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BRIEF REPORT

Effects of empagliflozin on cardiorespiratory fitness and significant interaction of loop diuretics

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The effects of empagliflozin on cardiorespiratory fitness in patients with type 2 diabetes mellitus (T2DM) and heart failure with reduced ejection fraction (HFrEF) are unknown. In this pilot study we determined the effects of empagliflozin 10 mg/d for 4 weeks on peak oxygen consumption (VO_2) in 15 patients with T2DM and HFrEF. As an exploratory analysis, we assessed whether there was an interaction of the effects of empagliflozin on peak VO_2 of loop diuretics. Empagliflozin reduced body weight (−1.7 kg; $P = .031$), but did not change peak VO_2 (from 14.5 mL kg^{-1} min^{-1} [12.6-17.8] to 15.8 [12.5-17.4] mL kg^{-1} min^{-1}; $P = .95$). However, patients using loop diuretics (N = 9) demonstrated an improvement, whereas those without loop diuretics (N = 6) experienced a decrease in peak VO_2 (+0.9 [0.1-1.4] vs −0.9 [−2.1 to −0.3] mL kg^{-1} min^{-1}; $P = .001$), and peak VO_2 changes correlated with the baseline daily dose of diuretics ($R = +0.83$; $P < .001$). Empagliflozin did not improve peak VO_2 in patients with T2DM and HFrEF. However, as a result of exploratory analysis, patients concomitantly treated with loop diuretics experienced a significant improvement in peak VO_2.

KEYWORDS

cardiorespiratory fitness, diuretics, empagliflozin, heart failure, SGLT2 inhibitors

1 | INTRODUCTION

Sodium glucose co-transporter (SGLT)-2 inhibitors such as empagliflozin and canagliflozin reduced the incidence of heart failure (HF) and HF hospitalizations in clinical trials including patients with type 2 diabetes mellitus (T2DM).[1,2] HF, like T2DM, is a chronic debilitating condition, and is associated with impaired functional capacity and reduced quality of life. The effects of SGLT-2 inhibitors on cardiorespiratory fitness (CRF) in patients with HF with reduced ejection fraction (HFrEF) are unknown.[3]

In this pilot study (ClinicalTrials.gov Identifier: NCT02862067), we hypothesized that empagliflozin would improve CRF, measured as changes in peak oxygen consumption (VO_2) at maximal cardiopulmonary exercise test (CPX) in patients with HFrEF and T2DM. Patients with T2DM and HFrEF share an exaggerated neurohormonal system activation, in particular, of the renin-angiotensin-aldosterone system (RAAS), which is a major driver of CRF and clinical outcomes in HFrEF, independent of the blood pressure-lowering effects.[4] By reducing glucose reabsorption in the proximal renal tubules and increasing the concentration of sodium at macula densa level, SGLT-2 inhibitors may

prevent renin secretion and overall RAAS activation in response to reduced sodium tubular levels. We therefore hypothesized that, despite increased diuresis and natriuresis, empagliflozin would not further activate the renin-angiotensin-aldosterone system (RAAS), known to be involved in the pathophysiology of HFrEF.

Finally, as an exploratory analysis, we planned to determine whether the effects of empagliflozin were influenced by concomitant treatment with loop diuretics, agents also known to promote natriuresis and commonly used in HFrEF to manage symptoms.

2 | METHODS

2.1 | Cardiorespiratory fitness and physical activity assessments

In this open-label single-arm prospective study, we assessed the effects of empagliflozin on peak VO_2 with CPX in 15 patients with stable symptomatic HFrEF (New York Heart Association [NYHA] class II-III, left ventricular EF [LVEF] < 50%) and T2DM (glycosylated haemoglobin [HbA1c] 6.5%-10.0%) using a metabolic cart interfaced with a treadmill and a conservative ramping protocol before and after treatment with empagliflozin 10 mg daily for 4 weeks, in which speed and grade were increased by approximately 0.6 estimated metabolic equivalents (MET) every 60 seconds.[5,6] Ventilatory gas analysis was performed using a VMax Encore metabolic cart (Carefusion, Yorba Linda, California) with a standard mouthpiece and nose clip setup. Calibration of the metabolic cart for volume and gas concentration was obtained before every test. Ventilatory gas analysis measurements were obtained for at least 3 minutes in the seated position before beginning exercise, continuously throughout exercise, and 2 minutes into the recovery period. Blood pressure (BP) was monitored with a Tango exercise BP system (Suntech Medical, Morrisville, North Carolina). BP measurements were monitored at rest, during exercise, and during the recovery period. Resting BP was measured according to clinical recommendations and using standardized methods. In brief, patients rested in a seated position for at least 10 minutes; an appropriately sized brachial artery pressure cuff was used, and pressure was measured with an automated device (Tango system, Suntech Medical, Morrisville, North Carolina).

Peak VO_2 is a strong independent predictor of events and is sensitive for detecting the efficacy of therapeutic interventions in HF patients.[5] Importantly, peak VO_2, measured by ventilatory expired gas analysis, is not biased by overexertion, and is insensitive to the placebo effect.[5,7]

Physical activity was assessed using the International Physical Activity Questionnaire-short version (IPAQ). The IPAQ-short is a 7-question questionnaire that estimates physical activity by assessing responses to questions concerning duration and intensity of daily physical activity.

2.2 | Cardiac function assessment

We assessed cardiac function using transthoracic Doppler echocardiography to measure LV end-diastolic and end-systolic volume, LVEF, early transmitral velocities (E) at pulsed wave Doppler spectra, early mitral annulus velocities by tissue Doppler averaged between lateral and septal (e′), and we calculated the E/e′ ratio.[8,9]

2.3 | Diuresis, natriuresis and RAAS activation assessments

We assessed the effects of empagliflozin on 24-hour diuresis, urinary sodium concentration (Na^+UR) and RAAS activation, measured as plasma renin activity (PRA), aldosterone plasma levels (ALD) and ALD/PRA ratio, following overnight fasting and after suspension of angiotensin II antagonists (ATII-A) and mineralocorticoid-receptor antagonists (MRA) for 24 hours. Chemical laboratory analyses were performed using clinical standard assays (LabCorp, Burlington, North Carolina).

2.4 | Dietary sodium, body weight and waist circumference assessments

Dietary sodium intake can affect fluid status and RAAS activation; therefore, we estimated sodium intake using a standardized 5-pass interview 24-hour dietary recall, as previously described.[10] Body weight and waist circumference were measured on the day of RAAS activation assessment. Waist circumference was measured according to the World Health Organization recommendations.[11]

2.5 | Statistical analysis

We used SPSS 24.0 (IBM Corp) for statistical analysis. Data are reported as median and interquartile range for potential deviation from the Gaussian distribution. Discrete variables are reported as a number and percentage. Interval changes between baseline and 4 weeks in peak VO_2 were analysed using the Wilcoxon test. Analysis of interaction was assessed with a general linear model for repeated measures for discrete variables or the Spearman correlation rank test for continuous variables. Multivariate analysis using a linear regression model was performed, using a stepwise approach including those variables associated with $P < .05$ at univariate analysis.

The Virginia Commonwealth University Institutional Review Board approved the study, and all patients provided written informed consent.

3 | RESULTS

3.1 | Baseline characteristics

Among the patients, 8 (53%) were women, 9 (60%) were White and 6 (40%) were Black Americans, median age was 60 (56-62) years, and body mass index (BMI) was 34 (31-37) kg/m^2. All patients were using ATII-A; 7 patients (47%) were using MRA and 9 (60%) patients were using loop diuretics. Median HbA1c was 7.8% (7.2-8.6), NTproBNP was 229 pg/mL (47-657), creatinine was 1.1 mg/dL (0.9-1.2), estimated glomerular filtration rate was 63 mL/min/1.73 m^2 (63-88), PRA was 5.4 ng/mL/h (2.5-20.0) and ALD was 9.3 ng/dL (6.8-13.7).

Median peak VO_2 was 14.5 mL kg^{-1} min^{-1} (12.6-17.8) or 57% (48-60) of predicted normative values.[5] Median LVEF was 41% (33-43), E/e′ was 10.9 (10.6-19.5) and e′ was 6.5 cm/s (5.5-7.4). Median 24-hour urinary volume excretion was 1725 mL (1307-2354) and median Na^+UR was 72.5 mmol/L (64.9-110.8). Median dietary sodium intake was 2869 mg (1701-3846).

3.2 | Body weight, fasting glycaemia, blood pressure and cardiorespiratory fitness

In the overall cohort, treatment with empagliflozin for 4 weeks increased 24-hour urine output (+43%; P = .007), reduced body weight (−1.7 kg, P = .031), reduced resting diastolic blood pressure (−8 mm Hg; P = .04) and led to a small, although statistically significant, reduction in E/e' ratio (from 10.9 [10.6-19.5] to 9.8 [8.3-16.9]; P = .035).

Empagliflozin did not, however, change peak VO_2 relative to body weight (from 14.5 [12.6-17.8] to 15.8 [12.5-17.4] mL kg^{-1} min^{-1}; P = .95) or when expressed in absolute values (from 1426 [1037-1672] to 1517 [1104-1726] mL min^{-1}; P = .95) in the overall cohort, nor did it change IPAQ-estimated physical activity (P = .59). We found a large variability in changes in peak VO_2, ranging from −2.9 to +2.5 mL kg^{-1} min^{-1}. None of the clinical variables, echocardiographic LV parameters or changes in IPAQ-estimated physical activity correlated with changes in peak VO_2 with empagliflozin (all P > .05). Moreover, neither the doses of ATII-A or MRA, nor the use of MRA, influenced the changes in peak VO_2 with empagliflozin. Importantly, dietary sodium intake did not change during the overall duration of the study (from 2869 [1701-3846] to 2571 [2098-3378] mg; P = .39). Treatment with empagliflozin for 4 weeks did not affect fasting glycaemia (from 140 [129-220] to 144 [107-166] mg/dL; P = .16).

3.3 | Loop diuretic use and effects on peak VO_2

A statistically significant interaction between loop diuretic use (9 [60%]) and effects on peak VO_2 was found, for both peak VO_2 relative to body weight (Figure 1A) (P = .001) and absolute peak VO_2 (P = .001), showing a dose-dependent relationship between diuretic dose and peak VO_2 changes (R = +0.83; P < .001) (Figure 1B), without differences in physical activity and blood pressure changes between the 2 groups (P = .28 and P = .77, respectively). The change in Na^+UR (Figure 1C) and in the ALD/PRA ratio also correlated positively with changes in peak VO_2 (R = +0.622; P = .023 and R = +0.52; P = 0.057, respectively). Neither ATII-A nor MRA doses correlated with changes in Na^+UR, PRA or ALD/PRA (all P > .05).

When investigating potential contributors to peak VO_2 changes in the overall cohort, the statistically significant predictors at univariate analysis were BMI, waist circumference, HbA1c and loop diuretic dose, but diuretic dose remained the only significant predictor for peak VO_2 changes at multivariate analysis (β coefficient = .623; P = .013).

A significant interaction between diuretic use and the effects of empagliflozin on Na^+UR was also found, showing a reduction in Na^+UR, a surrogate for renin activation[12] in patients treated with empagliflozin without loop diuretics, but not in those treated with loop diuretics (−32% vs 0%, respectively; P = .031). We found a non-

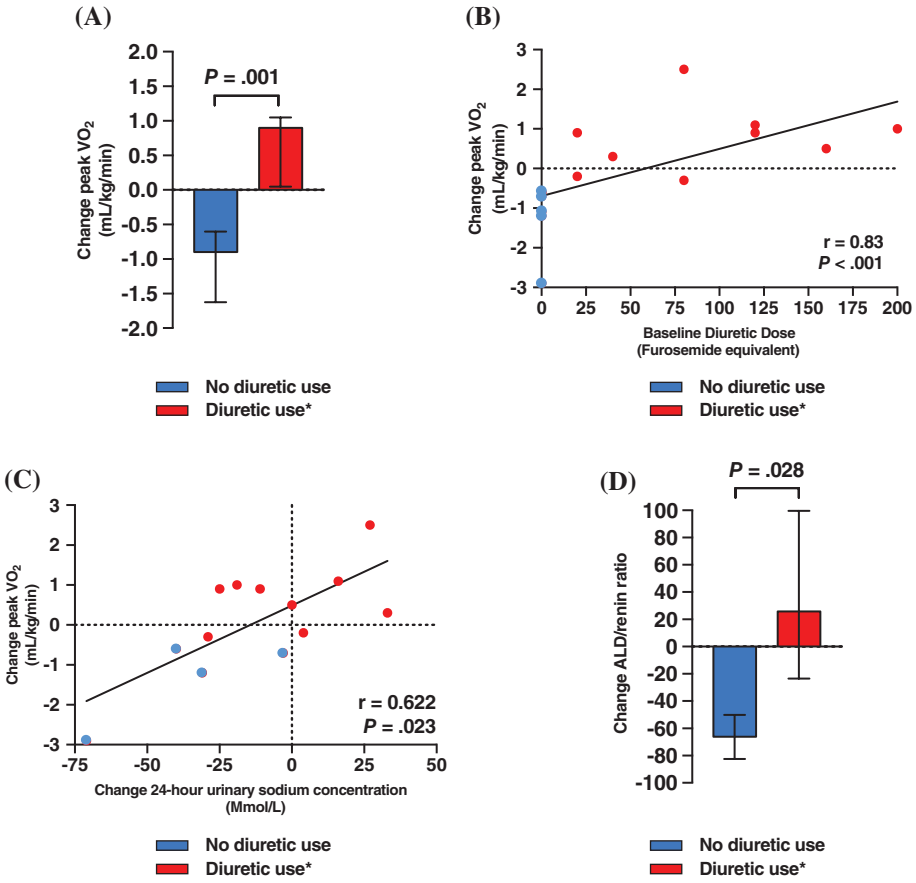

FIGURE 1 Greater peak oxygen consumption (VO_2) changes in patients with heart failure and reduced ejection fraction (HFrEF) receiving loop diuretics (A). Baseline diuretic dose (B) and changes in urinary sodium concentration (Na^+UR) (C) correlate with change in peak VO_2. Increased aldosterone (ALD)/renin ratio in patients receiving loop diuretics (D). Panel C excludes 2 patients not treated with diuretic because of laboratory internal issues for 24-hour urinary sodium concentration measurement, possibly the result of damaged samples. *diuretic use limited to loop diuretic use and expressed as furosemide-equivalent dose (mg/d)

significant trend for PRA changes without and with diuretics (+50% vs −22%, respectively; P = .21) and a significant interaction between use of diuretics and the ALD/PRA ratio, a more accurate marker for renin activation (decrease in ratio) vs aldosterone hypersecretion (increase) (−66% vs +26%, respectively; P = .028) (Figure 1D). Finally, we found a significant association between changes in resting diastolic BP and aldosterone plasma level changes (R = −0.55; P = .03). However, neither systolic nor diastolic resting BP were associated with changes in CRF (both P > .30).

4 | DISCUSSION

The data presented herein show, for the first time, that SGLT-2 inhibition with empagliflozin was associated with a highly heterogeneous response in terms of peak VO_2, Na^+UR, PRA and ALD/PRA that depended on the presence or absence of concomitant loop diuretic use. Although resulting from an exploratory analysis requiring confirmation in larger clinical trials, the combination of empagliflozin and loop diuretics appears to have synergistic effects on diuresis, without inducing RAAS activation, and resulting in an increase in Na^+UR concentration, and in a significant increase in peak VO_2. On the other hand, the use of empagliflozin without loop diuretics induced a paradoxical reduction in Na^+UR, resulting in more diluted urine, possibly as the result of RAAS activation, and in a lack of any improvement, or even a reduction, in peak VO_2. It is therefore possible that empagliflozin improves CRF in patients concomitantly treated with loop diuretics by reducing RAAS activation, which is well-known to be detrimental in HFrEF, but also in T2DM. Inhibition of RAAS activation reduces systemic vascular resistance, resulting in vasodilation, improved cardiac output, improved ventilatory efficiency, increased natriuresis/diuresis and improved CRF.[4,13]

Our study is however, limited by the small sample size and by the absence of assessment of O_2 delivery and/or utilization, which could have also affected the overall results, including the absence of significant improvements in fasting glycaemia. Specifically, that may be the result of our study being underpowered to detect changes in fasting glycaemia. However, we cannot exclude the possibility that the effects of empagliflozin in patients with established HFrEF are less pronounced than in non-HFrEF patients, or that it requires more time to achieve a similar effect, clearly requiring further and larger studies, specifically in the HFrEF population.[14] Moreover, changes in CRF did not simply reflect interval changes in physical activity which, however, was estimated using a subjective questionnaire that may not be as sensitive as other means such as accelerometers.

SGLT-2 inhibitors reduced HF-related events in randomized clinical trials[1,2] and in real-world data[15]; however, the effects of this class in well-characterized patients with established HFrEF, and more specifically, the effects on peak VO_2, remain unknown.

Here we report an interaction between empagliflozin and use of loop diuretics in patients with HFrEF, an interaction that was interestingly posited in a recent clinical trial.[2,16] The implications would be that the use of empagliflozin in HFrEF patients not treated with loop diuretics may be less beneficial. If confirmed in larger studies evaluating the role of SGLT-2 inhibitors, specifically in patients with HFrEF, this could greatly influence the clinical applications of these agents.

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Conflict of interest

A. A. has received research grants from and has served on an advisory board for Janssen. The other authors have nothing to disclose.

Author contributions

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