Systemic inflammation predicts diastolic dysfunction in patients with sleep disordered breathing

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To the Editor:

Heart failure with preserved ejection fraction (HFpEF) constitutes approximately half of all patients with heart failure and causes mortality similar to heart failure with reduced ejection fraction [1]. HFpEF is highly relevant as novel evidence-based therapies emerge but treatment options remain limited [1]. Diastolic dysfunction is a hallmark of HFpEF and is also very common in up to 80% of high-risk cardiovascular patients undergoing cardiac surgery [2]. Even without overt HFpEF, echocardiographic diastolic dysfunction is independently associated with increased mortality [3]. Another important characteristic of HFpEF is the frequent presence of comorbidities, with one of the most important being sleep disordered breathing (SDB). SDB affects over one billion patients in the general population and is highly prevalent in cardiovascular high-risk patients, which underscores its high socioeconomic relevance [4]. Interestingly, SDB patients frequently exhibit diastolic dysfunction [5]; however, the underlying mechanisms remain elusive thus far [6]. In this cross-sectional experimental study, we analysed the role of inflammation and fibrosis for diastolic dysfunction in cardiovascular high-risk patients stratified by the prevalence of SDB, which may provide a groundwork for future therapeutic strategies.

This study is part of the prospective observational CONSIDER-AF study (NCT02877745) that analyses patients undergoing elective coronary artery bypass grafting (CABG). Inclusion criteria were written informed consent, age between 18–85 years, an ejection fraction >45%, and the availability of preoperative blood probes. Exclusion criteria were mechanical ventilation, positive airway pressure support therapy, home oxygen therapy, preoperative use of inotropes or mechanical circulation support, severe obstructive pulmonary disease, and pre-existing treated SDB.

Before CABG surgery, all patients were tested for SDB by standard polygraphy (level 3 sleep study). A ⩾90% decrease in airflow for ⩾10 s defined apnoeas, ⩾30–90% for ⩾10 s plus ⩾4% desaturation hypopnoeas. An apnoea–hypopnoea index (AHI) ⩾15 events·h^{-1} defined SDB. Standard echocardiography was performed by experienced physicians, with additional assessment and grading (grades I, II and III) of diastolic dysfunction according to current guidelines [1]. For some patients, peripheral blood mononuclear cells (PBMCs) were isolated using the Leucosep kit (Greiner Bio-One International). Human myocardium was acquired from right-atrial appendage biopsies intraoperatively. Interleukin (IL)-1β mRNA and protein expression were quantified using TaqMan Gene Expression Assays (qPCR) and Western blot analysis, respectively, and normalised to β-actin expression. Plasma levels of pro-collagen III C-terminal pro-peptide (PIIICP) were measured by ELISA (Cloud-Clone Corp.).

Clinical and experimental data are presented as mean or relative frequency and mean±SEM, respectively. Comparisons are based on two-way ANOVA with Holm–Sidak's *post hoc* test and linear regression analysis. Comparisons for baseline characteristics were conducted by t-test, Mann–Whitney, Chi-squared or Fisher exact test, as appropriate. Multivariate linear regression analysis was conducted incorporating covariates that were different between patients without and with SDB (age, body mass index, heart failure, history of stroke and glomerular filtration rate). Two-sided p-values <0.05 were considered statistically significant.

SDB was detected in 124 out of 298 patients (41.6%). On average, patients were 67.2 years old, 82.9% were male, and presented with a variety of cardiovascular risk factors (*i.e.* hypertension,

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Systemic and myocardial inflammation are associated with diastolic cardiac dysfunction in patients with sleep disordered breathing, which may have therapeutic implications https://bit.ly/3vxAECC

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hypercholesterolaemia, current/previous smokers). While diastolic dysfunction was more severe in patients with SDB (grade III: 2.9% *versus* 13.0% in patients with SDB; p=0.017), its absolute prevalence was similar in both cohorts with 73.6% and 79.4% in patients without and with SDB, respectively. Atrial fibrillation was present in 12.6%, and heart failure in 12.8% of patients. Patients with SDB were older (65.9 *versus* 69.0 years; p<0.001), had a higher body mass index (28.1 *versus* 29.6 $kg \cdot m^{-2}$; p=0.003), more frequent heart failure (7.5% *versus* 20.2%; p=0.001) or history of stroke (6.3% *versus* 14.5%; p=0.019), and a lower renal function (glomerular filtration rate: 77.4 *versus* 70.2 $mL \cdot min^{-1}$; p=0.004).

Plasma C-reactive protein (CRP) values were positively correlated with the severity of SDB (AHI; p=0.011, r^2=0.022). Moreover, the average peripheral oxygen saturation acquired during polygraphy was negatively correlated with CRP values (figure 1a), which was independent of all tested potential clinical confounders (p=0.005, r^2=0.069). In patients with diastolic dysfunction, IL-1β mRNA levels in PBMCs were higher when SDB was diagnosed (figure 1b). Also, IL-1β mRNA values in SDB patients were ~5-fold higher when diastolic dysfunction was present (figure 1b). 27 PBMC patients' samples were large enough to measure both IL-1β mRNA and protein expression levels which were significantly correlated (p=0.018, r^2=0.203), further validating our findings. Similar to PBMCs, IL-1β mRNA expression in

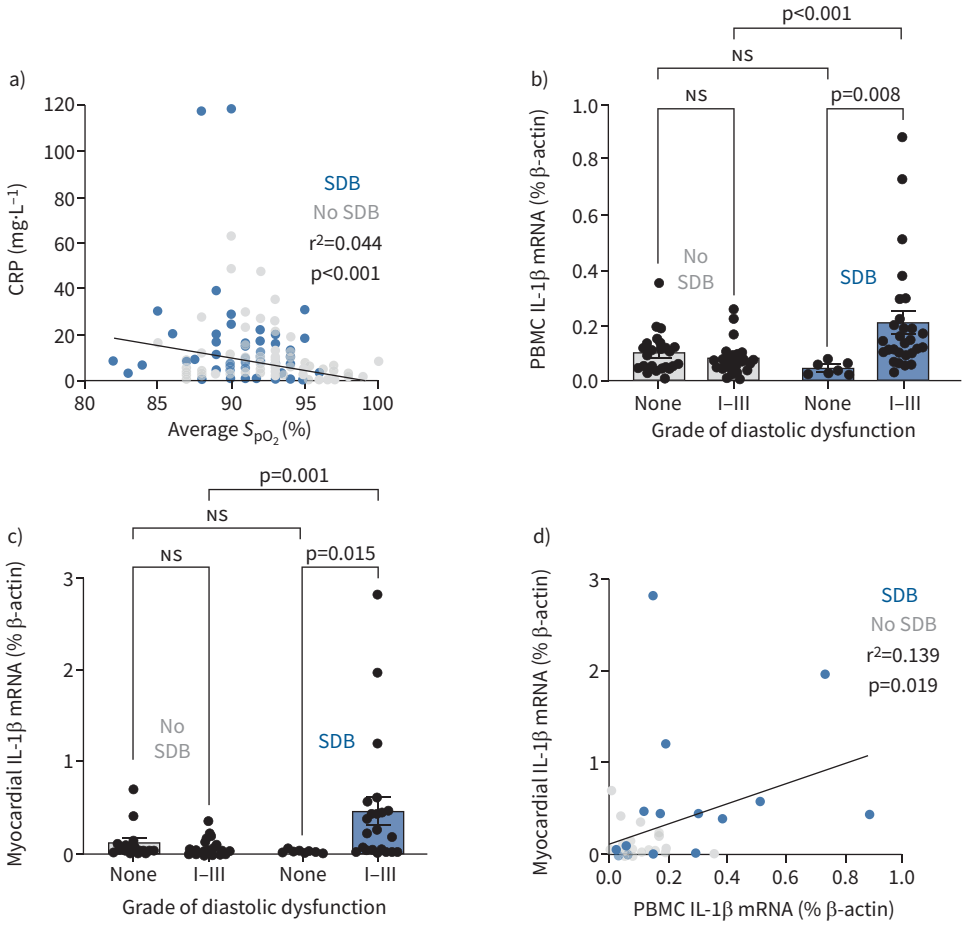

FIGURE 1 Inflammation predicts diastolic dysfunction in sleep disordered breathing (SDB). a) Linear regression analysis of average peripheral oxygen saturation (S_{pO_2}) during polygraphy and plasma C-reactive protein (CRP) values (n=298). b) Interleukin (IL)-1β mRNA levels (normalised to β-actin) in human peripheral blood mononuclear cells (PBMCs) of non-SDB patients without diastolic dysfunction (n=23), non-SDB patients with diastolic dysfunction (n=30), SDB patients without diastolic dysfunction (n=7), and SDB patients with diastolic dysfunction (n=28). c) IL-1β mRNA levels (normalised to β-actin) in human myocardium of non-SDB patients without diastolic dysfunction (n=14), non-SDB patients with diastolic dysfunction (n=31), SDB patients without diastolic dysfunction (n=9), and SDB patients with diastolic dysfunction (n=22). d) Linear regression analysis of IL-1β mRNA levels in human PBMCs and the corresponding myocardial levels (n=39). Statistical comparisons are based on linear regression analysis (a and d) or two-way ANOVA *post hoc* corrected by Holm–Sidak (b and c).

myocardium of patients with diastolic dysfunction was elevated when SDB was diagnosed (figure 1c). Mean values in the subgroup of SDB patients were ~20-fold higher when diastolic dysfunction was present. Importantly, myocardial and PBMC IL-1β mRNA expression were positively correlated (figure 1d).

PBMC IL-1β mRNA levels were positively correlated with ascending severity grade of diastolic dysfunction in SDB patients ($p=0.006$, $r^2=0.207$), which was also independent of potential confounders ($p=0.015$, $r^2=0.325$). However, this effect was absent in patients without SDB, where, in contrast, the pro-fibrotic blood marker PIIICP was positively correlated with the severity of diastolic dysfunction ($p<0.001$, $r^2=0.279$), independent of potential confounders ($p=0.003$, $r^2=0.303$).

Patients with diastolic dysfunction and HFpEF may present with a variety of symptoms, and current treatment options are limited [1]. This circumstance is likely due to several different pathomechanisms that can independently promote diastolic dysfunction, which explains the necessity of an individualised approach with respect to patient comorbidities [7, 8]. Frequently proposed mechanisms leading to diastolic dysfunction are atrial and ventricular structural and functional remodelling, atrial arrhythmias, hypertension, fibrosis and inflammatory processes [7]. Many of these risk factors are also associated comorbidities and/or consequences of SDB [9]. In the present study, we found systemic and myocardial inflammation to be increased in patients with diastolic dysfunction, but only when SDB was diagnosed. Previously, treatment with the IL-1-antagonist anakinra reduced N-terminal prohormone of brain natriuretic peptide and CRP levels in patients with impaired diastolic function [10]. However, a sustained improvement of clinical endpoints, including peak oxygen consumption, could not be reached, which the authors attributed to possible confounding comorbidities [10]. Therefore, it seems increasingly important to select the right patients who may benefit from anti-inflammatory therapy.

Continuous positive airway pressure (CPAP) therapy is currently the primary treatment option for SDB. However, CPAP therapy was not effective in reducing the long-term occurrence of adverse cardiovascular events [11]. In addition, even though cytokines have been shown to be increased in SDB [12], they could not be normalised by CPAP therapy [13]. It has further been evidenced that various comorbidities influence cytokine levels [14]. Therefore, we performed multivariate regression analyses, proving that our main findings were independent of potential clinical confounders.

In contrast to patients with SDB, PIIICP was more relevant in patients without SDB for predicting the severity of diastolic dysfunction. This indicates different mechanisms to be at play, as PIIICP can predict electric remodelling and fibrosis in human atria [15].

Due to the limited availability of human biomaterial, it was not possible to perform all experiments in all patients, which is a potential limitation of our study.

In conclusion, our study confirms the relationship between SDB, hypoxia and inflammation in high-risk patients undergoing cardiac surgery. We further found that inflammation might be an important mechanism promoting diastolic dysfunction in patients with SDB. Thus, patient-individualised anti-inflammatory strategies may be a promising therapeutic approach for patients with diastolic dysfunction and SDB, which will be tested in future experimental studies.

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