0.77 [1.53–2.25]2.02 [1.42–2.77]0.822C0 (/min/m²)0.77 [1.53–2.25]2.00 [1.42–2.77]0.822C0 (/min/m²)0.77 [1.53–2.25]2.00 [1.42–2.77]0.822C0 (/min/m²)0.77 [1.53–2.25]2.00 [1.42–2.77]0.822C0 (/min/m²)0.77 [2.59–4.48]3.91 [2.68–5.37]0.276Stroke volume (ml)3.77 [2.59–4.48]3.91 [2.68–5.37]0.276Stroke volume index (ml/m²)1.175 [2.306–40.97]3.143 [2.324–49.34]0.240CPI (w/m²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm³)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm³)3.616.50 [197–2767]1657.50 [1259–2863]0.002TPRi (dn*s/cm³)3.616.50 [2911–5024]	PALS (%)	18.45 [8.10–28.30]	19.25 [4.30–39.20]	0.351
LACT(%)845 [210–19.20]10.25 [1.60–21.60]0.618RAV (ml/m²)21.15 [13-26.10]20.10 [15–23]0.744RVLS free wall (%)21.65 [7.20–27.70]21.90 [13.90–29.80]0.271RVLS Global (%)18.15 [5.80–22.90]19.20 [11.30–27.70]0.072TAPSE (mm)21.60 [18–28]22 [17–26]0.904RV 5 '(cm/s)12.60 [11.20–25]12.45 [10-24.50]0.959peak TR vel (m/sec)2.36 [1.30–3.20]2.15 [1.44–2.90]0.056PASP (mm/mg)0.77 [15–40]24.50 [15–35]0.036TAPSE/PASP (mm/mmHg)0.73 [0.53–1.49]0.88 [0.60–1.73]0.036NICaS parametersWW0.0720.043CI (//min/m²)2.07 [1.53–2.25]2.20 [1.42–2.77]0.082CO (//min)3.77 [2.59–4.48]3.91 [2.68–5.37]0.120Stroke volume (ml)5.55 8 [41.05–76.08]5.502 [36.88–93.13]0.276Stroke volume (ml/m²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm³)3616.50 [2911–5024]3098.50 [1260–4684]0.001GGI9.08 [5.83–13.84]9.72 [7.66–13.98]0.115RR (/min)16.50 [1–21]16 [12–24]0.828RDW (ko)4462 [34 95-65]4509 [55 56.81]0.230	LACD(%)	9.15 [1.90-21.10]	9.35 [2.90–23.10]	0.573
RAVi (m/m²)       21.15 [13-26.10]       20.10 [15-23]       0.744         RAVi (m/m²)       21.65 [7.20-27.70]       21.90 [13.90-29.80]       0.271         RVLS free wall (%)       18.15 [5.80-22.90]       19.20 [11.30-27.70]       0.072         TAPSE (mm)       21.60 [18-28]       22 [17-26]       0.904         RV S (cm/s)       12.60 [11.20-25]       12.45 [10-24.50]       0.959         peak TR vel (m/sec)       2.36 [1.30-3.20]       2.15 [1.44-2.90]       0.056         PASP (mm/mg)       0.71 [0.53-1.49]       0.88 [0.60-1.73]       0.036         NICaS parameters	LACT(%)	8.45 [2.10–19.20]	10.25 [1.60-21.60]	0.618
RVLS free wall (%)       21.65 [7.20–27.70]       21.90 [13.90–29.80]       0.271         RVLS fee wall (%)       18.15 [5.80–22.90]       19.20 [11.30–27.70]       0.072         TAPSE (mm)       21.60 [18–28]       22 [17–26]       0.904         RV S' (cm/s)       12.60 [11.20–25]       12.45 [10-24.50]       0.959         peak TR vel (m/sec)       2.36 [1.30–3.20]       2.15 [1.44–2.90]       0.056         PASP (mmHg)       27 [15–40]       24.50 [15–35]       0.036         TAPSE/PASP (mm/mmHg)       0.73 [0.53–1.49]       0.88 [0.60–1.73]       0.096         NICaS parameters          0.027         MAP (mmHg)       95.50 [78–109]       87.50 [63–106]       0.043         Cl (/min/m <sup>2</sup> )       2.07 [1.53–2.25]       2.20 [1.42–2.77]       0.82         CO (/min)       3.77 [2.59–4.48]       3.91 [2.68–5.37]       0.120         Stroke volume (ml)       55.58 [41.05–76.08]       55.02 [36.88–93.13]       0.276         Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06–40.97]       31.43 [23.24–49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002	RAVi (ml/m <sup>2</sup> )	21.15 [13-26.10]	20.10 [15-23]	0.744
RVLS Global (%)       18.15 [5.80–2.2.9]       19.20 [11.30–27.70]       0.072         TAPSE (mm)       21.60 [18–28]       22 [17–26]       0.904         RV S' (cm/s)       12.60 [11.20–25]       12.45 [10-24.50]       0.959         peak TR vel (m/sec)       2.36 [1.30–3.20]       2.15 [1.44–2.90]       0.056         PASP (mmHg)       27 [15–40]       24.50 [15–35]       0.036         TAPSE/PASP (mm/mmHg)       0.73 [0.53–1.49]       0.88 [0.60–1.73]       0.996         NICaS parameters          0.043         Cl (/min/m <sup>2</sup> )       2.07 [1.53–2.25]       2.20 [1.42–2.77]       0.082         CO (/min)       3.77 [2.59–4.48]       3.91 [2.68–5.37]       0.120         Stroke volume (ml)       55.58 [41.05–76.08]       55.02 [36.88–93.13]       0.276         Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06–40.97]       31.43 [23.24–49.34]       0.240         CPI (w/m <sup>2</sup> )       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115 <t< td=""><td>RVI S free wall (%)</td><td>21.65 [7.20–27.70]</td><td>21.90 [13.90–29.80]</td><td>0.271</td></t<>	RVI S free wall (%)	21.65 [7.20–27.70]	21.90 [13.90–29.80]	0.271
TAPSE (m)       21.60 [18–28]       22 [17–26]       0.904         RV S' (cm/s)       12.60 [11.20–25]       12.45 [10-24.50]       0.959         peak TR vel (m/sec)       2.36 [1.30–3.20]       2.15 [1.44–2.90]       0.056         PASP (mmHg)       27 [15–40]       24.50 [15–35]       0.036         TAPSE/PASP (mm/mmHg)       0.73 [0.53–1.49]       0.88 [0.60–1.73]       0.096         NICaS parameters              MAP (mmHg)       95.50 [78–109]       87.50 [63–106]       0.043          Cl (/min/m <sup>2</sup> )       2.07 [1.53–2.25]       2.20 [1.42–2.77]       0.082          CO (l/min/m <sup>2</sup> )       2.07 [1.53–2.25]       2.20 [1.42–2.77]       0.082          Stroke volume (ml)       3.77 [2.59–4.48]       3.91 [2.68–5.37]       0.120         Stroke volume index (ml/m <sup>2</sup> )       15.75 [3.06–40.97]       31.43 [23.24–49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.001         TPR (dn*s/cm <sup>5</sup> )       3616.50 [2911–5024]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]	RVLS Global (%)	18.15 [5.80–22.90]	19.20 [11.30–27.70]	0.072
RV S' (cm/s)         12.60 [11.20–25]         12.45 [10-24.50]         0.959           peak TR vel (m/sec)         2.36 [1.30–3.20]         2.15 [1.44–2.90]         0.056           PASP (mmHg)         27 [15–40]         24.50 [15–35]         0.036           TAPSE/PASP (mm/mmHg)         0.73 [0.53–1.49]         0.88 [0.60–1.73]         0.096           NICaS parameters            0.043           Cl (/min/m <sup>2</sup> )         2.07 [1.53–2.25]         2.20 [1.42–2.77]         0.882           CO (/min)         3.77 [2.59–4.48]         3.91 [2.68–5.37]         0.120           Stroke volume (ml)         5.55 [41.05–76.08]         5.502 [36.88–93.13]         0.276           Stroke volume index (ml/m <sup>2</sup> )         31.75 [23.06–40.97]         31.43 [23.24–49.34]         0.240           CPI (w/m <sup>2</sup> )         0.43 [0.29–0.49]         0.42 [0.24–0.62]         0.937           TPR (dn*s/cm <sup>5</sup> )         2048.50 [1577–2767]         1657.50 [1259–2863]         0.002           TPR (dn*s/cm <sup>3</sup> )         3616.50 [2911–5024]         3098.50 [2400–4684]         0.001           GGI         9.08 [5.83–13.84]         9.72 [7.66–13.98]         0.115           RR (/min)         16.50 [11–21]         16 [12–24]         0.828	TAPSE (mm)	21.60 [18–28]	22 [17-26]	0.904
peak TR vel (m/sec)2.36 [1.30–3.20]2.15 [1.44–2.90]0.056PASP (mmHg)27 [15–40]24.50 [15–35]0.036TAPSE/PASP (mm/mmHg)0.73 [0.53–1.49]0.88 [0.60–1.73]0.096NICaS parametersMAP (mmHg)95.50 [78–109]87.50 [63–106]0.043Cl (/min/m²)2.07 [1.53–2.25]2.20 [1.42–2.77]0.082CO (/min)3.77 [2.59–4.48]3.91 [2.68–5.37]0.120Stroke volume (ml)55.58 [41.05–76.08]55.02 [36.88–93.13]0.276Stroke volume index (ml/m²)31.75 [23.06–40.97]31.43 [23.24–49.34]0.240CPi (w/m²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm <sup>5</sup> )2048.50 [1577–2767]1657.50 [1259–2863]0.002TPRi (dn*s/cm³)3616.50 [2911–5024]3098.50 [2400–4684]0.001GGI9.08 [5.83–13.84]9.72 [7.66–13.98]0.115RR (/min)16.50 [11–21]16 [12–24]0.828TBW (kq)44.62 [34.95-65]45.09 [35.30–55.68]0.30	RV S' (cm/s)	12.60 [11.20–25]	12.45 [10-24.50]	0.959
PASP (m/m)         27 [15-40]         24.50 [15-35]         0.036           TAPSE/PASP (mm/mmHg)         0.73 [0.53-1.49]         0.88 [0.60-1.73]         0.096           NICaS parameters           0.043         0.043           Cl (/min/m <sup>2</sup> )         95.50 [78-109]         87.50 [63-106]         0.043           Cl (/min/m <sup>2</sup> )         2.07 [1.53-2.25]         2.20 [1.42-2.77]         0.082           CO (l/min)         3.77 [2.59-4.48]         3.91 [2.68-5.37]         0.120           Stroke volume (ml)         55.58 [41.05-76.08]         55.02 [36.88-93.13]         0.276           Stroke volume index (ml/m <sup>2</sup> )         31.75 [23.06-40.97]         31.43 [23.24-49.34]         0.240           CPi (w/m <sup>2</sup> )         0.43 [0.29-0.49]         0.42 [0.24-0.62]         0.937           TPR (dn*s/cm <sup>5</sup> )         2048.50 [1577-2767]         1657.50 [1259-2863]         0.002           TPRi (dn*s/cm <sup>3</sup> )         3616.50 [2911-5024]         3098.50 [2400-4684]         0.001           GGI         9.08 [5.83-13.84]         9.72 [7.66-13.98]         0.115           RR (/min)         16.50 [11-21]         16 [12-24]         0.828	peak TR vel (m/sec)	2.36 [1.30–3.20]	2.15 [1.44-2.90]	0.056
TAPSE/PASP (mm/mmHg)0.73 [0.53–1.49]0.88 [0.60–1.73]0.096NICaS parametersMAP (mmHg)95.50 [78–109]87.50 [63–106] <b>0.043</b> Cl (l/min/m²)2.07 [1.53–2.25]2.20 [1.42–2.77]0.082CO (l/min)3.77 [2.59–4.48]3.91 [2.68–5.37]0.120Stroke volume (ml)55.58 [41.05–76.08]55.02 [36.88–93.13]0.276Stroke volume index (ml/m²)31.75 [23.06–40.97]31.43 [23.24–49.34]0.240CPi (w/m²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm <sup>5</sup> )2048.50 [1577–2767]1657.50 [1259–2863]0.002TPRi (dn*s/cm³)3616.50 [2911–5024]3098.50 [2400–4684]0.001GGI9.08 [5.83–13.84]9.72 [7.66–13.98]0.115RR (l/min)16.50 [11–21]16 [12–24]0.828TBW (kq)44 62 [34 95–65]45 09 [35 30–55 68]0.230	PASP (mmHg)	27 [15-40]	24.50 [15-35]	0.036
NICaS parameters       95.50 [78–109]       87.50 [63–106]       0.043         Cl (l/min/m <sup>2</sup> )       2.07 [1.53–2.25]       2.20 [1.42–2.77]       0.082         CO (l/min)       3.77 [2.59–4.48]       3.91 [2.68–5.37]       0.120         Stroke volume (ml)       55.58 [41.05–76.08]       55.02 [36.88–93.13]       0.276         Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06–40.97]       31.43 [23.24–49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (//min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kq)       4462 [34 95–65]       45 09 [35 30–55 68]       0.230	TAPSE/PASP (mm/mmHa)	0.73 [0.53–1.49]	0.88 [0.60–1.73]	0.096
MAP (mmHg)95.50 [78–109]87.50 [63–106]0.043Cl (l/min/m²)2.07 [1.53–2.25]2.20 [1.42–2.77]0.082CO (l/min)3.77 [2.59–4.48]3.91 [2.68–5.37]0.120Stroke volume (ml)55.58 [41.05–76.08]55.02 [36.88–93.13]0.276Stroke volume index (ml/m²)31.75 [23.06–40.97]31.43 [23.24–49.34]0.240CPi (w/m²)0.43 [0.29–0.49]0.42 [0.24–0.62]0.937TPR (dn*s/cm <sup>5</sup> )2048.50 [1577–2767]1657.50 [1259–2863]0.002TPR idn*s/cm <sup>3</sup> )3616.50 [2911–5024]3098.50 [2400–4684]0.001GGI9.08 [5.83–13.84]9.72 [7.66–13.98]0.115RR (l/min)16.50 [11–21]16 [12–24]0.828TBW (kq)4462 [34 95–65]45 09 [35 30–55 68]0.230	NICaS parameters			
Cl (//min/m²)2.07 [1.53-2.25]2.20 [1.42-2.77]0.082CO (l/min)3.77 [2.59-4.48]3.91 [2.68-5.37]0.120Stroke volume (ml)55.58 [41.05-76.08]55.02 [36.88-93.13]0.276Stroke volume index (ml/m²)31.75 [23.06-40.97]31.43 [23.24-49.34]0.240CPi (w/m²)0.43 [0.29-0.49]0.42 [0.24-0.62]0.937TPR (dn*s/cm <sup>5</sup> )2048.50 [1577-2767]1657.50 [1259-2863]0.002TPR idn*s/cm <sup>3</sup> )3616.50 [2911-5024]3098.50 [2400-4684]0.001GGI9.08 [5.83-13.84]9.72 [7.66-13.98]0.115RR (l/min)16.50 [11-21]16 [12-24]0.828TBW (kq)4462 [34 95-65]45.09 [35.30-55 68]0.230	MAP (mmHa)	95.50 [78–109]	87.50 [63–106]	0.043
CO (l/min)       3.77 [2.59–4.48]       3.91 [2.68–5.37]       0.120         Stroke volume (ml)       55.58 [41.05–76.08]       55.02 [36.88–93.13]       0.276         Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06–40.97]       31.43 [23.24–49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002         TPRi (dn*s/cm <sup>3</sup> )       3616.50 [2911–5024]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (l/min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kq)       44 62 [34 95–65]       45 09 [35 30–55 68]       0.230	Cl (l/min/m <sup>2</sup> )	2.07 [1.53–2.25]	2.20 [1.42–2.77]	0.082
Strik (200 mm)       55.78 [41.05 - 76.08]       55.02 [36.88 - 93.13]       0.276         Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06 - 40.97]       31.43 [23.24 - 49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29 - 0.49]       0.42 [0.24 - 0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577 - 2767]       1657.50 [1259 - 2863]       0.002         TPRi (dn*s/cm <sup>3</sup> )       3616.50 [2911 - 5024]       3098.50 [2400 - 4684]       0.001         GGI       9.08 [5.83 - 13.84]       9.72 [7.66 - 13.98]       0.115         RR (l/min)       16.50 [11 - 21]       16 [12 - 24]       0.828         TBW (kg)       44 62 [34 95 - 65]       45 09 [35 30 - 55 68]       0.230	CO(l/min)	3 77 [2 59–4 48]	3 91 [2 68–5 37]	0.120
Stroke volume index (ml/m <sup>2</sup> )       31.75 [23.06-40.97]       31.43 [23.24-49.34]       0.240         CPi (w/m <sup>2</sup> )       0.43 [0.29-0.49]       0.42 [0.24-0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577-2767]       1657.50 [1259-2863]       0.002         TPRi (dn*s/cm <sup>3</sup> )       3616.50 [2911-5024]       3098.50 [2400-4684]       0.001         GGI       9.08 [5.83-13.84]       9.72 [7.66-13.98]       0.115         RR (l/min)       16.50 [11-21]       16 [12-24]       0.828         TBW (kg)       44 62 [34 95-65]       45 09 [35 30-55 68]       0.230	Stroke volume (ml)	55.58 [41.05-76.08]	55.02 [36.88–93.13]	0.276
CPi (w/m²)       0.43 [0.29–0.49]       0.42 [0.24–0.62]       0.937         TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002         TPRi (dn*s/cm <sup>3</sup> )       3616.50 [2911–5024]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (l/min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kq)       44 62 [34 95–65]       45 09 [35 30–55 68]       0.230	Stroke volume index (ml/m <sup>2</sup> )	31.75 [23.06–40.97]	31.43 [23.24–49.34]	0.240
TPR (dn*s/cm <sup>5</sup> )       2048.50 [1577–2767]       1657.50 [1259–2863]       0.002         TPR (dn*s/cm <sup>3</sup> )       3616.50 [2911–5024]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (l/min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kg)       44 62 [34 95–65]       45 09 [35 30–55 68]       0.230	$CPi (w/m^2)$	0.43 [0.29–0.49]	0.42 [0.24–0.62]	0.937
TPRi (dn*s/cm³)       3616.50 [2911–5024]       3098.50 [2400–4684]       0.001         GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (l/min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kg)       44 62 [34 95–65]       45 09 [35 30–55 68]       0.230	TPB ( $dn^*s/cm^5$ )	2048 50 [1577-2767]	1657 50 [1259-2863]	0.002
GGI       9.08 [5.83–13.84]       9.72 [7.66–13.98]       0.115         RR (l/min)       16.50 [11–21]       16 [12–24]       0.828         TBW (kg)       44.62 [34.95-65]       45.09 [35.30-55.68]       0.230	TPRi ( $dn^*s/cm^3$ )	3616 50 [2911–5024]	3098 50 [2400-4684]	0.002
RR (l/min)     16.50 [11–21]     16 [12–24]     0.828       TBW (kg)     44.62 [34.95-65]     45.09 [35.30-55.68]     0.230	GGI	9 08 [5 83–13 84]	9 72 [7 66–13 98]	0.115
TBW (kg)     44.62 [34.95-65]     45.09 [35.30-55.68]     0.230	BB (l/min)	16 50 [11-21]	16 [12-24]	0.878
	TBW (kg)	44.62 [34.95-65]	45.09 [35.30-55.68]	0.020

#### Table 3 (continued)

	Baseline	Follow-up	<i>p</i> -value
General characteristics			
TBW (% weight)	59.75 [49.40-77.46]	58.83 [49.80–72.50]	0.601
Basal impedence (ohm)	296.50 [226–384]	308 [244–373]	0.297

Values are expressed as median [min-max] or n (%)

SPB- Systolic blood pressure; DPB- Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV- End-diastolic volume; ESV- End-systolic volume; EF- Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMI- Left Ventricular Mass Index; LAVi- Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial contraction strain; RAVi- Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP-Pulmonary artery systolic pressure; TAPSE- Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

over 12 weeks, with reductions significantly correlated with pulmonary capillary wedge pressure (PCWP), suggesting a direct effect on cardiac preload [48]. Collectively, our and these findings therefore highlight the complex interplay between SGLT2i, volume modulation, and cardiac function.

HFpEF is not a single disease but rather a heterogeneous syndrome encompassing multiple clinical phenotypes. Among these, cardiometabolic HFpEF is the most prevalent, driven by metabolic disorders such as obesity and hypertension. These conditions contribute to lipid accumulation and the activation of maladaptive inflammatory pathways, ultimately leading to progressive fibrosis and organ dysfunction [49]. In our study, 70% of patients were overweight or obese. Our findings indicate that in overweight or obese HF patients (independent from EF subtypes), SGLT2 inhibitors provided benefits comparable to those seen in HFpEF, further supporting the notion that obesity shares key pathophysiological features with HFpEF-commonly referred to as cardiometabolic HFpEF [50]. Accordingly, our findings preliminary indicate that SGLT2i may exert early vascular effects in overweight HFpEF patients, potentially contributing beyond fluid offloading. However, given the ongoing uncertainty regarding the vascular impact of SGLT2i, our findings should be interpreted as hypothesis-generating and require confirmation in larger, well-powered clinical trials to establish their clinical significance.

#### Limitations

In interpreting the results of the current study, it is important to acknowledge its inherent. limitations. Our study was designed as an exploratory, hypothesis-generating investigation to assess the early hemodynamic effects of SGLT2i in overweight HF (and HFpEF in particular) patients, using non-invasive bioimpedance assessments (NICaS system). We fully acknowledge that the small sample size of our study limits the statistical power and generalizability of our findings. However, it is important to emphasize that preliminary studies of this nature play a crucial role in shaping future research directions by identifying potential mechanistic trends that warrant further investigation. Similar small-scale hemodynamic studies have provided valuable insights into HF pathophysiology and treatment responses, serving as a foundation for subsequent larger trials. Notably, the recently published subanalysis of the EMPAG-HF trial underscores the relevance of early hemodynamic assessments in understanding the acute effects of SGLT2i, despite sample size constraints [51]. While our results should be interpreted with caution, they contribute to the growing body of evidence supporting the hemodynamic benefits of SGLT2i in HF. Future multicenter trials with larger cohorts will be essential to validate our findings and establish their clinical implications more definitively.

Additionally, the decision to conduct follow-up assessments at 30 days may not have captured effects that necessitate longer observation periods. The observational nature of this study further limits the generalizability of its findings.

#### Conclusions

Our findings suggest that early hemodynamic responses to SGLT2i may differ across HF subtypes, with overweight/obese HFpEF patients showing a reduction in vascular resistance, while HFrEF/HFmrEF patients appear to primarily benefit from volume unloading. These preliminary observations align with the concept of HFpEF as a cardiometabolic disorder driven by vascular dysfunction and metabolic dysregulation, with overweight/obesity as a key contributing factor.

While our data indicate that SGLT2i therapy may be associated with improved vascular compliance and ventricular-arterial coupling, as reflected by reductions in TPR, the overall vascular impact of SGLT2i remains incompletely understood. Given the complex interplay between arterial stiffness, endothelial function, and disease progression in HFpEF, further investigation is warranted to confirm whether these hemodynamic benefits translate into sustained clinical improvements.

Additionally, the observed improvements in echocardiographic parameters—including reductions in LAVi and PASP—suggest a potential role for SGLT2i in favorable cardiac remodeling and enhanced right

#### Table 4 Difference between baseline and after 1 mo of treatment in HFrEF/HFmrEF patients

	Baseline	Follow-up	<i>p</i> -value
General characteristics			
Weight (kg)	68 [46-99.20]	66 [46.30–97]	0.019
SBP (mmHg)	125 [100–140]	110 [100–140]	0.318
DBP (mmHg)	69 [63–80]	68 [45–89]	0.498
HR (bpm)	67 [54–83]	61 [53–93]	0.777
6MWT (m)	420 [120-480]	435 [120–510]	0.193
Sat% $O_{2}$ at basal time	96 [94–100]	98 [95–100]	0.334
Sat% $\Omega_2$ at 6 min	97 [88–99]	97 50 [94–99]	0.439
Biochemical parameters		57.50[57:55]	0.100
Hb (a/dL)	13 30 [9 90-15 50]	14 40 [10 40–15 40]	0.040
HCT (%)	40.80 [32.60-44.50]	40.80 [33.60-45.10]	0.424
Creatinine (mg/dL)	1 05 [1 00-1 46]	1 06 [0 97–1 53]	0.699
Azotemia (mg/dL)	105 [1.00 1.10]	1.00 [0.57 1.55]	0.975
$A_2 O(EP) (mig/(1.72m^2))$	49 [33-32]	44 [39-40] 67 50 [47 82 20]	0.945
	1750 [206 7287]		0.501
Easting blood glucose (mg/dL)	04 [76 122]	02.50 [227-0927]	0.594
Fasting blood glucose (mg/dL)	94 [70-133]	92.30 [72-143]	0.695
Echocardiography parameters	120 [0( 240]	142 [05 224]	0744
	130 [86-240]	143 [85–236]	0.744
ESV (mL)	65.50 [44–193]	/1.60 [44–169]	0.352
	111 [/6-158]	104 [56-202]	0.726
EF (%)	43.40 [19.60–49.60]	41 [22-53.40]	0.296
LVGLS (%)	10.20 [4.80–15.40]	10.20 [4./0–16./0]	0.570
E wave (cm/sec)	/6.50 [37.20–111]	/9 [33–109]	0.628
A wave (cm/sec)	79.10 [34.60–91.70]	74.40 [35.60–97.50]	0.502
E/A	0.80 [0.40–2.30]	0.80 [0.40–1.90]	0.740
Sept E'(cm/sec)	6.10 [3.10–10.60]	6.10 [3.26–8.10]	0.046
Lat E'(cm/sec)	7.14 [4.80–13.10]	7.20 [4.13–12.40]	0.428
E/E'	12.80 [4.50–18.80]	11.10 [5.30–21.50]	0.881
LAVi (ml/m²)	45.50 [38-58.60]	41 [32-44.90]	0.021
PALS (%)	11.40 [4.60–22.80]	14.70 [5.50–22.30]	0.568
LACD(%)	6.40 [10.50–1.90]	7 [5.40–10.90]	0.739
LACT(%)	8.20 [1.40–19.20]	6.80 [0.80–16.80]	0.281
RAVi (ml/m <sup>2</sup> )	23.20 [16.20-44.30]	20.20 [18–45]	0.431
RVLS free wall (%)	14.10 [7.2–23.50]	17.45 [9.70–29.80]	0.356
RVLS Global (%)	11.40 [5.80–18.10]	15.50 [7.50–22.80]	0.268
TAPSE (mm)	23 [21.30–24]	22.10 [11–26]	0.983
RV S' (cm/s)	13.10 [9.20–15.90]	11.20 [6.70–14]	0.157
peak TR vel (m/sec)	2.52 [1.76–2.76]	2.20 [1.44–2.53]	0.139
PASP (mmHg)	30 [23–38]	25 [15–33]	0.013
TAPSE/PASP (mm/mmHg)	0.85 [0.69–0.96]	0.76 [0.33–1.73]	0.255
NICaS parameters			
MAP (mmHg)	91 [76–96]	76 [63–104]	0.200
CI (I/min/m <sup>2</sup> )	1.85 [1.46–2.85]	2.04 [1.42-2.75]	0.453
CO (l/min)	3.83 [2.54–4.48]	3.56 [2.87–5.37]	0.503
Stroke volume (ml)	57.17 [32.94–70.45]	61.21 [40.42-93.13]	0.539
Stroke volume index (ml/m²)	28.21 [18.95-44.55]	31.09 [26.36-44.06]	0.695
CPi (w/m²)	0.39 [0.23–0.58]	0.38 [0.24–0.62]	0.834
TPR (dn*s/cm <sup>5</sup> )	1867 [1577–2475]	1893 [1259–2123]	0.191
TPRi (dn*s/cm <sup>3</sup> )	3545 [2582–4611]	3112 [2660-4271]	0.147
GGI	8.80 [6.85–15.35]	10.60 [7.66–12.79]	0.507
RR (l/min)	18 [14–20]	17 [12–20]	0.396
TBW (kg)	50.63 [31.83-65]	42.13 [30.60-55.68]	0.050

#### Table 4 (continued)

	Baseline	Follow-up	<i>p</i> -value
General characteristics			
TBW (% weight)	66.33 [51.45–74.45]	58.68 [55.13-66.50]	0.047
Basal impedence (ohm)	321 [226–391]	386 [244–407]	0.028

Values are expressed as median [min-max] or n (%)

SPB– Systolic blood pressure; DPB– Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV– End-diastolic volume; ESV– End-systolic volume; EF– Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi– Left Ventricular Mass Index; LAVi– Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi– Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP–Pulmonary artery systolic pressure; TAPSE– Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water



Fig. 1 Early echocardiographic effects of SGLT2i in HFrEF/HFmrEF patients

ventricular-pulmonary artery coupling. However, while these findings may indicate effects beyond simple fluid offloading, their mechanistic basis remains speculative and requires validation in larger, well-powered studies.

Overall, our results should be interpreted as hypothesis-generating, as they are derived from a relatively small cohort with limited generalizability. Future multicenter trials with larger sample sizes are essential to establish the robustness of these findings and determine their long-term clinical significance. Finally, non-invasive hemodynamic monitoring may offer valuable insights for precision-guided HF therapy, particularly in overweight/ obese HFpEF patients, but further research is needed to refine its clinical utility.



Fig. 2 Early hemodynamic effects of SGLT2i in HFrEF/HFmrEF patients

#### Table 5 Difference between baseline and after 1 mo of treatment in HFpEF patients

	Baseline	Follow-up	<i>p</i> -value
General characteristics			
Weight (kg)	67.30 [51-84.10]	65.50 [54–87]	0.122
SBP (mmHg)	135 [103–150]	120 [104–141]	0.030
DBP (mmHg)	70 [55–90]	72 [47–90]	0.101
HR (bpm)	61 [55–90]	66 [47–99]	0.170
6MWT (m)	390 [120–480]	335 [120–540]	0.438
Sat% $O_2$ at basal time	97 [95–100]	97 [94–100]	0.337
Sat% $O_2$ at 6 min	97 [95–98]	97 [94–99]	0.613
Biochemical parameters			
Hb (g/dL)	12.80 [9.60–14.60]	12.95 [9.70–15.40]	0.342
HCT (%)	39.80 [30.30-44.40]	40 [29.80-47.90]	0.517
Creatinine (mg/dL)	0.91 [0.75–2.04]	1.05 [0.77–1.68]	0.539
eGFR (mL/min/1.73m2)	64 [30-89.10]	55.40 [37.30-88.30]	0.125
NT-proBNP (pg/mL)	870 [231–6631]	384 [146.60–1803]	0.219
Fasting blood glucose (mg/dL)	88 [81–108]	88 [65–110]	0.837
Glycated hemoglobin (%)	6 [5.12–6.40]	5.80 [5.10–6.70]	0.742
Echocardiography parameters			
EDV (mL)	94.60 [62.60–155]	89.50 [60–150]	0.077
ESV (mL)	40.60 [26.60-71.30]	38.20 [26-77.90]	0.056
LVMi (g/m <sup>2</sup> )	90.45 [52.50-121.50]	94.68 [53.43-123.39]	0.246
EF (%)	55.90 [51–60]	58 [51.90–62.80]	0.085
LVGLS (%)	18.70 [15.80-22.90]	18.25 [15-23.20]	0.946
E wave (cm/sec)	78.60 [47.20–130]	81.80 [43.50–121]	0.935
A wave (cm/sec)	87 [44.50–135]	78.90 [58.20–135]	0.811
E/A	0.80 [0.60–1.30]	0.75 [0.70–1.10]	0.090
Sept E'(cm/sec)	7.62 [5.33–17.70]	7.65 [12.60;5.55]	0.764
Lat E'(cm/sec)	8.95 [3.92–12.40]	9.14 [5.44–14.50]	0.758
E/E'	9.20 [6.30–17.60]	8.30 [5.40–17.90]	0.935
LAVi (ml/m <sup>2</sup> )	41.37 [26.15-63]	40.32 [23.29-62.25]	0.005
PALS (%)	21.70 [8.10–46.50]	24 [4.30–60.50]	0.216
LACD(%)	10.50 [5-25.10]	11.70 [2.90–41.60]	0.535
LACT(%)	9.50 [0.60-21.40]	11.20 [1.60–21.60]	0.464
RAVi (ml/m <sup>2</sup> )	20 [13–31]	21 [15–30]	0.758
RVLS free wall (%)	22.60 [11.60-27.74]	22.70 [15.9–30.60]	0.452
RVLS Global (%)	19.30 [10.30-22.90]	19.70 [11.30–27.70]	0.268
TAPSE (mm)	22 [18–28]	22 [20–28]	0.720
RV S' (cm/s)	12.60 [11.20–25]	12.60 [10-24.50]	0.518
peak TR vel (m/sec)	2.61 [1.30–3.20]	2.21 [1.67–2.92]	0.108
PASP (mmHg)	32 [15–40]	26 [16–38]	0.134
TAPSE/PASP (mm/mmHg)	0.73 [0.53–1.49]	0.87 [0.60–1.25]	0.154
NICaS parameters			
MAP (mmHg)	94 [74–109]	85 [68–106]	0.046
CI (I/min/m <sup>2</sup> )	2.10 [1.53–3.70]	2.25 [1.32–3.68]	0.130
CO (l/min)	3.77 [2.59–5.47]	3.81 [2.14–5.58]	0.136
Stroke volume (ml)	54.96 [41.05–76.08]	56.20 [36.88–84.41]	0.424
Stroke volume index (ml/m <sup>2</sup> )	32.82 [23.06-48.69]	31.86 [23.24–49.34]	0.359
CPi (w/m <sup>2</sup> )	0.44 [0.29–0.61]	0.44 [0.20–0.60]	0.974
TPR (dn*s/cm <sup>5</sup> )	2073 [1082–2767]	1676 [1061–2863]	0.009
TPRi (dn*s/cm <sup>3</sup> )	3681 [1600–5024]	3085 [1608–4684]	0.005
GGI	9.30 [5.83–17.70]	9.65 [8-18.90]	0.164
RR (l/min)	16 [11–21]	16 [11–24]	0.628
TBW (kg)	40.80 [33.20–58.10]	41.86 [31.60-48.30]	0.524

#### Table 5 (continued)

	Baseline	Follow-up	<i>p</i> -value
General characteristics			
TBW (% weight)	62 [49.40–77.50]	60.10 [49.80-73.45]	0.957
Basal impedence (ohm)	311 [226–385;]	317 [283–410]	0.610

Values are expressed as median [min-max] or n (%)

SPB- Systolic blood pressure; DPB- Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV- End-diastolic volume; ESV- End-systolic volume; EF- Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi- Left Ventricular Mass Index; LAVi- Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi- Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP-Pulmonary artery systolic pressure; TAPSE- Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water



Fig. 3 Early echocardiographic effects of SGLT2i in HFpEF patients



Fig. 4 Early hemodynamic effects of SGLT2i in HFpEF patients

#### **Supplementary Information**

The online version contains supplementary material available at https://doi.or g/10.1186/s12933-025-02699-4.

Supplementary Material 1

#### Author contributions

Nadia Salerno: Writing- review & editing, Writing- original draft, Funding acquisition, Data curation. Angela Sciacqua and Salvatore De Rosa: Supervision. Jessica Jelapi, Angelica Cersosismo, Isabella Leo, Assunta Di Costanzo, Giuseppe Armentaro: Formal analysis, Data curation. Daniele Torella:: Writing- review & editing, Writing- original draft, Funding acquisition, Conceptualization. Sabato Sorrentino:: Writing- review & editing, Writing- original draft, Formal analysis, Data curation.

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#### Availability of data and materials

Data is provided within the manuscript or supplementary information files.

#### Declarations

#### Ethics approval and consent to participate

The study was approved by the Local Ethics Committee (Protocol Register No. 170, May 30, 2024). All patients provided written informed consent before participating in the study.

#### **Consent for publication**

All authors listed above approved the manuscript for publication.

#### **Competing interests**

The authors declare no competing interests.

#### Author details

<sup>1</sup>Department of Experimental and Clinical Medicine, Magna Graecia University, 88100 Catanzaro, Italy

<sup>2</sup>Department of Medical and Surgical Sciences, Magna Graecia University, 88100 Catanzaro, Italy Received: 18 February 2025 / Accepted: 20 March 2025 Published online: 26 March 2025

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