Early View

Research letter

**Dapagliflozin initiation in chronic heart failure patients improves central sleep apnoea**

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Title:
Dapagliflozin initiation in chronic heart failure patients improves central sleep apnoea.

Running title:
Dapagliflozin initiation favourably impacts central sleep apnoea.

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Take home message:

Dapagliflozin decreases central sleep apnoea in central sleep apnoea patients, thereby sparing the initiation of ventilatory therapy.
To the Editor:

Optimizing medical cardiac treatment for central sleep apnoea (CSA) in patients with chronic heart failure (CHF) remains under debate with an expert-grade C recommendation [1, 2]. Investigating the impact of established and emerging heart failure therapy on CSA is considered as a research priority [3].

Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that modulates sodium-glucose transport proteins in the renal tubules. SGLT2 inhibitors were originally developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus but were also identified as potential CHF therapy. SGLT2 inhibitors have a diuretic action but can exert antihypertrophic, antifibrotic, and antiremodeling properties [4]. Thus, SGLT2 inhibitors are an emerging CHF therapy recommended by the 2021 European Society of Cardiology guidelines for patients with reduced left ventricular ejection fraction to reduce the risk of HF-related hospitalisation and death (Grade A) [5]. In 2022, a randomised controlled trial concluded that dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with CHF and a mildly reduced or preserved ejection fraction [6]. Whether dapagliflozin impacts CSA in CHF-patients is unknown.

Methods

We present here data from a monocentric, open-label, real-life study conducted from September 22, 2020, to October 18, 2021. The study design was similar to the previously one investigating the impact of sacubitril/valsartan (SV) treatment on sleep apnoea [7], except for the investigated drug (a 10 mg dose of dapagliflozin was administered once daily instead of SV).

Briefly, consecutive patients eligible for dapagliflozin (i.e., CHF-patients who remain symptomatic (NYHA classes II–IV) despite optimal treatment including SV when appropriate) were screened for sleep apnoea (SA) including nocturnal ventilatory polygraphy. For patients
receiving dapagliflozin after the initial ventilatory polygraphy, with an initially central Apnoea Hypopnoea Index (cAHI) ≥5/h and/or an obstructive Apnoea Hypopnoea Index (oAHI) ≥ 15/h, a polygraphy control was performed 3 months later. Based on the initial ventilatory polygraphy results, two groups were drawn; group G1: cAHI ≥ 5/h and oAHI < 15/h; group G2: oAHI ≥ 15/h regardless of the cAHI. The study complied with the Declaration of Helsinki and was reviewed and approved by the Montpellier University Hospital Institutional Review Board (agreement number: 202100950 and 202201048). Statistics presented here were similarly performed to the ENTRESTO-SAS study [7].

Results

A total of 43 consecutive patients were screened (see Figure 1, panel a), 18 patients analysed (G1=12 patients, G2=6 patients), 94.4% male with a median (IQ25; 75) age of 57 (48.3; 65.5) years, ischemic CHF for 44.4%, atrial fibrillation for 27.8%. Nine patients had CHF with a reduced left ventricular ejection fraction, 7 patients had CHF with mildly reduced ejection fraction and 2 patients had CHF with preserved ejection fraction. One patient presented a stroke, one patient presented a non-severe chronic kidney disease, no patient was treated with baclofen, ticagrelor or opioids.

Patients were initially treated with angiotensin-converting-enzyme inhibitor or angiotensin-receptor-blocker for 5.6%, beta-blockers for 88.9%, spironolactone for 66.7%, loop diuretics for 72.2%, SV for 94.4%, cardiac defibrillator for 73.3%, cardiac resynchronization for 26.7%. At 3 months, there was no significant change in these treatments except for the dapagliflozin introduced after the initial polygraphy. No patient presented a cardiac event between the two ventilatory polygraphy (excepted the excluded patient, see Figure 1, panel a). No patient was treated with Continuous Positive Airway Pressure (CPAP).
At 3 months in G1 + G2 patients, the AHI primary outcome decreased statistically significantly by a median -7.2/h (-10.7; -4.3), p<0.001, see Figure 1 panel b). The cAHI decreased statistically significantly by a median -4.5 (-9.9; -1.4), p=0.012; the oAHI did not decrease statistically significantly by a median -1.1 (-3.0; 1.9), p=0.360. In G1 patients, the cAHI decreased statistically significantly by a median – 8.2 (-11.2; -4.3), p=0.006. In G2 patients, the oAHI did not decrease statistically significantly by a median -3.5 (-10.0; -1.7), p=0.094. For 3/11 G1 patients with an initial AHI ≥ 15/h, the final AHI was <15/h with dapagliflozin initiation avoiding a CPAP trial proposed by the current guidelines in symptomatic patients [2]. In G1+G2 patients, cycle length of Cheyne-Stokes respiration (CSR) showed a trend to decrease (from a median of 47.95 (40.25; 50.65) seconds to 35.75 (0.0; 45.45), p=0.06), time spent with CSR decreased statistically significantly (from a median of 47.99 (6.72; 131.25) minutes to 5.90 (0.0; 21.84), p=0.001), percentage of CSR decreased statistically significantly (from a median of 9.17% (1.54; 26.79) to 1.26% (0.0; 5.12), p=0.010).

In G1+G2 patients, median NT-proBNP level did not decrease statistically significantly (from 1529 (476; 2673) ng/L to 842.5 (308; 1533), p=0.102), the degree of dyspnoea showed a trend to decrease (New York Heart Association functional class I/II/II respectively 27.8%/55.6%/16.7% to 61.1%/33.3%/5.6%, p=0.072), LVEF did not increase statistically significantly (from 31.5 (27.2; 40.7) % to 35.5 (30.5; 41.5), p=0.132). The Spearman coefficient \( r \) was -0.64 for the relative AHI difference and relative LVEF difference (p=0.004); 0.52 for the relative AHI difference and relative NT-proBNP difference (p=0.027) (relative variable difference defined as (initial variable minus final variable)/initial variable). The Spearman coefficient \( r \) was -0.52 for the relative AHI central difference and relative LVEF difference (p=0.028).

After 3 months, Epworth Sleepiness Scale did not decrease statistically significantly (from 10.5 (6.75; 12.25) to 6.5 (3.5; 8.25), p=0.140), Pichot Fatigue Questionnaire did not decrease
statistically significantly (from 10.5 (4.50; 17.25) to 8.5 (5.5; 11.75), p=0.527). Body mass index (BMI) did not decrease statistically significantly from a median of 26.19 (25.11; 28.69) kg/m² to 26.18 (24.55; 28.94) kg/m², p=0.938.

**DISCUSSION**
To the best of our knowledge, we report here the first study investigating the impact of dapagliflozin on sleep apnoea in CHF patients. Interestingly, we observed a significant favourable effect of dapagliflozin on CSA, and this effect was observed in a cohort of patients treated with the 2021 recommended treatment [1].

We have recently reported that SV initiation [7] to be a candidate for CSA treatment in CHF patients avoiding for 10/29 patients a CPAP trial proposed by the current guidelines in symptomatic patients [2]. In this new cohort of SV-treated CSA patients, initiation of dapagliflozin avoids a CPAP trial for 3/11 patients, additional 3/11 patients having a final AHI between 15 and 16/h.

In contrast to Tang et al. [8] (excluding CHF-patients), we observed a non-significant effect on oAHI. We cannot rule out the possibility of a type II error in our study because of a smaller number of patients (only 6 patients with obstructive sleep apnoea versus 18 patients in Tang et al. [8]). In addition, Tang et al. [8] reported a significant difference for BMI (28.17± 1.21 kg/m² initially versus 25.92 ± 0.92 kg/m² after 24 weeks of treatment) whereas we report no significant difference.

To explain dapagliflozin impact on CSA, we hypothesized that the drug improving cardiac function, it might decrease central events classically considered related to the HF severity. In this regard, it is important to consider the significant correlation for the relative AHI central difference and relative LVEF difference. Studies are needed to test the hypothesis that the beneficial effect of dapagliflozin on AHI is related to biomarkers such as LVEF and/or NT-ProBNP.
In conclusion, given these results and as previously published [7], we believe that an optimal medical treatment of CSA CHF-patients (i.e., including SV and dapagliflozin treatment) is a prerequisite before considering a recommended CPAP trial in symptomatic patients [2].
REFERENCES


FIGURE LEGENDS

Figure 1. Panel a): Study flow chart. Panel b): Apnoea hypopnoea index before versus after 3 months of Dapagliflozin. AHI: Apnoea Hypopnoea Index.
a) Screened patients, n=43

- Not included patients (n=7)
  - Refused to participate (n=2), logistical issues (n=3)

Included patients, n=36

- Excluded patients (n=8)
  - No sleep apnoea (n=5), discontaining treatment (n=2), lost to follow-up (n=1), no ventilatory polygraphy at 3 months (n=1), cardiac resynchronization defibrillator therapy after initial ventilatory polygraphy (n=2)

Analysed patients, n=28

5 months assessment, n=28

Group 1, n=12
Patients with AHICentral ≥ 5 / h and AHIApotitive < 15 / h

Group 2, n=6
Patients with AHIApotitive ≥ 15 / h

b) Graph showing change in Apnoea Hypopnoea Index (event/hour) over time with baseline and final data points.