ORIGINAL ARTICLE

Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure

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Abstract

Aims   Impairment of vascular function contributes to the progression of chronic heart failure (HF) by increasing the afterload. Treatment with selective sodium-glucose cotransporter 2 (SGLT2) inhibitors improves the prognosis of HF, but the precise mechanisms remain unclear. The aim of this study was to analyse the effect of empagliflozin on vascular function in patients with HF.

Methods and results   In an investigator initiated, double-blind, randomized, placebo-controlled, parallel-group, clinical study, patients with HF NYHA II-III and an ejection fraction of 49% or less were randomized 2:1 to receive empagliflozin 10 mg once daily or placebo for 3 months. A total of 74 patients (15% female), aged 66 ± 9 years, with a mean ejection fraction of 39 ± 8% and a median NTproBNP of 558 pg/mL (IQR 219–1051 pg/mL), were included. Vascular parameters such as central systolic blood pressure (cSBP), central pulse pressure (cPP), forward (FPH), and reflected pressure pulse height (RPH) decreased under resting conditions after 1 and 3 months (1 month: cSBP −6.4 ± 8.3 mmHg, $P < 0.001$, cPP −3.0 ± 6.6 mmHg, $P = 0.004$, FPH −2.5 ± 4.5 mmHg, $P = 0.001$, RPH −1.6 ± 3.0 mmHg, $P = 0.001$; 3 months: cSBP −4.6 ± 8.4 mmHg, $P = 0.001$, cPP −3.1 ± 4.8 mmHg, $P < 0.001$, FPH −1.7 ± 3.7 mmHg, $P = 0.004$, RPH −1.4 ± 2.5 mmHg, $P = 0.001$) in patients treated with empagliflozin ($n = 45$). In accordance, cSBP and cPP decreased in patients with empagliflozin treatment under 24 h ambulatory conditions after 1 and 3 months (1 month: cSBP −4.8 ± 10.1 mmHg, $P = 0.003$, cPP −2.0 ± 5.7 mmHg, $P = 0.026$; 3 months: cSBP −4.7 ± 9.0 mmHg, $P = 0.002$, cPP −2.1 ± 6.4 mmHg, $P = 0.044$). In the placebo group, there was no significant change after 1 and 3 months. The decrease in cSBP under resting conditions (−5.7 ± 2.4 mmHg, $P = 0.019$) after 1 month and in cSBP (−6.0 ± 2.6, $P = 0.027$) as well as in pulse wave velocity (−0.5 ± 0.2 m/s, $P = 0.021$) under 24 h ambulatory conditions after 3 months was greater in the empagliflozin group than in the placebo group.

Conclusions   We found an improvement of vascular function after treatment with empagliflozin that indicates decreased afterload of the left ventricle and may contribute to the beneficial effects of SGLT2 inhibition in HF.

Introduction

Chronic heart failure (HF) is still a major cause of morbidity and mortality, affecting estimated 64 million people world-wide and thus constituting a global health concern, which is increasing with the aging population.[1] Despite on-going improvement of cardiac diagnostics and therapy, the quality of life and the survival rate of patients with diagnosed heart failure remains poor. The 2019 Guidelines on diabetes, pre-diabetes, and cardiovascular diseases, developed in

collaboration with the European Association for the Study of Diabetes, highlighted the selective sodium-glucose cotransporter 2 (SGLT2) inhibitors as recommended diabetes mellitus treatment to reduce the risk of heart failure hospitalizations in patients with HF and diabetes.[2] The 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment emphasized the SGLT2 inhibitor as a valuable add-on in patients with HF who are already receiving beta-blockers, angiotensin receptor-neprilysin inhibitors or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone receptor antagonist, regardless of the presence of diabetes mellitus.[3] In the new guidelines on acute and chronic heart failure of the European Society of Cardiology, to be released in 2021, the SGLT2 inhibitors will certainly represent a new therapeutic cornerstone in the treatment strategy of HF.

Pivotal large randomized controlled trials demonstrated that SGLT2 inhibitors prevent major adverse cardiovascular events as well as the occurrence of hospitalizations for heart failure and progression of chronic kidney disease in patients with type 2 diabetes.[4] Moreover, a reduction in the incidence of heart failure hospitalizations and mortality by the treatment with SGLT2 inhibitors was also demonstrated in patients with previously diagnosed HF in both patients with and without diabetes.[5,6] The SGLT2 inhibitors, initially developed as antidiabetic medication, have been proven to exert nephroprotective and cardioprotective effects in patients with and without diabetes. However, the precise underlying mechanisms are still unclear and remain to be elucidated.

It is common knowledge that impairment of vascular function plays a central role in the development and progression of HF (ventricular-arterial coupling).[7,8] A key marker of vascular changes is arterial stiffness, which increases with the aging process and, which has been identified as a strong predictor of cardiovascular events and death.[9,10] The reduced compliance in the arterial system leads to increased pulse wave velocity (PWV) in the arterial vascular tree and thereby to increased central systolic blood pressure (cSBP) and central pulse pressure (cPP), both augmenting the afterload imposed on the left ventricle.[11] In patients with HF, increased vascular tone due to activation of the sympathetic nervous system and renin-angiotensin-aldosterone system additionally leads to a reduction of the arterial compliance and thereby to an increased cardiac afterload. Data on the effects of SGLT2 inhibition on vascular function in patients with HF have not yet been thoroughly analysed and constitute the aim of this current study.

Methods

Study design

This was an investigator initiated, double-blind, randomized, placebo-controlled, parallel-group, prospective phase II single centre study, performed at the Clinical Research Unit (CRC) of the Department of Nephrology and Hypertension, University Hospital Erlangen-Nuremberg, Germany, in order to analyse changes of vascular function and of tissue sodium content in patients with HF after SGLT2 inhibition with empagliflozin. Patients with HF were recruited between July 2017 and March 2020 by local newspaper advertisement, referring physicians and from the cardiology outpatient clinic of the University Hospital. The patients were consecutively enrolled, if all inclusion criteria and none of the exclusion criteria were fulfilled. After the run-in phase, the first vascular examination took place (baseline). Patients were then consecutively randomized (2:1) to receive either empagliflozin 10 mg once daily or placebo. The 2:1 randomization was chosen to increase the power for comparing the effects of the SGLT2 inhibitor empagliflozin versus baseline. Subsequent vascular examinations were performed after 1 and 3 months of treatment. Each patient provided written informed consent prior to study inclusion. The study was conducted in accordance with local laws, the Declaration of Helsinki, and the principles of good clinical practice guidelines. The local ethics committee of the University of Erlangen-Nuremberg approved the study protocol. The study was registered at http://www.clinicaltrials.gov (NCT03128528).

Study population

Individuals, aged between 18 and 85 years, were included in the study, if they had a HF with reduced (HFrEF) or mid-range ejection fraction (HFmrEF), according to the ESC guidelines' definition, in stable condition [New York Heart Association (NYHA) II-III].[12] Patients could have diabetes or not; however, key exclusion criteria were any other form of diabetes than type 2 diabetes, the use of insulin, or any SGLT2 inhibitor 10 weeks prior to inclusion. Patients with glycosylated haemoglobin (HbA1c) $\geq$ 10% or fasting plasma glucose $\geq$ 240 mg/dL, an estimated glomerular filtration rate $<$ 30 mL/min/1.73 m^2, NYHA IV or the use of loop diuretics above furosemide $>$ 80 mg/day were excluded. If the patients had experienced a stroke, transient ischaemic attack, instable angina pectoris, or myocardial infarction within the last 6 months prior to study inclusion, no inclusion was possible.

Clinical parameters

Demographic data including medical history and any concomitant medication were recorded at the first visit (screening). At the randomization visit (baseline), fasting blood samples were drawn to measure N-terminal prohormone of brain natriuretic peptide (NTproBNP), fasting plasma glucose,

HbA1c, and other clinical safety markers such as creatinine and liver enzymes.

Office blood pressure (BP) and heart rate were assessed according to European Society of Hypertension/European Society of Cardiology guideline recommendations, in seated position after 5 min rest by a validated device (Dinamap Pro 100V2; Criticon, Norderstedt, Germany).[13] In addition, 24 h ambulatory peripheral BP was provided by a validated device (Mobil-O-Graph, I.E.M., Aachen, Germany).[14,15]

Vascular function

The vascular analyses were performed at three time points, at baseline and after 1 and 3 months of treatment.

Pulse wave analysis and pulse wave velocity

Brachial systolic BP is often different from cSBP as systolic BP undergoes various alterations from the heart, central aorta to the artery of the arm. Over the past years, central BP devices emerged, and in 2017, the Artery Society released recommendations on validation protocols for these devices and demanded invasive central BP as being the reference.[16] One of these validated, highly reliable systems is the SphygmoCor XCEL System (AtCor Medical, Sydney, Australia), which was used in this study to assess vascular parameters under resting conditions.[17] Peripheral brachial BP was measured with a conventional brachial oscillometric device which records the volumetric displacement related to the volume of the brachial artery within the cuff around the upper arm. The system then calculates the central aortic pressure wave from the peripheral signal by a validated transfer function.[18] The obtained aortic central waveforms gave us data on cSBP and central diastolic BP, cPP, augmentation pressure, forward and reflected pressure pulse height. The forward pressure pulse height describes the first systolic peak of the aortic wave from the left ventricle to the periphery of the arterial tree, whereas the reflected pulse pressure height describes the second systolic peak from the reflection of the forward wave from segments of the arterial tree.

Further, the SpygmoCor XCEL system enables us to determine the aortic PWV using simultaneously the carotid pulse acquired by applanation tonometry and the femoral pulse acquired by a femoral cuff around the upper thigh. The software calculates the PWV by measuring the foot-to-foot transit time between carotid and femoral pulse divided by the physical distance measured. The cuff-based assessment of carotid-femoral PWV by SphygmoCor Xcel, introduced 2012, has been validated against the accepted tonometric method, giving comparable results and being in accordance with the Artery Society guidelines for validation of non-invasive haemodynamic measurement devices.[19,20] The non-invasive assessment of central aortic pulse wave and PWV was performed in a quiet temperature controlled examination room with the patient being in supine position. The coefficient of variation for the Sphygmocor device was below 10%.

Twenty-four hour ambulatory blood pressure and ambulatory vascular parameters

Twenty-four hour ambulatory brachial BP was assessed by an oscillometric brachial-cuff based sphygmomanometer (Mobil-O-Graph, I.E.M., Aachen, Germany), which has been shown to be valid and reproducible in the past.[14,15] The BP cuff over the brachial artery was inflated to the diastolic BP level, and the pressure oscillations were registered. From this peripheral signal, central aortic pulse wave was gained by a transducer and generated by a computer software. PWV was then derived from the ARCSolver algorithm integrating age, cSBP, and the data derived from the pulse wave analysis.[21] Pulse wave analysis has been validated against common tonometric method, and PWV has been validated against intraaortic catheter measurements and found to produce reliable and valid data.[22,23]

Statistical analysis

Data are presented as percentages, means with standard deviation (SD) for normally distributed parameters, or median with interquartile range (IQR) in all other cases. Statistical significance of changes between baseline and 1 or 3 months treatment with empagliflozin or placebo were determined using paired t-test, whereas for differences between 1 or 3 months treatment with empagliflozin compared with placebo, an unpaired t-test was used. A two-sided P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics software, version 24.0 (IBM Corporation, Chicago, IL, USA).

Results

Study population

Out of 87 patients screened, 75 patients were randomized. One patient had to be excluded due to a major protocol violation by receiving incorrect study medication. Out of the intention-to-treat population ($n = 74$), 66 completed all three vascular exams. The loss of eight patients is explained by arrhythmias preventing measurements of high quality, for example, runs of bigeminy, trigeminy, atrial fibrillation, or isolated premature beats and following compensatory beats, at the time of the vascular exam. The mean age of the patients was 66 ± 9 years, 15% being female and 23% had type 2 diabetes mellitus. Mean left ventricular ejection fraction was 39 ± 8%, and median NTproBNP was 558 pg/mL (IQR 219–1051 pg/mL). Forty of the 66 patients (61%) had HFmrEF, and myocardial ischaemia was the predominant

cause for heart failure (73%). The patients were receiving appropriate treatment for heart failure (*Table 1*).

There was no significant difference between the two treatment groups regarding HF classification, cause of HF, or distribution in medication (data not shown). All patients were adherent to the study medication. Patients randomized to the empagliflozin group had significant glucosuria at 1 and 3 months (full adherence), and none of the placebo group had evidence of glucosuria in the 24 h urine (no drop-ins).

Vascular function

Under office conditions, the key parameters of vascular function, namely, cSBP, cPP, and forward and reflected pulse pressure height, were improved after 1 month ($P < 0.001$, $P = 0.004$, $P = 0.001$, $P = 0.001$) and 3 months ($P = 0.001$, $P < 0.001$, $P = 0.004$, $P = 0.001$) of empagliflozin compared with baseline (*Tables 2* and *3*). Comparing the two treatment arms, under resting conditions, the decrease of cSBP and of forward pressure pulse height was greater after 1 month ($P = 0.019$, $P = 0.035$), and the decrease of cPP ($P = 0.030$) was greater after 3 months in the empagliflozin group. With respect to the 24 h ambulatory daily life measurements, the key parameters cSBP and cPP were improved after one ($P = 0.003$, $P = 0.026$) and 3 months ($P = 0.002$, $P = 0.044$) of treatment with empagliflozin to baseline. Comparing the two treatment arms, the decrease of 24 h ambulatory cSBP and of 24 h ambulatory PWV was greater after 3 months ($P = 0.027$, $P = 0.021$) in the empagliflozin group. There was no change in the placebo group after 1 and 3 months compared with baseline in either condition.

Office and 24 h ambulatory peripheral blood pressure

Office systolic BP decreased after treatment with empagliflozin by 9.8 ± 13.2 mmHg after 1 month ($P < 0.001$) and by 6.0 ± 16.6 mmHg after 3 months ($P = 0.020$) compared with baseline. Office diastolic BP was lower after treatment with empagliflozin by 3.8 ± 7.3 mmHg after 1 month ($P = 0.001$) and by −2.0 ± 7.8 mmHg after 3 months ($P = 0.096$) compared with baseline. 24 h

ambulatory BP was also reduced, both systolic and diastolic after 1 month ($P = 0.007$, $P = 0.004$) and 3 months ($P = 0.033$, $P = 0.040$), whereas no change was observed in the placebo group for either condition.

Clinical characteristics

After one and 3 months treatment with empagliflozin effected weight loss, improved HbA1c concentration and increased serum creatinine were observed, findings repeatedly shown by others before (*Tables 4* and *5*). With regard to the urinary parameters, the 24 h urinary sodium excretion and 24 h urinary volume increased after 1 month versus baseline, but the changes were no longer significant after 3 months. The 24 h glucose excretion was after one and 3 months treatment with empagliflozin 35 and 37 g/day, respectively.

Discussion

Treatment with empagliflozin improved vascular function under office as well as 24 h daily life conditions in our patients with stable HF compared with baseline as well as to placebo (*Figure 1*). Further, in accordance with other trials, we found reduced brachial office and 24 h ambulatory BP, improved metabolic control and body weight loss under treatment with empagliflozin.

This study is the first to analyse the effects of the treatment of SGLT2 inhibitor empagliflozin on vascular function in patients with stable HF and reduced ejection fraction. Increased arterial stiffness augments the haemodynamic load afflicted to the left ventricle and thereby represents a relevant process leading to the development and worsening of heart failure. Our data indicate that empagliflozin causes a decrease in the stiffness of the aorta and the proximal branches, reducing thereby the afterload of the left ventricle. The observed effect is not only evident after a short period of treatment but also persists over 3 months. The underlying mechanisms are multifaceted and not fully elicited. In our study, the empagliflozin treatment lowered cSBP and cPP under office conditions and consistently 24 h daily life conditions.

Table 1 Medical therapy at baseline of the intention-to-treat population ($n = 74$) and categorized by treatment group

Drug class	All ($n = 74$)	Empagliflozin ($n = 48$)	Placebo ($n = 26$)
AT1 receptor antagonist, % (n)	42 (31)	44 (21)	39 (10)
ACE inhibitor, % (n)	49 (36)	41 (20)	61 (16)
Mineralocorticoid receptor antagonist, % (n)	55 (41)	50 (24)	65 (17)
Diuretic, % (n)	55 (41)	56 (27)	55 (14)
Beta-blocker, % (n)	69 (51)	69 (33)	69 (18)
Calcium channel blocker, % (n)	16 (12)	15 (7)	19 (5)

ACE, angiotensin-converting enzyme; AT1, angiotensin I receptor.

Table 2 Changes in office, 24 h ambulatory blood pressure, and vascular parameters under ambulatory as well as resting conditions after 1 month of treatment with empagliflozin or placebo

Parameters	E, baseline	E, absolute value 1 month	E, change from baseline	P-value E vs. baseline	P, baseline	P, absolute value 1 month	P, change from baseline	P-value P vs. baseline	Between-group difference	P-value E vs. P
Peripheral office BP										
Systolic BP (mmHg)	123.1 ± 20.0	113.4 ± 16.1	−9.8 ± 13.2	<0.001	122.6 ± 16.7	120.7 ± 16.8	−1.8 ± 10.3	0.482	−7.9 ± 3.3	0.018
Diastolic BP (mmHg)	72.9 ± 9.0	69.1 ± 7.2	−3.8 ± 7.3	0.001	73.9 ± 7.9	73.2 ± 8.1	−0.6 ± 8.1	0.722	−3.2 ± 2.0	0.119
Heart rate (b.p.m.)	65.3 ± 11.8	63.5 ± 12.3	−1.9 ± 12.2	0.307	65.4 ± 12.2	64.3 ± 11.8	−1.1 ± 10.5	0.648	0.2 ± 3.5	0.963
Peripheral 24 h ambulatory BP										
Systolic BP (mmHg)	119.3 ± 15.6	115.0 ± 11.2	−4.3 ± 10.4	0.007	121.8 ± 15.7	120.5 ± 15.6	−1.3 ± 8.7	0.467	−2.9 ± 2.5	0.251
Diastolic BP (mmHg)	72.5 ± 9.0	69.9 ± 6.3	−2.6 ± 6.1	0.004	74.8 ± 8.8	74.7 ± 10.3	−0.2 ± 5.0	0.869	−2.5 ± 1.5	0.096
Pulse pressure (mmHg)	46.8 ± 10.2	45.1 ± 8.8	−1.7 ± 6.3	0.071	47.0 ± 10.0	45.8 ± 9.1	−1.3 ± 5.1	0.250	−0.4 ± 1.5	0.779
Heart rate (b.p.m.)	67.5 ± 11.6	65.5 ± 11.8	−2.0 ± 8.2	0.095	65.9 ± 10.0	65.5 ± 9.5	−0.3 ± 5.8	0.777	−1.7 ± 1.9	0.384
Central office vascular parameters										
Systolic BP (mmHg)	117.1 ± 14.5	110.7 ± 11.2	−6.4 ± 8.3	<0.001	117.0 ± 18.1	116.3 ± 15.0	−0.7 ± 10.7	0.759	−5.7 ± 2.4	0.019
Diastolic BP (mmHg)	75.7 ± 9.6	72.3 ± 8.6	−3.4 ± 6.0	0.001	76.4 ± 12.0	76.9 ± 9.3	0.5 ± 8.8	0.802	−3.8 ± 1.8	0.038
Pulse pressure (mmHg)	41.4 ± 8.8	38.4 ± 8.5	−3.0 ± 6.6	0.004	40.6 ± 9.1	39.4 ± 8.6	−1.2 ± 6.8	0.422	−1.8 ± 1.7	0.289
Forward pressure pulse height (mmHg)	27.5 ± 6.0	24.9 ± 5.0	−2.5 ± 4.5	0.001	27.3 ± 6.3	27.2 ± 5.6	−0.1 ± 4.2	0.923	−2.4 ± 1.1	0.035
Reflected pressure pulse height (mmHg)	17.3 ± 3.8	15.7 ± 3.3	−1.6 ± 3.0	0.001	17.1 ± 3.6	16.0 ± 3.7	−1.1 ± 2.8	0.083	−0.6 ± 0.7	0.460
Pulse wave velocity (m/s)	8.7 ± 2.0	8.3 ± 1.8	−0.4 ± 1.1	0.012	8.4 ± 1.7	8.3 ± 1.6	−0.1 ± 1.1	0.611	−0.3 ± 0.3	0.253
Central 24 h ambulatory vascular parameters										
Systolic BP (mmHg)	111.8 ± 14.2	107.0 ± 11.4	−4.8 ± 10.1	0.003	114.0 ± 14.1	113.2 ± 14.9	−0.8 ± 9.4	0.700	−4.0 ± 2.6	0.131
Diastolic BP (mmHg)	74.5 ± 9.4	71.7 ± 6.6	−2.9 ± 6.7	0.006	76.3 ± 9.7	76.3 ± 11.9	0.0 ± 5.9	0.971	−2.9 ± 1.7	0.093
Pulse pressure (mmHg)	37.2 ± 8.8	35.3 ± 8.4	−2.0 ± 5.7	0.026	37.7 ± 9.8	36.9 ± 8.3	−0.9 ± 5.0	0.444	−1.1 ± 1.5	0.861
Pulse wave velocity (m/s)	9.6 ± 1.6	9.5 ± 1.5	−0.1 ± 0.4	0.109	9.1 ± 1.5	9.1 ± 1.4	0.0 ± 0.3	0.829	−0.1 ± 0.1	0.257

BP, blood pressure; E, empagliflozin; P, placebo.
Data are mean ± standard deviation.

Table 3 Changes in office, 24 h ambulatory blood pressure, and vascular parameters under ambulatory as well as resting conditions after 3 months of treatment with empagliflozin or placebo

Parameters	E, baseline	E, absolute value 3 months	E, change from baseline	P-value E vs. baseline	P, baseline	P, absolute value 3 months	P, change from baseline	P-value P vs. baseline	Between-group difference	P-value E vs. P
Peripheral office BP										
Systolic BP (mmHg)	123.1 ± 20.0	117.2 ± 15.5	−6.0 ± 16.6	0.020	122.6 ± 16.7	122.5 ± 19.1	−0.1 ± 11.1	0.969	−5.9 ± 4.0	0.147
Diastolic BP (mmHg)	72.9 ± 9.0	70.9 ± 9.4	−2.0 ± 7.8	0.096	73.9 ± 7.9	71.4 ± 7.2	−2.5 ± 7.1	0.121	0.6 ± 2.0	0.780
Heart rate (b.p.m.)	65.3 ± 11.8	66.5 ± 14.4	1.2 ± 13.5	0.555	65.4 ± 12.2	62.8 ± 11.5	−2.5 ± 8.6	0.191	4.7 ± 3.9	0.232
Peripheral 24 h ambulatory BP										
Systolic BP (mmHg)	119.9 ± 15.2	116.6 ± 12.4	−3.4 ± 10.2	0.033	123.4 ± 15.5	126.5 ± 18.0	3.1 ± 7.6	0.073	−6.5 ± 2.5	0.012
Diastolic BP (mmHg)	73.2 ± 8.4	71.0 ± 7.6	−2.2 ± 7.0	0.040	75.4 ± 9.1	77.0 ± 10.6	1.7 ± 4.1	0.079	−3.9 ± 1.4	0.007
Pulse pressure (mmHg)	46.8 ± 10.3	45.6 ± 9.0	−1.2 ± 7.2	0.289	48.0 ± 9.8	50.0 ± 11.2	2.0 ± 5.7	0.131	−3.1 ± 1.8	0.088
Heart rate (b.p.m.)	67.7 ± 11.8	66.9 ± 12.1	−0.8 ± 9.5	0.564	65.4 ± 10.2	64.7 ± 11.2	−0.7 ± 6.2	0.627	−0.2 ± 2.3	0.946
Central office vascular parameters										
Systolic BP (mmHg)	116.6 ± 13.5	112.0 ± 11.0	−4.6 ± 8.4	0.001	117.2 ± 18.5	116.9 ± 14.6	−0.3 ± 11.8	0.908	−4.3 ± 2.6	0.104
Diastolic BP (mmHg)	75.4 ± 9.7	74.0 ± 8.6	−1.5 ± 7.0	0.191	76.3 ± 12.2	75.7 ± 8.5	−0.6 ± 8.6	0.766	−0.9 ± 2.0	0.652
Pulse pressure (mmHg)	41.2 ± 7.9	38.1 ± 7.4	−3.1 ± 4.8	<0.001	40.9 ± 9.1	41.2 ± 9.4	0.2 ± 7.1	0.873	−3.3 ± 1.5	0.030
Forward pressure pulse height (mmHg)	27.2 ± 5.8	25.5 ± 5.4	−1.7 ± 3.7	0.004	27.6 ± 6.3	27.7 ± 6.6	0.0 ± 5.4	0.974	−1.8 ± 1.3	0.175
Reflected pressure pulse height (mmHg)	17.2 ± 3.2	15.7 ± 3.3	−1.4 ± 2.5	0.001	17.2 ± 3.6	16.9 ± 4.4	−0.3 ± 3.4	0.657	−1.1 ± 0.7	0.141
Pulse wave velocity (m/s)	8.8 ± 2.0	8.7 ± 1.7	−0.1 ± 0.9	0.684	8.4 ± 1.8	8.4 ± 1.7	0.0 ± 1.0	0.825	−0.1 ± 0.2	0.672
Central 24 h ambulatory vascular parameters										
Systolic BP (mmHg)	112.6 ± 14.7	107.9 ± 11.2	−4.7 ± 9.0	0.002	113.7 ± 12.8	114.9 ± 14.0	1.2 ± 9.7	0.600	−6.0 ± 2.6	0.027
Diastolic BP (mmHg)	75.4 ± 9.1	72.7 ± 7.8	−2.6 ± 7.8	0.043	76.3 ± 10.0	77.8 ± 10.6	1.6 ± 3.5	0.079	−4.2 ± 1.5	0.007
Pulse pressure (mmHg)	37.3 ± 9.0	35.1 ± 7.8	−2.1 ± 6.4	0.044	37.4 ± 9.2	37.1 ± 7.8	−0.3 ± 8.6	0.872	−1.8 ± 2.0	0.382
Pulse wave velocity (m/s)	9.6 ± 1.5	9.3 ± 1.6	−0.2 ± 0.9	0.121	9.0 ± 1.6	9.3 ± 1.8	0.3 ± 0.7	0.055	−0.5 ± 0.2	0.021

BP, blood pressure; E, empagliflozin; P, placebo.
Data are mean ± standard deviation.

Table 4 Changes in clinical characteristics after 1 month of treatment with empagliflozin or placebo

| Parameters	E, baseline	E, absolute value 1 month	E, change from baseline	P-value E vs. baseline	P, baseline	P, absolute value 1 month	P, change from baseline	P-value P vs. baseline	Between-group difference	P-value E vs. P
Weight (kg)	88.3 ± 13.7	87.8 ± 13.8	−0.5 ± 1.3	0.015	89.1 ± 13.5	89.4 ± 14.1	0.3 ± 1.5	0.366	−0.80 ± 0.37	0.032
BMI (kg/m^2)	28.7 ± 3.9	28.6 ± 4.0	−0.2 ± 0.4	0.012	28.9 ± 3.3	29.0 ± 3.6	0.1 ± 0.5	0.366	−0.27 ± 0.12	0.028
Fasting plasma glucose (mg/dL)	100.7 ± 13.5	97.1 ± 11.9	−3.6 ± 8.5	0.007	103.2 ± 21.3	107.5 ± 31.0	4.3 ± 12.5	0.133	−7.90 ± 2.64	0.004
HbA1c (%)	5.8 ± 0.6	5.8 ± 0.5	−0.1 ± 0.2	0.081	5.9 ± 0.8	5.9 ± 0.8	0.0 ± 0.2	0.716	−0.07 ± 0.06	0.192
Haemoglobin (g/dL)	13.7 ± 1.2	13.9 ± 1.3	0.2 ± 0.8	0.148	13.8 ± 1.1	13.8 ± 1.1	−0.0 ± 0.8	0.808	0.21 ± 0.21	0.314
Haematocrit (%)	40.7 ± 3.8	41.5 ± 3.8	0.7 ± 2.5	0.054	41.0 ± 2.8	40.8 ± 3.1	−0.2 ± 2.2	0.688	0.95 ± 0.66	0.153
Serum sodium (mmol/L)	138.3 ± 3.3	138.0 ± 3.0	−0.2 ± 1.7	0.346	138.6 ± 2.1	138.5 ± 1.7	−0.1 ± 1.4	0.754	0.15 ± 0.43	0.729
Serum urea (mg/dL)	40.0 ± 14.4	42.1 ± 13.0	2.1 ± 10.7	0.191	43.8 ± 11.3	46.2 ± 10.8	2.4 ± 8.1	0.182	−0.32 ± 2.62	0.904
Serum creatinine (mg/dL)	1.00 ± 0.22	1.07 ± 0.26	0.07 ± 0.1	0.001	1.05 ± 0.28	1.07 ± 0.29	0.02 ± 0.1	0.215	0.05 ± 0.03	0.076
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75.7 ± 15.5	71.1 ± 15.8	−4.6 ± 8.3	<0.001	74.7 ± 20.3	73.3 ± 20.8	−1.4 ± 3.6	0.091	−3.24 ± 1.46	0.030
24 h urinary volume (mL)	1887 ± 672	2281 ± 717	394 ± 658	<0.001	1976 ± 733	1983 ± 652	7.1 ± 558	0.954	387 ± 166	0.023
24 h urinary sodium (mmol)	165.8 ± 61.1	190.9 ± 80.0	25.1 ± 83.8	0.053	198.6 ± 85.0	193.8 ± 91.4	−4.8 ± 70.6	0.758	29.9 ± 21.2	0.163
24 h UACR (mg/g crea)	287 ± 790	124 ± 314	−163 ± 481	0.229	55.9 ± 50.0	109 ± 123	53.3 ± 91.1	0.142	−216 ± 174	0.228

E, empagliflozin; HbA1c, glycosylated haemoglobin; P, placebo; UACR, urine albumin to creatinine ratio.
Data are mean ± standard deviation.

Table 5 Changes in clinical characteristics after 3 months of treatment with empagliflozin or placebo

Parameters	E, baseline	E, absolute value 3 months	E, change from baseline	P-value E vs. baseline	P, baseline	P, absolute value 3 months	P, change from baseline	P-value P vs. baseline	Between-group difference	P-value E vs. P
Weight (kg)	88.3 ± 13.7	87.5 ± 13.6	−0.8 ± 1.8	0.004	89.1 ± 13.5	89.6 ± 14.1	0.5 ± 2.4	0.354	−1.35 ± 0.54	0.015
BMI (kg/m^2)	28.7 ± 3.9	28.5 ± 4.0	−0.3 ± 0.6	0.005	28.9 ± 3.3	29.1 ± 3.6	0.2 ± 0.8	0.341	−0.42 ± 0.17	0.017
Fasting plasma glucose (mg/dL)	100.7 ± 13.5	94.0 ± 13.3	−6.7 ± 9.3	<0.001	102.8 ± 21.7	103.2 ± 22.4	0.5 ± 8.5	0.815	−7.11 ± 2.4	0.005
HbA1c (%)	5.8 ± 0.6	5.7 ± 0.5	−0.1 ± 0.3	0.044	5.9 ± 0.8	5.9 ± 0.8	0.0 ± 0.3	0.680	−0.11 ± 0.1	0.131
Haemoglobin (g/dL)	13.7 ± 1.2	14.2 ± 1.3	0.5 ± 0.8	<0.001	13.8 ± 1.1	13.9 ± 1.3	0.1 ± 0.7	0.423	0.40 ± 0.22	0.070
Haematocrit (%)	40.7 ± 3.8	42.9 ± 4.0	2.2 ± 2.4	<0.001	41.0 ± 2.8	41.5 ± 3.4	0.4 ± 1.9	0.311	1.74 ± 0.60	0.005
Serum sodium (mmol/L)	138.3 ± 3.3	138.6 ± 3.0	0.3 ± 2.1	0.372	138.6 ± 2.1	138.9 ± 1.8	0.2 ± 1.4	0.448	0.05 ± 0.52	0.922
Serum urea (mg/dL)	40.0 ± 14.4	40.5 ± 13.1	0.4 ± 10.1	0.769	43.8 ± 11.3	44.7 ± 12.1	0.9 ± 8.9	0.648	−0.46 ± 2.57	0.895
Serum creatinine (mg/dL)	1.00 ± 0.22	1.07 ± 0.23	0.1 ± 0.1	0.003	1.05 ± 0.28	1.09 ± 0.32	0.0 ± 0.1	0.162	0.02 ± 0.03	0.521
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75.7 ± 15.5	71.1 ± 15.9	−4.6 ± 10.0	0.003	74.7 ± 20.3	72.6 ± 21.0	−2.1 ± 7.0	0.184	−2.53 ± 2.43	0.301
24 h urinary volume (mL)	1887 ± 672	2116 ± 653	229 ± 653	0.023	1976 ± 733	2002 ± 727	26.2 ± 832.4	0.887	203 ± 189	0.287
24 h urinary sodium (mmol)	165.8 ± 61.1	182.7 ± 82.6	16.9 ± 85.3	0.195	198.6 ± 85.0	183.7 ± 83.6	−14.9 ± 93.3	0.474	31.8 ± 23.3	0.178
24 h UACR (mg/g crea)	360 ± 886	119 ± 266	−241 ± 621	0.226	61.7 ± 50.9	117 ± 109	54.9 ± 73.0	0.094	−296 ± 238	0.232

E, empagliflozin; HbA1c, glycosylated haemoglobin; P, placebo; UACR, urine albumin to creatinine ratio.
Data are mean ± standard deviation.

Figure 1 (Left) Change from baseline after 1 month of treatment with empagliflozin with corresponding *P* values. (Right) Change from baseline after 3 months of treatment with empagliflozin with corresponding *P* values.
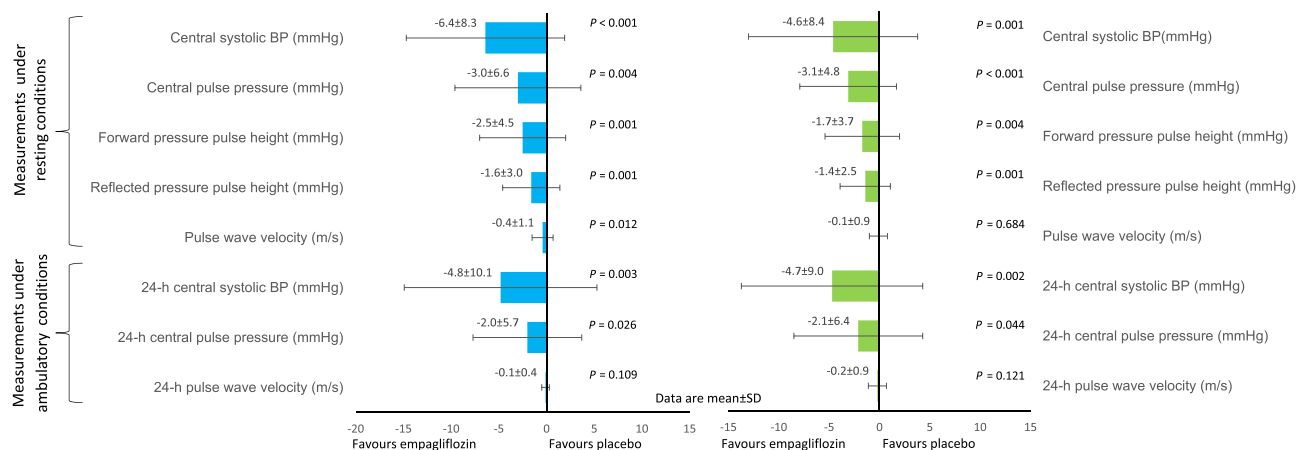
Increased cPP was shown to be linked to cardiovascular morbidity and mortality in several studies in the past, independently of cardiovascular risk factors and co-morbidities.[24] Chilton *et al.* previously analysed *post hoc* the data of five trials conducted in patients with type 2 diabetes and demonstrated not only a reduction in BP but also a significantly reduced cPP under the treatment of empagliflozin compared with placebo.[25] In a previous study of our group, a 6 week empagliflozin treatment in patients with type 2 diabetes led to a significant reduction of −5.14 mmHg in cSBP and −2.77 mmHg in cPP under resting conditions.[26] These findings are in accordance with our current findings of −5.7 mmHg after 1 month and −4.3 mmHg after 3 months for cSBP and of −1.8 mmHg after 1 month and −3.3 mmHg after 3 months for cPP in the empagliflozin group. We also found a significant decrease in cSBP and PWV under 24 h ambulatory daily life conditions, numerically similar to the results of our previous work.[26,27] In another randomized controlled trial analysing the effect of canagliflozin compared with perindopril on vascular function in patients with type 2 diabetes and arterial hypertension, a significant decrease in SBP and DBP under office conditions and 24 h ambulatory conditions as well as in office cSBP was observed, supporting our findings with empagliflozin in patients with stable HF.[28] In a *post hoc* analysis of pooled data from four phase 3 studies, patients with type 2 diabetes showed a reduction of SBP and DBP as well as pulse pressure after 26 weeks treatment with canagliflozin.[29] After 6 months treatment with tofogliflozin, an improved arterial stiffness was observed in patients with type 2 diabetes.[30]

Other research groups analysed changes in BP and arterial stiffness after SGLT2 inhibition mainly in patients with type 2 diabetes and type 1 diabetes. Despite the considerable changes in pathophysiology and the disease course, it is important to mention shortly trials conducted in patients with

type 1 diabetes. In trials with patients with type 1 diabetes, an 8 week treatment with empagliflozin as well as a 12 weeks treatment with empagliflozin on top of metformin significantly reduced office PWV.[31,32] Dapagliflozin led in 26 patients with type 2 diabetes to an acute reduction of PWV (10.1 ± 1.6 to 8.9 ± 1.6 m/s, *P* < 0.05), independent of BP reduction, compared with hydrochlorothiazide after 2 days of treatment.[33]

We observed a significant reduction of 24 h PWV in our cohort of patients with stable HF after 12 weeks treatment with empagliflozin compared with placebo, while there was no significant reduction in PWV under resting conditions. In non-diabetic patients with HFrEF, a 6 month treatment with empagliflozin showed a significant reduction of PWV assessed by cardiac magnetic resonance.[34] This discrepancy to our results may be due to inaccuracy of the measurement of the linear distance from surface points on the body to estimate the arterial path length by the Sphygmocor operator.

In patients with HF, SGLT2 inhibitors improve the loading condition of the left ventricle by two mode of actions. SGLT2 inhibitors block the reabsorption of sodium and glucose in the proximal tubule, thereby causing natriuresis, glucosuria, and osmotic diuresis with the consequence of the reduction of the preload. Indeed, 24 h urine volume excretion increased by approximately 394 mL after 1 month and 229 mL after 3 months, accompanied by increased haematocrit. Besides reduction of the intravascular volume, our data support that by empagliflozin treatment, the afterload is diminished by reducing the stiffness of the arterial system indicated by the decrease in cSBP, cPP, forward pressure pulse height, and reflected pressure pulse height in our patients with HF. In a recently published trial with 70 euvolemic patients with HFrEF, pulmonary capillary wedge pressure was reduced after 12 weeks treatment with empagliflozin compared with placebo.[35] These findings underline the reduction of the

filling pressure of the left ventricle and consequently the unloading of the left ventricle with enhancement of the sub-endocardial blood flow.

Many previous clinical studies analysed the effect of SGLT2 inhibitors in patients with type 1 and 2 diabetes and showed no compensatory increase of the office or 24 h heart rate accompanying the BP reduction, due to the lack of the reflex sympathetic nervous system activation.[31,36,37] We found as well no notable change of heart rate under treatment with empagliflozin, underlying the sympathoinhibitory effect of the SGLT2 inhibition in patients with overactive sympathetic nervous system.

One limitation may be the small sample size and short duration of our study; however, our power calculation indicated that the number of participants is large enough to detect significant differences, in particular in the empagliflozin group, in the face of the 2:1 randomization in favour of empagliflozin. In our group, we focused our analysis on patients with reduced ejection fraction because the first studies showed a significant reduction of hospitalizations rate and overall mortality in this group. We did not address patients with heart failure with preserved ejection fraction, and this would require a separate study. Nevertheless, our data of improved vascular function support the findings of the large clinical trials in patients with HFmrEF and HFrEF.

Conclusions

In conclusion, we demonstrated that the treatment with the SGLT2 inhibitor empagliflozin exerts beneficial effects on vascular function in patients with HF and reduced ejection fraction. This improvement of vascular function by increased arterial and aortic compliance is linked to a reduction of the afterload of the left ventricle. We suggest that the resulting improvement of ventricular-arterial coupling may contribute to the improved prognosis observed in patients with HF under SGLT2 inhibition.

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Conflict of interest

R.E.S. received speaker fees and advisory board fees, and P.B. has received research funding (related and unrelated to the present work) from Boehringer Ingelheim Pharma GmbH & Co. KG during the conduct of the study. All other authors declare that they have no competing interests.

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