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Impact of SGLT2 inhibitors on endothelial function and echocardiographic parameters in dilated cardiomyopathy

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Background Dilated cardiomyopathy (DCM) is a common cause of heart failure with reduced ejection fraction (HFrEF) in industrialized countries and a major contributor to morbidity and mortality. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated significant benefits in HFrEF management; however, their impact on endothelial function in this patient population remains less explored. This study aims to evaluate the effects of SGLT2i on endothelial function and echocardiographic parameters in patients with DCM.

Methods This observational, longitudinal, monocentric study enrolled patients with DCM and HFrEF. Endothelial function was assessed using peripheral arterial tonometry (EndoPAT) at baseline, 6 months, and 12 months following the initiation of sodium-glucose cotransporter-2 inhibitors (SGLT2i). The enrollment period spanned from November 2021 to November 2022. The primary endpoint was the change in reactive hyperemia index (RHI) over time. In addition, a subgroup analysis was conducted to compare the effects of different SGLT2i agents (empagliflozin vs. dapagliflozin) and DCM etiology (ischemic vs. idiopathic) on endothelial function.

Results A total of 102 patients were included, predominantly male (72%), with a median age of 75 years and an average baseline left ventricular ejection fraction (LVEF) of 32.9 ± 7.9%. NYHA class II/III was observed in 76% of participants, and ischemic etiology accounted for 53% of DCM cases. The baseline RHI value was 1.15 ± 0.34. At 6 months, it significantly increased to 1.40 ± 0.34 ($P < 0.0001$), reflecting an absolute change of 0.25 ± 0.03 (ΔRHI baseline – 6 months). Between 6 and 12 months, the RHI showed a further significant increase to 1.69 ± 0.36 ($P < 0.0001$), with an additional change of 0.29 ± 0.03 (ΔRHI 6 – 12 months). The overall change in RHI from baseline to 12 months (ΔRHI baseline – 12 months) was 0.54 ± 0.04 ($P < 0.0001$). No significant differences in RHI were observed between patients treated with dapagliflozin and those receiving empagliflozin ($P = 0.589$), nor between different DCM etiologies (ischemic vs. idiopathic, $P = 0.463$). The enhancement in RHI was associated with a reduction in the incidence of hospitalization for heart failure (AUC 0.783, $P < 0.001$). Progressive improvement in left ventricular function was observed through echocardiographic parameters. Although EDV and ESV showed a decreasing trend (EDV: 176.2 ± 64.9 to 167.6 ± 31.1 ml, $P = 0.335$; ESV: 124.5 ± 52.7 to 116.8 ± 24.6 ml, $P = 0.606$), these changes were not statistically significant. LVEF improved significantly from 32.9 ± 7.9% at baseline to 36.8 ± 5.5% at 6 months and 37.1 ± 4.9% at 12 months ($P < 0.001$). The E/A ratio declined from 1.5 ± 0.5 to 1.1 ± 0.3 ($P = 0.023$) and the E/E' ratio decreased from 18.1 ± 5.1 to 11.1 ± 2.8 ($P = 0.027$).

Left atrial volume significantly decreased from 108 to 100 ml ($P = 0.041$), and pulmonary artery systolic pressure dropped from 44 to 39 mmHg at 6 months and 35 mmHg at 12 months ($P < 0.001$).

Conclusion SGLT2i therapy significantly improves endothelial function in patients with DCM suggesting a potential vascular benefit beyond their well established cardioprotective effects.

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Keywords: dilated cardiomyopathy, echocardiography, EndoPAT, endothelial function, heart failure, heart failure with reduced ejection fraction, sodium-glucose cotransporter-2 inhibitors

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Introduction

Dilated cardiomyopathy (DCM) is a condition characterized by reduced contractility and dilation of the left ventricle (LV) or both ventricles.[1] The incidence is estimated at five to seven cases per 100 000 people per year,[2] with a global prevalence of approximately 2.5 million cases, reflecting a 27% increase over the past decade.[3] Although men had higher DCM-related mortality rates than women,[4]

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epidemiological data on sex-related differences in DCM remain scarce. Few studies have explored sex-specific variations in phenotype, disease severity, and clinical outcomes, highlighting the need for further research in this area.[5] As a result, DCM is a relatively common cause of heart failure with reduced ejection fraction (HFrEF) in industrialized countries and a significant contributor to morbidity and mortality.[1,6] According to the 2021 European Society of Cardiology (ESC) guidelines,[6] the cornerstone of HFrEF management includes pharmacological strategies aimed at symptom relief, disease progression attenuation, and reduction of morbidity and mortality.[7] Among several pivotal drugs for HFrEF, sodium-glucose co-transporter 2 inhibitors (SGLT2i) have emerged as key agents due to their cardiovascular and renal protective effects, independently of glycemic status.[6,8–12] These effects are thought to be mediated through mechanisms such as neurohumoral modulation, hemodynamic improvements, and reductions in preload and afterload due to their glycosuric action.[13–15] Although the precise mechanisms remain under investigation, SGLT2i have been associated with a reduction in the production of reactive oxygen species (ROS), leading to decreased inflammation and interstitial fibrosis in both the kidney and heart, as well as improvements in endothelial function and mitochondrial activity.[16–18] Indeed, endothelial function plays a critical role in vascular homeostasis, inflammation, and angiogenesis.[19] Peripheral arterial tonometry (PAT) has emerged as a noninvasive tool for assessing endothelial function, initially developed for evaluating vascular changes during sleep and later adapted for vascular reactivity testing.[20] The method relies on the same physiological mechanisms as flow-mediated vasodilation, with reactive vasodilation induced by transient ischemia in the upper limb. This noninvasive procedure allows the reactive hyperemia index (RHI) or its natural logarithm (lnRHI) to be obtained. This technique measures reactive vasodilation following transient ischemia in the upper limb, providing the RHI or its natural logarithm (lnRHI). Importantly, PAT-derived RHI values hold significant predictive value for cardiovascular risk stratification, with RHI of 1.67 or less indicating endothelial dysfunction and an increased risk of adverse cardiovascular events.[21,22]

Given the emerging evidence on the vascular effects of SGLT2i, this study aims to evaluate their potential therapeutic impact on endothelial function in patients with DCM and HFrEF.

Materials and methods

Population of the study

The study was conducted between November 2021 and November 2022 at the Department of Cardiology of Spedali Civili in Brescia, Italy. Ethical approval was granted by the local ethics committee, and all participants provided written informed consent before enrollment.

A total of 102 patients with a documented diagnosis of DCM were included. Inclusion criteria were Caucasian ethnicity, age at least 18 years, ischemic or idiopathic DCM with a left ventricular ejection fraction (LVEF) less than 40%, and receipt of optimal medical therapy at baseline, excluding sodium-glucose cotransporter-2 inhibitors (SGLT2i).

Exclusion criteria included non-Caucasian ethnicity, age less than 18 years, recent acute coronary syndrome (within the last 3 months), congenital cardiomyopathy, chronic renal failure stage IV–V [estimated glomerular filtration rate (eGFR) <20 ml/min], rheumatological or orthopedic diseases of the upper limbs that could interfere with the use of PAT (EndoPAT), lack of optimized medical therapy, or prior use of SGLT2i therapy. Demographic, clinical, and pharmacological data at the initiation of SGLT2i therapy were collected from medical records.

Study design

This was a longitudinal, observational, monocentric study. Instrumental examinations were conducted to evaluate endothelial function and parameters of cardiac function at the time of enrollment, and subsequently at 6 and 12 months after the initiation of therapy with SGLT2i. This approach aimed to demonstrate the benefits of the treatment over time. The procedures performed at the beginning and at the end of the study period were transthoracic echocardiography and PAT using Endo-PAT 2000 (Itamar Medical Ltd., Caesarea, Israel).

Transthoracic echocardiography

The echocardiographic evaluations were performed using a Vivid q ultrasound device (GE Healthcare, Milwaukee, Wisconsin, USA). Tele-diastolic and tele-systolic volumes of the LV were measured using the Simpson biplane method, and the LVEF was determined.[23] For diastolic function, the transmitral flow was evaluated by the ratio of peak transmitral early (E) and late (A) velocities. In addition, tissue Doppler imaging assessed the systolic and diastolic velocities (S', E', and A') of the lateral and septal margins of the mitral annulus. The mean values were recorded, and the mean E/e' ratio was calculated. Lastly, the left atrium volume (LAV) was measured using the disc method in tele-systole, using the apical four-chamber view.[24]

The extent of valvular disease was evaluated according to guidelines.[25] Right ventricular function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) and its systolic velocity (S'). Systolic pulmonary artery pressure (PASP) was calculated using the formula: $4 \times (\text{TRVmax})_2 +$ right atrial pressure (RAP).[23]

Peripheral arterial tonometry

The evaluation of endothelial function was conducted using PAT with the Endo-PAT 2000 (Itamar Medical Ltd, Caesarea, Israel). This noninvasive, quick, and operator-independent procedure assesses peripheral microvascular endothelial function through specialized software. The measurement was conducted in an independent space with a very quiet environment and constant temperature. The device employs two probes placed on the distal phalanges of the second fingers on both hands. The probes feature an external rigid coating and internal neoprene inflatable membranes, which create a pressure of 70 mmHg. This pressure helps to limit motion artifacts and prevent venous stasis related to the veno-arteriolar vasoconstriction reflex and blood reflux, which are factors that could compromise the results.[26]

During the evaluation, the patient is seated with both arms resting on special armrests to relax and extend the arms, minimizing finger movements. An aneroid sphygmomanometer is placed above the right antecubital fossa. The test consists of three phases, each lasting 5 min:

(1) Basal phase: the system measures the sphygmic signal magnitude in the peripheral vascular system at rest for each finger.
(2) Occlusive phase (ischemic): the pressure cuff on the right arm is inflated to 50/60 mmHg above the systolic arterial pressure to occlude the brachial artery. During this phase, no signal is detected by the right finger probe, while the left finger probe continues to produce a signal.
(3) Hyperemic phase: after 5 min, the pressure cuff is deflated, and the magnitude of the hyperemic response is measured at the right finger.
(4) The software analyzes the data to produce the RHI. This is based on the ratio of the sphygmic signal between the experimental and control arms during the reactive hyperemic phase, normalized for the same ratio during the basal phase.[27] The RHI cut-off is 1.67, with lower values indicating endothelial dysfunction.[28]

Statistical analysis

The normality of distribution of the parameters was assessed by using the Kolmogorov–Smirnov test. Continuous variables with Gaussian distribution were reported as mean ± standard deviation and compared by Student's *t*-test, whereas variables with nonnormal distribution were reported as median (interquartile range) and compared by Mann–Whitney *U* test. Categorical variables are presented as number (percentage) and comparisons were made with Fisher's exact test when the expected frequency was below 5, otherwise the chi-squared test (Yates corrected).

RHI values were evaluated through multiple comparisons using analysis of variance (ANOVA).

A logistic regression analysis was then performed to identify the correlation of ΔRHI (baseline – 12 months) with the probability of hospitalization for heart failure (HHF). The area under the curve (AUC) was calculated to estimate the performance for ΔRHI to detect HHF.

A *P*-value less than 0.05 in two-sided tests was considered statistically significant.

Statistical analysis was performed using SPSS (version 25, IBM Corp., Armonk, New York, USA) and GraphPad Prism version 9.4.0 for Windows (GraphPad Software Version 9.4.0, San Diego, California, USA).

Results

Baseline characteristics in the general population

In the present study, out of an initial cohort of 150 patients, 33 were excluded due to incomplete data, 10 for nonoptimized medical therapy and an additional 5 were excluded for presenting with heart failure and acute coronary syndrome. Ultimately, 102 patients were enrolled.

The follow-up was 367 ± 2 days. During the follow-up period, no patients died, and 11 patients had a second HHF. The majority of participants were male (73, 72%). The median age was 75 years, and the average baseline LVEF was 32.9 ± 7.9%. NYHA class IV was observed in 4% of cases, while NYHA class II and III were prevalent in 76% of patients (49 and 27%, respectively). Ischemic disease accounted for 53% of DCM cases. Regarding cardiovascular risk factors, arterial hypertension was prevalent in 59% of patients, dyslipidemia in 44%, and type 2 diabetes mellitus in 26%, respectively. Nine patients were active smokers, while atrial fibrillation was present in 31%. A cardiac implantable electronic device (CIED) was previously implanted in 75% of patients, and chronic kidney disease (CKD) was noted in 28%. As affected by HFrEF, the baseline medical therapy included beta blocker for all patients (100%), loop diuretics (96%), mineralocorticoid receptor antagonist (MRA, 60%), and angiotensin receptor-neprilysin inhibitor (ARNI, 53%). A lower percentage of patients were taking angiotensin-converting enzyme inhibitors (ACEi, 31%) and angiotensin receptor blocker (ARB, 17%).

Baseline characteristics according to SGLT2i drug

Following data collection and patient screening, treatment with SGLT2i was initiated: 52 patients (51%) were taking 10 mg dapagliflozin, while 50 patients (49%) were taking 10 mg of empagliflozin (Table 1). Men represented 72% of the total cohort, with a slightly higher proportion in the empagliflozin group (77 vs. 67%), although this difference

Table 1 **Baseline population characteristics according to SGLT2i**

Total population = 102		**Empaglifozin = 50**	**Dapaglifozin = 52**	*P*
General characteristics				
Age (years)	75 [82; 62]	76 [80; 62]	75 [82; 60]	0.617
Male sex, *n* (%)	73 (72)	36 (77)	37 (67)	0.910
Height (cm)	171 [178; 165]	170 [175; 165]	172 [178; 165]	0.310
Weight (kg)	73 [80; 65]	72 [80; 65]	75 [81; 66]	0.468
Smoker, *n* (%)	9 (9)	7 (14)	2 (3)	0.149
Dyslipidemia, *n* (%)	45 (44)	21 (42)	24 (46)	0.673
Diabetes, *n* (%)	27 (26)	11 (22)	16 (30)	0.314
Hypertension, *n* (%)	60 (59)	28 (56)	32 (62)	0.565
Cerebrovascular disease, *n* (%)	7 (7)	6 (12)	1 (2)	0.044
Coronary artery disease, *n* (%)	43 (42)	25 (50)	18 (36)	0.109
Prior myocardial infarction, *n* (%)	38 (37)	19 (38)	19 (37)	0.872
Prior PCI, *n* (%)	37 (36)	19 (38)	18 (36)	0.715
Prior CABG, *n* (%)	3 (3)	2 (4)	1 (2)	0.534
CIED, *n* (%)	76 (75)	37 (74)	39 (75)	0.432
PM	7 (6)	4 (8)	3 (6)	
ICD	44 (43)	21 (42)	23 (44)	
CRT-D	20 (20)	10 (20)	10 (19)	
CRT-P	5 (5)	2 (4)	3 (6)	
Peripheral artery disease, *n* (%)	11 (11)	5 (10)	6 (12)	0.804
Atrial fibrillation, *n* (%)	32 (31)	20 (40)	12 (23)	0.062
CKD, *n* (%)	29 (28)	19 (38)	10 (19)	0.034
COPD, *n* (%)	2 (2)	0 (0)	2 (4)	0.169
NYHA class, *n* (%)				0.972
I	20 (20)	10 (20)	10 (19)	
II	50 (49)	23 (46)	27 (52)	
III	28 (27)	15 (30)	13 (25)	
IV	4 (4)	2 (4)	2 (4)	
DCM type, *n* (%)	102 (100)	50 (100)	52 (100)	0.109
Idiopathic	48 (47)	20 (40)	28 (54)	
Ischemic	54 (53)	30 (60)	24 (46)	
SBP (mmHg)	115 [124; 110]	120 [124; 110]	110 [120; 108]	0.053
DBP (mmHg)	70 [70; 60]	70 [70; 60]	65 [70; 60]	0.066
HR (bpm)	65 [73; 63]	63 [70; 60]	66 [73; 63]	0.207
Echocardiography parameters				
EDV (ml)	176.2 ± 64.9	180.3 ± 53.1	172 ± 76.6	0.586
ESV (ml)	124.5 ± 52.7	131.9 ± 56.6	117 ± 48.8	0.256
EDD (mm)	61.6 ± 7.1	63 ± 7.1	60.2 ± 7	0.070
ESD (mm)	56.1 ± 2.7	56 ± 2.8	56.2 ± 2.6	0.905
EF (%)	32.9 ± 7.9	31.9 ± 8.1	33.8 ± 7.6	0.224
E/A	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	0.609
E/E	18.1 ± 5.1	18.5 ± 5.9	17.7 ± 4.3	0.232
MR grade, *n* (%)	102 (100)	50 (100)	52 (100)	0.481
None	17 (17)	9 (18)	8 (15)	
Mild	39 (38)	20 (40)	19 (37)	
Moderate	46 (45)	21 (42)	25 (48)	
LAV (ml)	108 [130; 83]	110 [130; 81]	106 [116; 83]	0.667
TAPSE (mm)	20 [22; 18]	20 [22; 18]	20 [22; 17]	0.386
RV S' (cm/s)	11 [12; 10]	11 [12; 10]	12 [12; 10]	0.137
FAC (%)	40 [41; 38]	40 [40; 38]	39 [41; 37]	0.633
PASP (mmHg)	44 [54; 37]	43 [50; 37]	45 [54; 35]	0.786
TR grade *n* (%)	102 (100)	50 (100)	52 (100)	0.874
None	5 (5)	2 (4)	3 (6)	
Mild	44 (43)	24 (48)	20 (38)	
Moderate	52 (51)	23 (46)	29 (56) 0 (0) 0 (0)	
Massive	1 (1)	1 (2)		
Torrential	0 (0)	0 (0)		
Drugs therapy				
Beta blocker, *n* (%)	102 (100)	50 (100)	52 (100)	0.567
Bisoprolol	93 (91)	46 (92)	47 (90)	
Carvedilol	5 (5)	2 (4)	3 (6)	
Metoprolol	2 (2)	2 (4)	0 (0)	
Nebivolol	2 (2)	0 (0)	2 (4)	

Table 1 (*continued*)

Total population = 102		Empaglifozin = 50	Dapaglifozin = 52	*P*
ACEi, *n* (%)	31 (31)	16 (32)	15 (29)	0.984
Enalapril	17 (17)	9 (18)	8 (15)	
Ramipril	11 (11)	5 (10)	6 (12)	
Other	3 (3)	2 (4)	1 (2)	
ARB, *n* (%)	17 (17)	8 (16)	9 (18)	0.562
Candesartan	5 (5)	3 (6)	2 (4)	
Valsartan	7 (7)	3 (6)	4 (8)	
Losartan	3 (3)	2 (4)	1 (2)	
Other	2 (2)	0 (0)	2 (4)	
ARNI, *n* (%)	54 (53)	25 (50)	29 (56)	0.556
MRA, *n* (%)	61 (60)	32 (64)	29 (56)	0.330
Spirinolactone	3 (3)	1 (2)	2 (4)	
Eplerenone	6 (6)	3 (6)	3 (6)	
Potassium canreonate	52 (51)	28 (56)	24 (46)	
Loop diuretic, *n* (%)	98 (96)	48 (96)	50 (96)	0.238

Values are expressed as mean ± standard deviation or median [interquartile range]. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilisin inhibitor; CABG, coronary artery bypass graft surgery; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DCM, dilated cardiomyopathy; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FAC, fractional area change; HR, heart rate; ICD, implantable cardioverter-defibrillator; IVSd, interventricular septum thickness; LA, left atrium; LAV, left atrial volume; LWPd, left posterior wall thickness; MR, mitral regurgitation; MRA, mineralocorticoids receptor antagonists; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; PM, pacemaker; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

was not statistically significant ($P = 0.910$). Notably, a higher prevalence of cerebrovascular disease was observed in the empagliflozin group (12 vs. 2%; $P = 0.044$), while the prevalence of CKD was also significantly higher in patients receiving empagliflozin (38 vs. 19%; $P = 0.034$).

No significant differences were found in the rates of coronary artery disease, prior myocardial infarction, or prior revascularization procedures between the two groups.

Similar, baseline echocardiographic assessment revealed no significant differences.

Both groups received optimal guideline-directed medical therapy, with similar rates of beta-blocker (92 vs. 90%), ACEi (32 vs. 29%), ARB (16 vs. 18%), and ARNI use (50 vs. 56%). MRA therapy was also more prevalent in the empagliflozin-treated group (64 vs. 56%), although the difference between the two groups was not statistically significant ($P = 0.330$).

Baseline characteristics according to dilated cardiomyopathy subtype

Baseline population characteristics according to DCM type are summarized in Table 2.

Regarding cardiovascular risk factors, smoking habit tended to be more frequent in the idiopathic DCM group (15 vs. 4%; $P = 0.075$), but this did not reach statistical significance. The burden of comorbidities such as cerebrovascular disease, CKD, and peripheral artery disease was comparable between groups. Most patients were classified as NYHA class II (49%) or III (27%), with no significant differences between the idiopathic and ischemic subgroups ($P = 0.341$). The LVEF in the overall cohort was 32.9 ± 7.9%, with a trend toward a lower LVEF in the idiopathic group (31.9 ± 8.1%) compared with the ischemic group (33.8 ± 7.6%), although this difference was not statistically significant ($P = 0.060$). The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were slightly larger in the idiopathic group, but these differences did not reach statistical significance.

The use of ACEi and ARB was comparable between groups, while ARNI were more commonly prescribed in the idiopathic DCM group (73 vs. 35%, $P = 0.054$), approaching statistical significance.

Endothelial function

Figure 1 illustrates the RHI measurements for a patient, recorded both before initiating therapy with an SGLT2i and 365 days after treatment initiation.

In the study population, the baseline RHI value was 1.15 ± 0.34. At 6 months, it significantly increased to 1.40 ± 0.34 ($P < 0.0001$), reflecting an absolute change of 0.25 ± 0.03 (ΔRHI baseline − 6 months). Between 6 and 12 months, the RHI showed a further significant increase to 1.69 ± 0.36 ($P < 0.0001$), with an additional change of 0.29 ± 0.03 (ΔRHI 6 − 12 months).

Table 2 **Baseline population characteristics according to dilated cardiomyopathy etiology**

Total population = 102		**Idiopathic = 48**	**Ischemic = 54**	*P*
General characteristics				
Age (years)	75 [82; 62]	78 [82; 62]	74 [78; 62]	0.194
Male sex, *n* (%)	73 (72)	38 (79)	35 (65)	0.358
Height (cm)	171 [178; 165]	170 [178; 165]	172 [176; 165]	0.586
Weight (kg)	73 [80; 65]	75 [80; 67]	73 [81; 65]	0.971
Smoker, *n* (%)	9 (9)	7 (15)	2 (4)	0.075
Dyslipidemia, *n* (%)	45 (44)	19 (40)	26 (48)	0.156
Diabetes, *n* (%)	27 (26)	15 (31)	12 (22)	0.422
Hypertension, *n* (%)	60 (59)	29 (60)	31 (57)	0.539
Cerebrovascular disease, *n* (%)	7 (7)	3 (6)	4 (7)	0.712
CIED, *n* (%)	76 (75)	38 (79)	38 (70)	0.315
PM	7 (6)	3 (6)	4 (7)	
ICD	44 (43)	20 (42)	24 (44)	
CRT-D	20 (20)	13 (27)	7 (13)	
CRT-P	5 (5)	2 (4)	3 (5)	
Peripheral artery disease, *n* (%)	11 (11)	4 (8)	7 (13)	0.352
Atrial fibrillation, *n* (%)	32 (31)	12 (25)	20 (37)	0.085
CKD, *n* (%)	29 (28)	16 (33)	13 (24)	0.661
COPD, *n* (%)	2 (2)	0 (0)	2 (4)	0.237
NYHA class, *n* (%)				0.341
I	20 (20)	7 (15)	13 (24)	
II	50 (49)	27 (56)	23 (43)	
III	28 (27)	16 (33)	12 (22)	
IV	4 (4)	2 (4)	2 (4)	
SBP (mmHg)	115 [124; 110]	115 [121; 110]	115 [124; 109]	0.875
DBP (mmHg)	70 [70; 60]	70 [70; 60]	70 [70; 60]	0.177
HR (bpm)	65 [73; 63]	66 [71; 63]	64 [73; 60]	0.872
Echocardiography parameters				
EDV (ml)	176.2 ± 64.9	177.3 ± 71.6	175.1 ± 58.1	0.893
ESV (ml)	124.5 ± 52.7	125.9 ± 62.6	123.1 ± 42.7	0.128
EDD (mm)	61.6 ± 7.1	62.7 ± 5.9	60.5 ± 8.3	0.083
ESD (mm)	56.1 ± 2.7	56.2 ± 3.1	56 ± 2.3	0.859
EF (%)	32.9 ± 7.9	31.9 ± 8.1	33.8 ± 7.6	0.060
E/A	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	0.800
E/E	18.1 ± 5.1	18.8 ± 5.9	17.4 ± 4.3	0.431
MR grade, *n* (%)	102 (100)	48 (100)	54 (100)	0.562
None	17 (17)	9 (17)	8 (15)	
Mild	39 (38)	19 (40)	20 (37)	
Moderate	46 (45)	20 (42)	26 (48)	
LAV (ml)	108 [130; 83]	109 [130; 79]	107 [118; 83]	0.740
TAPSE (mm)	20 [22; 18]	20 [22; 18]	20 [22; 18]	0.837
RV S' (cm/s)	11 [12; 10]	11 [12; 10]	12 [12; 10]	0.740
FAC (%)	40 [41; 38]	40 [41; 38]	40 [40; 38]	0.662
PASP (mmHg)	44 [54; 37]	44 [54; 38]	43 [50; 37]	0.577
TR grade *n* (%)	102 (100)	48 (100)	54 (100)	0.568
None	5 (5)	2 (4)	3 (5)	
Mild	44 (43)	20 (42)	24 (44)	
Moderate	52 (51)	26 (50)	26 (48)	
Massive	1 (1)	0 (0)	1 (1)	
Torrential	0 (0)	0 (0)	0 (0)	
Drugs therapy				
Beta blocker, *n* (%)	102 (100)	48 (100)	54 (100)	0.554
Bisoprolol	93 (91)	46 (96)	47 (87)	
Carvedilol	5 (5)	1 (1)	4 (7)	
Metoprolol	2 (2)	1 (1)	1 (1)	
Nebivolol	2 (2)	0 (0)	2 (4)	
ACEi, *n* (%)	31 (31)	14 (29)	17 (31)	0.170
Enalapril	17 (17)	8 (17)	9 (17)	
Ramipril	11 (11)	6 (13)	5 (9)	
Other	3 (3)	0 (0)	3 (5)	
ARB, *n* (%)	17 (17)	10 (20)	7 (13)	0.443
Candesartan	5 (5)	4 (8)	1 (1)	
Valsartan	7 (7)	2 (4)	5 (9)	

Table 2 (*continued*)

Total population = 102		Idiopathic = 48	Ischemic = 54	*P*
Losartan	3 (3)	3 (6)	0 (0)	
Other	2 (2)	1 (1)	1 (1)	
ARNI, *n* (%)	54 (53)	35 (73)	19 (35)	0.054
MRA, *n* (%)	61 (60)	30 (63)	31 (57)	0.134
Spirinolactone	3 (3)	2 (4)	1 (1)	
Eplerenone	6 (6)	4 (8)	2 (4)	
Potassium canreonate	52 (51)	24 (50)	28 (52)	
Loop diuretic, *n* (%)	98 (96)	46 (96)	52 (96)	0.216

Values are expressed as mean ± standard deviation or median [interquartile range]. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilisin inhibitor; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DCM, dilated cardiomyopathy; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FAC, fractional area change; HR, heart rate; ICD, implantable cardioverter-defibrillator; IVSd, interventricular septum thickness; LA, left atrium; LAV, left atrial volume; LWPd, left posterior wall thickness; MR, mitral regurgitation; MRA, mineralocorticoids receptor antagonists; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PM, pacemaker; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

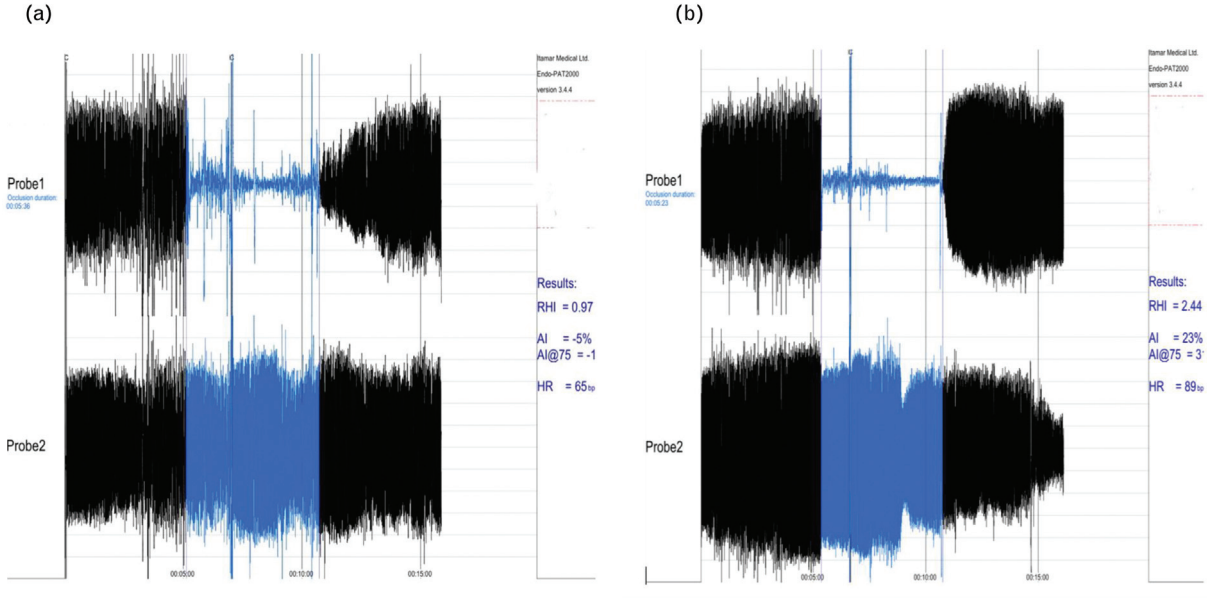
Overall, these findings demonstrate a statistically significant improvement in endothelial function among patients with DCM receiving SGLT2i therapy, as indicated by the progressive increase in RHI values over time ($P < 0.0001$), with a total change of 0.54 ± 0.04 from baseline to 12 months (ΔRHI baseline – 12 months) (Fig. 2 and Table 3).

Changes in endothelial function across SGLT2i drug

In the dapagliflozin group, the baseline RHI value was 1.13 ± 0.32. After 6 months of treatment, it significantly increased to 1.39 ± 0.32 ($P < 0.001$), reflecting an absolute change of 0.26 ± 0.02. Between 6 and 12 months, the RHI exhibited a further significant increase, reaching 1.68 ± 0.34 ($P < 0.001$), with an additional change of 0.29 ± 0.03. The overall change from baseline to 12 months (ΔRHI baseline – 12 months) was 0.55 ± 0.04 ($P < 0.0001$).

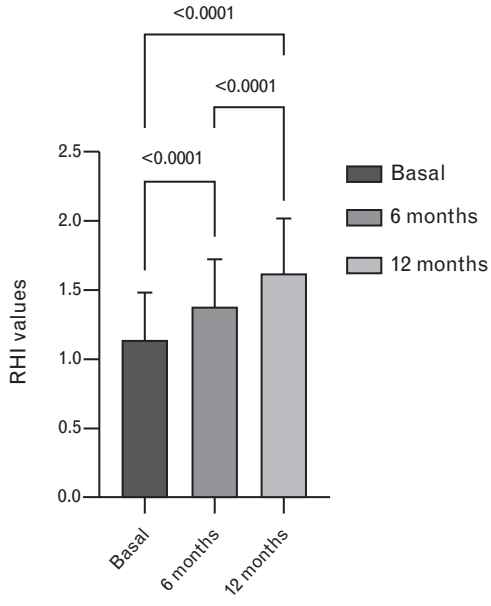
Similarly, in the empagliflozin group, the baseline RHI was 1.17 ± 0.36. At the 6-month follow-up, it increased significantly to 1.41 ± 0.36 ($P < 0.001$), showing an absolute change of 0.24 ± 0.02. Between 6 and 12 months, the RHI further improved to 1.70 ± 0.37 ($P < 0.001$), with an additional change of 0.27 ± 0.03. The overall change from

Fig. 1



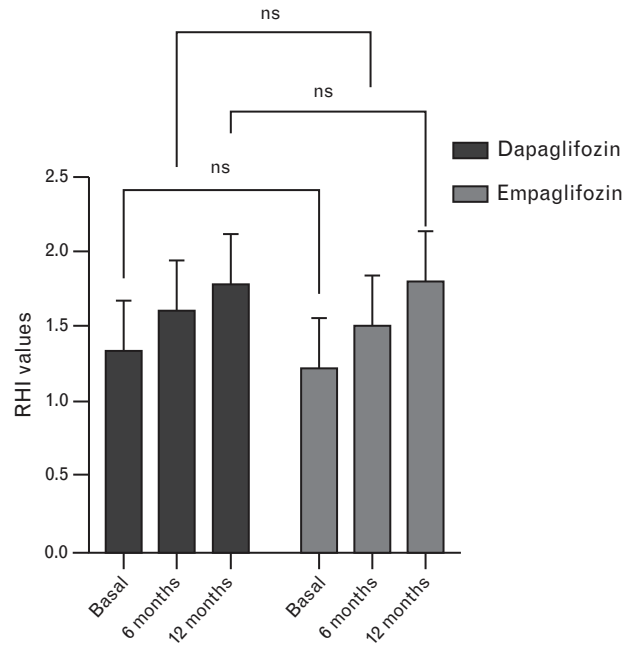
A patient basal RHI (a) and 12 months after SGLT2i therapy (b).

Fig. 2



Basal, 6- and 12-month RHI values after SGLT2i therapy.

Fig. 3



Reactive hyperemia index values in SGLT2i-treated patients.

baseline to 12 months (ΔRHI baseline – 12 months) was 0.51 ± 0.04 ($P < 0.0001$).

No significant difference was observed in the extent of endothelial function improvement between patients treated with empagliflozin and those receiving dapagliflozin ($P = 0.589$) (Fig. 3 and Table 4).

Changes in endothelial function across dilated cardiomyopathy etiology

At baseline, patients with ischemic DCM exhibited a slightly higher RHI compared with those with idiopathic DCM (1.19 ± 0.30 vs. 1.11 ± 0.38). After 6 months of SGLT2i therapy, both groups demonstrated a significant improvement in endothelial function. In the idiopathic DCM group, RHI increased from 1.11 ± 0.38 to 1.35 ± 0.38, reflecting an absolute change of 0.24 ± 0.01 ($P < 0.001$). Similarly, in the ischemic DCM group, RHI improved from 1.19 ± 0.30 to 1.44 ± 0.30, with an absolute change of 0.25 ± 0.02 ($P < 0.001$). Further improvements in endothelial function were observed at 12 months of SGLT2i therapy. In the idiopathic DCM group, RHI increased to 1.66 ± 0.39, marking an overall change of 0.55 ± 0.02 from baseline ($P < 0.001$). In the ischemic DCM group, RHI increased to 1.71 ± 0.32, with an overall change of 0.52 ± 0.02 ($P < 0.0001$). Although the increase in RHI was slightly more pronounced in the ischemic DCM group, the difference

Table 3 Reactive hyperemia index variation in general population

Total population	RHI basal	RHI 6 months	RHI 12 months	ΔRHI basal–6 months	*P*	ΔRHI 6–12 months	*P*	ΔRHI basal–12 months	*P*
	1.15 ± 0.34	1.40 ± 0.34	1.69 ± 0.36	0.26 ± 0.02	<0.0001	0.29 ± 0.03	<0.0001	0.54 ± 0.04	<0.0001

Values are expressed as mean ± standard deviation. RHI, reactive hyperemia index.

Table 4 Reactive hyperemia index variation according to SGLT2i

Groups	RHI basal	RHI 6 months	RHI 12 months	ΔRHI basal–6 months	ΔRHI 6–12 months	ΔRHI basal–12 months	*P*
Empaglifozin = 50	1.17 ± 0.36	1.41 ± 0.36	1.70 ± 0.37	0.24 ± 0.02	0.27 ± 0.03	0.51 ± 0.04	0.589
Dapaglifozin = 52	1.13 ± 0.32	1.39 ± 0.32	1.68 ± 0.34	0.26 ± 0.02	0.29 ± 0.03	0.55 ± 0.04	

Values are expressed as mean ± standard deviation. RHI, reactive hyperemia index.

Table 5 Reactive hyperemia index variation according to dilated cardiomyopathy etiology

Groups	RHI basal	RHI 6 months	RHI 12 months	ΔRHI basal–6 months	ΔRHI 6–12 months	ΔRHI basal–12 months	*P*
Idiopathic = 48	1.11 ± 0.38	1.35 ± 0.38	1.66 ± 0.39	0.24 ± 0.01	0.31 ± 0.02	0.55 ± 0.02	0.463
Ischemic = 54	1.19 ± 0.30	1.44 ± 0.30	1.71 ± 0.32	0.25 ± 0.02	0.27 ± 0.02	0.52 ± 0.02	

Values are expressed as mean ± standard deviation. RHI, reactive hyperemia index.

between the two DCM etiologies remained statistically non-significant ($P = 0.463$), suggesting a comparable degree of baseline endothelial dysfunction between the two groups (Table 5 and Fig. 4).

Changes in echocardiographic parameters

Over the 12-month follow-up period, a progressive improvement in left ventricular function was observed. Although EDV and ESV showed a trend toward reduction (EDV: 176.2 ± 64.9 ml at baseline to 167.6 ± 31.1 ml at 12 months, $P = 0.335$; ESV: 124.5 ± 52.7 ml at baseline to 116.8 ± 24.6 ml at 12 months, $P = 0.606$), these changes were not statistically significant.

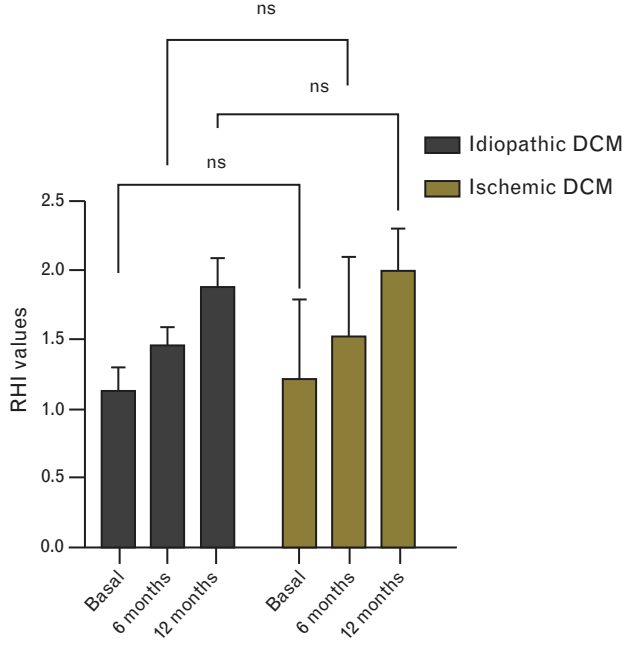
LVEF significantly improved over time, increasing from 32.9 ± 7.9% at baseline to 36.8 ± 5.5% at 6 months and 37.1 ± 4.9% at 12 months ($P < 0.001$).

Diastolic function parameters also exhibited favorable changes. The E/A ratio showed a significant decline from 1.5 ± 0.5 at baseline to 1.1 ± 0.3 at 12 months ($P = 0.023$), suggesting a shift towards improved diastolic filling dynamics. Similarly, the E/E' ratio decreased significantly from 18.1 ± 5.1 at baseline to 11.1 ± 2.8 at 12 months ($P = 0.027$), indicating a reduction in left ventricular diastolic stiffness and improved relaxation. Left atrial volume (LAV) also showed also a significant decrease over time (108 ml at baseline to 100 ml at 12 months, $P = 0.041$).

Lastly, pulmonary artery systolic pressure (PASP) decreased from 44 mmHg at baseline to 39 mmHg at 6 months and further to 35 mmHg at 12 months ($P < 0.001$).

These results indicate a positive effect of SGLT2i on pulmonary hemodynamics, potentially leading to improved clinical status, reduced left ventricular diastolic stiffness, and enhanced myocardial relaxation. Table 6 summarizes the echocardiographic results.

Fig. 4



Reactive hyperemia index values in patients according to dilated cardiomyopathy etiology.

Changes in echocardiographic across SGLT2i drug

The echocardiographic analysis over 12 months was conducted separately for patients treated with empagliflozin ($n = 50$) and dapagliflozin ($n = 52$) (Table 7).

Both groups exhibited a decreasing trend in EDV and ESV, with a slightly greater reduction observed in the empagliflozin group. However, the differences between the two therapies were not statistically significant ($P = 0.825$ and $P = 0.823$, respectively). LVEF showed significant improvement in both groups. In the empagliflozin group, LVEF increased from 31.9 ± 8.1 to 36.1 ± 4.9%, while the dapagliflozin group demonstrated a comparable enhancement from 33.8 ± 7.6 to 38 ± 4.8% ($P = 0.903$), indicating no significant difference between the two treatments.

Diastolic function parameters also improved, with a reduction in the E/A ratio over time and a marked decrease in E/E' in both groups. Notably, E/E' showed a greater reduction in the dapagliflozin group (from 17.7 ± 4.3 at baseline to 11.6 ± 2 at 12 months) compared with the empagliflozin group (from 18.5 ± 5.9 to 10.5 ± 3.5), though this difference did not reach statistical significance ($P = 0.066$). Additionally, PASP decreased from 43 to 36 mmHg in the empagliflozin group and from 45 to 32 mmHg in the dapagliflozin group, but the between-group difference was not statistically significant ($P = 0.095$).

Table 6 Echocardiographic parameters variation in general population

Baseline		6 months	12 months	*P*
EDV (ml)	176.2 ± 64.9	171.2 ± 31.1	167.6 ± 31.1	0.335
ESV (ml)	124.5 ± 52.7	120.9 ± 37.5	116.80 ± 24.6	0.606
EF (%)	32.9 ± 7.9	36.8 ± 5.5	37.1 ± 4.9	<0.001
E/A	1.5 ± 0.5	1.3 ± 0.6	1.1 ± 0.3	0.023
E/E	18.1 ± 5.1	13.7 ± 4.9	11.1 ± 2.8	0.027
LAV (ml)	108 [130; 83]	103 [112; 78]	100 [108; 74]	0.041
PASP (mmHg)	44 [54; 37]	39 [45; 35]	35 [40; 30]	<0.001

Values are expressed as mean ± standard deviation or median [interquartile range]. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAV, left atrial volume; PASP, pulmonary artery systolic pressure.

Table 7 Echocardiographic parameters variation according to SGLT2i

Empaglifozin = 50				Dapaglifozin = 52			*P*
Baseline		6 months	12 months	Baseline	6 months	12 months	
EDV (ml)	180.3 ± 53.1	172 ± 33.8	165.2 ± 33.8	172 ± 76.6	170.4 ± 28.4	170 ± 28.4	0.825
ESV (ml)	131.9 ± 56.6	128.9 ± 41.5	122.7 ± 27.8	117 ± 48.8	112.9 ± 33.5	110.8 ± 21.3	0.823
EF (%)	31.9 ± 8.1	36.4 ± 6.2	36.1 ± 4.9	33.8 ± 7.6	37.2 ± 4.8	38 ± 4.8	0.903
E/A	1.4 ± 0.5	1.2 ± 0.6	1 ± 0.4	1.5 ± 0.5	1.4 ± 0.5	1.2 ± 0.2	0.788
E/E	18.5 ± 5.9	14.4 ± 5.6	10.5 ± 3.5	17.7 ± 4.3	12.9 ± 4.1	11.6 ± 2	0.066
LAV (ml)	110 [130; 81]	106 [112; 75]	100 [108; 73]	106 [116; 83]	102 [109; 78]	98 [106; 74]	0.538
PASP (mmHg)	43 [50; 37]	40 [45; 35]	36 [40; 28]	45 [54; 35]	38 [40; 35]	32 [38; 30]	0.095

Values are expressed as mean ± standard deviation or median [interquartile range]. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAV, left atrial volume; PASP, pulmonary artery systolic pressure.

Changes in echocardiographic across dilated cardiomyopathy etiology

The effect of SGLT2i therapy on cardiac structure and function was also evaluated based on DCM etiology (idiopathic vs. ischemic). Both groups demonstrated a reduction in EDV and ESV over time, with a slightly greater decrease observed in the idiopathic DCM group. However, these differences did not reach statistical significance ($P = 0.090$ for EDV and $P = 0.514$ for ESV) (Table 8).

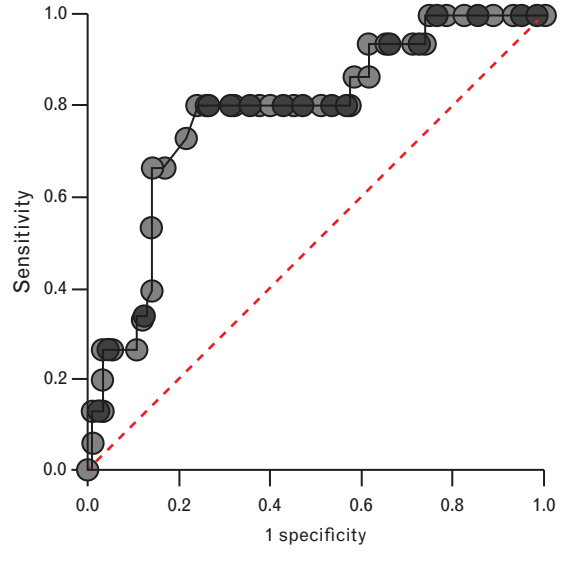
LVEF significantly improved in both groups, increasing from 31.9 ± 8.1 to 36.3 ± 4.9% in patients with idiopathic DCM and from 33.8 ± 7.6 to 37.9 ± 4.8% in those with ischemic DCM. However, the degree of improvement was comparable between the groups ($P = 0.450$).

Regarding diastolic function, LAV decreased over time in both groups, with a slightly greater reduction observed in idiopathic DCM. Despite this trend, the difference did not reach statistical significance ($P = 0.073$).

Risk of hospitalization for heart failure

During the follow-up period, 11 patients had a second HHF. The enhancement in RHI (ΔRHI basal − 12 months: 0.54 ± 0.04, $P < 0.0001$) was significantly associated with a reduction in the incidence of HHF. This relationship was quantitatively supported by the area under the receiver operating characteristic (ROC) curve (AUC) of 0.783 ($P < 0.001$), indicating a strong predictive value of improved endothelial function for a lower risk of HHF events (Fig. 5). These findings highlight the potential vascular benefits of SGLT2i therapy, suggesting that improvements in endothelial function may contribute to better clinical outcomes beyond their established cardioprotective effects.

Fig. 5



Correlation between reactive hyperemia index improvement and the probability of hospitalization for heart failure.

Discussion

To the best of our knowledge, this is the first study to demonstrate the possible effect of SGLT2i on endothelial function in DCM patients. Present data obtained from this longitudinal, observational, monocentric study demonstrated that 1-year treatment with SGLT2i had positive effects on the improvement in endothelial dysfunction in a consistent cohort of symptomatic patients with DCM and reduced LVEF. In addition, the improvement in RHI was associated with a reduction in HHF.

Although ischemic cardiomyopathy is the most common cause of heart failure, it remains uncertain whether endothelial dysfunction is directly related to heart failure itself or the underlying atherosclerosis. In contrast, idiopathic DCM, a leading indication for heart transplantation, also presents with endothelial dysfunction, which may persist even after transplantation.[29,30] In our study, no significant differences were observed in RHI between the different DCM etiologies. Moreover, endothelial function improved similarly in both ischemic and idiopathic groups, indicating that SGLT2i therapy provides vascular benefits regardless of the underlying etiology. Few studies showed an amelioration of endothelial function in DCM patients. Amore *et al.*[31] enrolled 15 patients with DCM and reduced LVEF. They showed an increase in RHI ($P = 0.001$) after 6 months of sacubitril-valsartan treatment. Therefore, previous studies have evaluated the prognostic value of endothelial function in heart failure patients. Kim *et al.*[22] evaluated 90 patients (mean age, 63.7 ± 13.2 years). During a median follow-up of 3.66 years, they demonstrated that a RHI less than 1.48 was significant associated with adverse events ($P < 0.001$). Similarly, Fujisue *et al.*[21] showed that Ln-RHI was independently associated with heart failure related events in 362 HFrEF patients (per 0.1, hazard ratio: 0.84, 95% confidence interval: 0.75–0.95, $P = 0.005$). Conversely, two prospective studies involving patients with heart failure with preserved ejection fraction (HFpEF) have shown that RHI can predict cardiovascular events more effectively than conventional risk stratification methods.[32,33] Moreover, lnRHI has been demonstrated to predict adverse events related to heart failure. In another recent study, an independent predictive role for cardiovascular events was confirmed in a cohort of patients with CKD.[34]

Lastly, SARS-CoV-2 infection has been linked to alterations in cardiac markers, indicating myocardial damage.[35–37] Cimino *et al.*[38] demonstrated that in-vivo endothelial dysfunction occurs in SARS-CoV-2-infected patients, even in the absence of cardiovascular risk factors or preexisting cardiac conditions. For instance, early diagnosis in individuals without traditional cardiovascular risk factors could be crucial for enabling closer cardiovascular monitoring and potentially improving clinical outcomes. Several factors are responsible for endothelial dysfunction such as smoking, diabetes, hypertension, renal disease, dyslipidemia, and aging.[39] These conditions, in concert with declining nitric oxide bioavailability (a major determinant of endothelial function), contribute to cardiac hypertrophy, fibrosis, ventricular remodeling, and progression of atherosclerotic disease.[40] In our study, the endothelium-dependent response in conditions of reactive hyperemia was evaluated, in order to estimate any changes over time in the endothelial function of the patients before and after 12 months of SGLT2i therapy. Indeed, the introduction of SGLT2i therapy leads to a significant change in endothelial function (expressed as RHI) compared with baseline values. These findings suggest that PAT measures have a significant role in identifying the benefit of SGLT2i therapy in DCM with reduced LVEF population. The assessment of endothelial function with subsequent changes could be applied in normal clinical practice in these patients, like many other known markers of heart failure. SGLT2i therapy is the new standard therapy for heart failure according to the latest ESC guidelines.[6,8] The inclusion of this category of drugs in the treatment of heart failure is due to the evidence of a whole series of studies which have demonstrated how these drugs are able to improve the cardiovascular outcomes in patients with HF.[6,8,10–12,41] Consistently with previous studies, our findings indicate that both SGLT2 inhibitors produce comparable improvements in left ventricular function, left ventricular volumes, diastolic performance, and pulmonary pressures, regardless of DCM etiology. This reinforces the concept of a class-wide effect of SGLT2i therapy on cardiac remodeling. In detail, Yu *et al.*[42] demonstrated that SGLT2i therapy facilitated reverse cardiac remodeling, especially of left atrial structure.

Several mechanisms directly and indirectly contributed to cardiac health (i.e. osmotic diuresis and natriuresis, body weight reduction, increase in ketone bodies, reduction of the content liver fat, LDL and triglycerides; inhibition of sodium-hydrogen exchange, reduction of cardiac fibrosis),[43] but many putative mechanisms remain unclear or are supported only by preclinical model studies or small human studies.[44–47] In the absence of a single main effect or unifying hypothesis, it is suggested that multiple different mechanisms could contribute to the overall cardio/nephroprotective effects of SGLT2i.[18,48] Whatever the exact molecular pathway, the extra glycemic ancillary effects of this drug class reduced the risk of cardiovascular events, HHF and progression of diabetic kidney disease.[6,49]

For this reason, it is essential to continue researching this class of drugs to gain a deeper understanding of the molecular mechanisms underlying their observed effects and to assess their potential impact on clinical practice.

Table 8 Echocardiographic parameters variation according to dilated cardiomyopathy etiology

Idiopathic = 48				Ischemic = 54			
Baseline		**6 months**	**12 months**	**Baseline**	**6 months**	**12 months**	*P*
EDV (ml)	177.3 ± 71.6	168.3 ± 25.6	165.2 ± 26	175.1 ± 58.1	174.1 ± 36.6	170 ± 36.1	0.090
ESV (ml)	125.9 ± 62.6	121.5 ± 42.3	115.1 ± 26.9	123.1 ± 42.7	120.3 ± 32.7	118.4 ± 22.3	0.514
EF (%)	31.9 ± 8.1	35.9 ± 4.7	36.3 ± 4.9	33.8 ± 7.6	37.7 ± 6.2	37.9 ± 4.8	0.450
E/A	1.4 ± 0.5	1.3 ± 0.5	1 ± 0.4	1.5 ± 0.5	1.3 ± 0.6	1.2 ± 0.2	0.831
E/E	18.8 ± 5.9	13.5 ± 5.7	11.4 ± 3.4	17.4 ± 4.3	13.9 ± 4.1	10.8 ± 2.1	0.536
LAV (ml)	109 [130; 79]	104 [112; 73]	98 [107; 70]	107 [118; 83]	102 [109; 78]	101 [108; 74]	0.073
PASP (mmHg)	44 [54; 38]	40 [48; 35]	33 [43; 32]	43 [50; 37]	38 [42; 35]	36 [38; 29]	0.610

Values are expressed as mean ± standard deviation or median [interquartile range]. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAV, left atrial volume; PASP, pulmonary artery systolic pressure.

Limitations

In interpreting the results of the current study, it is important to acknowledge its inherent limitations. One of the primary limitations of this study is its observational design, which inherently restricts the ability to establish definitive causal relationships. In addition, the relatively small cohort of 102 patients, all recruited from a single center, may limit the generalizability of the findings to broader populations. Larger, multicenter studies are needed to confirm these results and provide a more comprehensive understanding of the observed effects. In addition, the decision to conduct follow-up assessments at 12 months may not have captured effects that necessitate longer observation periods. Another limitation of this study is the absence of a control group, which prevents direct comparisons and makes it challenging to isolate the effects of the intervention from other potential influencing factors.

Conclusion

SGLT2i therapy demonstrates beneficial effects on endothelial function in DCM patients with reduced LVEF, regardless of the specific SGLT2i used or the underlying DCM etiology. Although the precise mechanisms remain to be fully elucidated, improved endothelial function may contribute to better cardiovascular outcomes by enhancing vascular health and reducing the progression of heart failure. Future research should focus on clarifying these pathways and assessing the potential role of PAT in monitoring endothelial function during SGLT2i therapy, which could help guide treatment decisions and optimize patient management.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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GRAPHICAL ABSTRACT