Impact of hyperventilation and apnea on myocardial oxygenation in patients with obstructive sleep apnea – An oxygenation-sensitive CMR study

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Impact of hyperventilation and apnea on myocardial oxygenation in patients with obstructive sleep apnea – An oxygenation-sensitive CMR study☆

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A B S T R A C T

Background: Oxygenation-sensitive cardiovascular magnetic resonance imaging (OS-CMR) is an emerging technique that can monitor changes in myocardial oxygenation in vivo. Obstructive sleep apnea syndrome (OSAS) is associated with endothelial and microcirculatory dysfunction and increased cardiovascular morbidity and mortality. Little is known about myocardial responses to apnea in patients with OSAS.

We hypothesized that the coronary vascular response to hyperventilation and long breath-hold is diminished in patients with OSAS when compared to healthy volunteers.

Methods: Twenty-nine OSAS patients and 36 healthy volunteers were prospectively enrolled. All CMR scans were performed on a clinical 3T system. Participants performed a breathing maneuver with 60 s of hyperventilation followed by a maximal breath-hold. During the breath-hold, OS-CMR images were continuously acquired and signal intensity changes were measured by a blinded reader.

Results: Patients with OSAS were older than healthy volunteers ($p < 0.01$) and presented more co-morbidities; 66% were currently treated with nocturnal positive airway pressure. Compared to healthy participants, the expected increase of myocardial oxygenation during the first 15 s of the breath-hold was significantly lower in patients with OSAS ($2.6 \pm 8.3\%$ vs. $6.7 \pm 5.6\%$; $p < 0.05$), and remained reduced at all time points during the breath-hold. Importantly this result was mainly driven by patients under continuous positive airway pressure (CPAP), suggesting that CPAP might have a greater impact on increase of myocardial oxygenation rather than OSAS itself.

Conclusions: The myocardial vascular response to combined breathing maneuvers of hyperventilation followed by voluntary apnea is blunted in patients with obstructive sleep apnea. Clinical studies should now further define the clinical role of oxygenation-sensitive CMR in patients with respiratory disorders.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common condition affecting at least 10% of the general population [1]. OSAS, characterized by recurrent upper airway collapse during sleep with subsequent functional apnea, is associated with significant morbidity [2], especially cardiovascular disease and mortality [3]. However, little is known in regard to the impact of apnea on coronary vascular function in these patients. On one hand, various

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physiological pathways including endothelial function are impaired in patients with OSAS [4], which could worsen microvascular function and lead to tissue injury. On the other hand, the frequent exposure to transient hypoxia may lead to ischemic preconditioning, an effective mechanism of cardioprotection during ischemia [5]. These pathophysiological considerations are of crucial importance when considering the recent warnings as regards the SERVE-HF study (NCT00733343) [6]. In this clinical trial, patients with both stable heart failure (HF) with reduced left ventricular ejection fraction (LVEF) and predominantly central apnea were treated by adaptive servo-ventilation. Surprisingly, a warning on the mortality in the treated patients led recently to withdraw the ventilation. Even if the patients considered in the present study are different (patients with HF were excluded), these recent findings underline that the pathophysiology is not perfectly understood in patients with SAS.

Oxygenation-sensitive cardiovascular magnetic resonance imaging (OS-CMR) is an emerging and promising technique that can investigate the oxygenation at the level of tissues or blood. This approach uses the paramagnetic properties of deoxygenated hemoglobin, also known as the blood oxygen level-dependent (BOLD) effect, as an endogenous contrast [7–9]. The signal intensity of tissue in BOLD- or OS-CMR images is inversely correlated with the concentration of deoxygenated hemoglobin, which is in turn a result of the oxygen supply-demand balance and thus blood flow and blood volume [10]. Applied to the heart, OS-CMR has been shown to consistently and accurately detect changes in myocardial oxygenation in vivo [11]. This provides incremental information in coronary artery disease [12,13] and allows for verifying changes in blood flow [14] and myocardial oxygenation, for example during stress-induced myocardial ischemia [15–19].

Breathing maneuvers have been proposed as a physiological vasoactive stimulus leading to consistent myocardial signal intensity changes in oxygenation-sensitive MR images [8,20–23]. Mostly related to changes in blood carbon dioxide (CO_2), a breath-hold (leading to hypercapnia with a net increase of blood CO_2) is an effective vasodilator, whereas hyperventilation with hypocapnia causes vasoconstriction [8,20–22]. By combining these maneuvers, the achievable changes in pCO_2 are increased, resulting in a more extended range in vascular resistance with greater changes in OS signal intensity.

Because of an abnormal coronary vascular response in patients with OSAS, we hypothesized that the coronary vascular response to hyperventilation and long breath-hold is diminished in patients with OSAS when compared to healthy volunteers, as reflected by changes in myocardial oxygenation during voluntary apnea following hyperventilation.

Methods

Subjects

Thirty patients with OSAS and 37 healthy volunteers were prospectively included in this single-center study. Documented patient characteristics included cardiovascular risk factors and treatment by continuous positive airway pressure (CPAP).

All patients were referred to the Montreal Heart Institute with known OSAS as confirmed by polysomnography. Healthy participants were recruited by public advertisements and voluntary enrolment. Data of 19 healthy participants were already used in a previously published healthy control study [23].

Exclusion criteria

Participants with classical contra-indication for CMR imaging (e.g. pacemaker, implanted defibrillator, metal devices or implants, and known claustrophobia), severe HF, previous known myocardial infarct, or unstable coronary artery disease were excluded. Additional exclusion criteria for the healthy participants included smoking during the previous 6 months, other known cardiovascular or respiratory disease, or treatment with vasoactive medication.

Experimental protocol

The trial was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee. All participants gave their signed informed consent for the study.

CMR

Imaging was performed with a clinical 3T MRI system (MAGNETOM Skyra 3T; Siemens, Erlangen, Germany) using an 18-channel cardiac phased array coil. Images were obtained during breath-holds at comfortable end-expiration. LV function was assessed using an electrocardiogram (ECG) gated balanced steady-state free precession (SSFP) sequence (echo time/TE and repetition time/TR 1.43 ms and 3.3 ms, respectively; flip angle 65°; voxel dimensions 1.6 mm × 1.6 mm × 6.0 mm; matrix 192 × 120; bandwidth 962 Hz), covering the entire left ventricle by a short-axis stack or by six LV-centered radial long-axis slices with plus 3 short-axis views. OS-CMR images were acquired in one mid-ventricular short-axis slice using an ECG triggered SSFP sequence (TE/TR 1.70 ms/3.4 ms; flip angle 35°; voxel dimensions 2.0 mm × 2.0 mm × 10.0 mm; matrix 192 × 120, bandwidth 1302 Hz). Image acquisition was continuously repeated throughout the entire voluntary breath-hold.

The breathing maneuver (Fig. 1) was a combined hyperventilation/breath-hold in which participants breathed rapidly and deeply for 60 s aiming for a rate of approximately 30 breaths/min or more. This was followed by a maximal voluntary breath-hold performed at end-expiration. OS-CMR images were acquired continuously throughout the breath-hold. During hyperventilation, the patients were monitored through live video feed, and were instructed to change breathing depth and pace if the performance was insufficient. When participants indicated their need for inspiration by an alarm bell, image acquisition was stopped. Furthermore, the CMR images were simultaneously verified during the breath-hold to ensure compliance. This

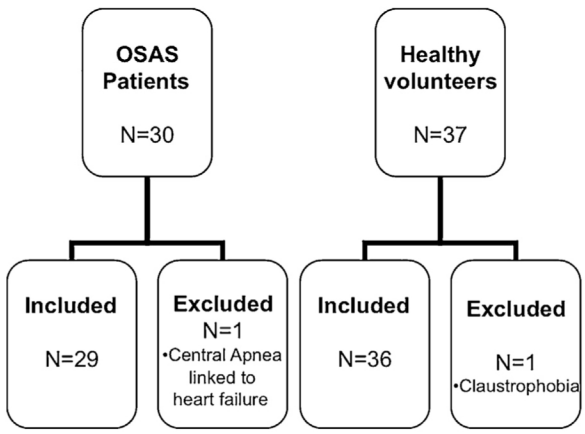


Fig. 1. Schematic of the combined breathing maneuver. Participants performed 60 s of hyperventilation aiming for a respiratory rate of 30 breaths/min, followed immediately by a long breath-hold. The breath-hold was continuously imaged with oxygenation-sensitive cardiovascular magnetic resonance imaging. OSAS, obstructive sleep apnea syndrome.

approach allows the investigation of pathophysiological mechanisms accurately. For instance, at the beginning of the breath-hold, we expect mostly vasodilatation without any desaturation, reflecting the high physiological adaptability.

Image analysis

All images were analyzed using certified software (cvi[42] version 4.1, Circle Cardiovascular Imaging, Calgary, AB, Canada). Analysis of left ventricular function was performed from epicardial and endocardial contours in diastolic and systolic images. For OS-CMR images, end-systolic images were used for analysis. The mean myocardial signal intensity (SI) in the OS-CMR images was automatically calculated after manual tracing of endocardial and epicardial contours. SI was expressed as % change (ΔSI[%]) using the first image of the breath-hold as the baseline and measured at 15 s, 30 s, 45 s, as well as at the end of the breath-hold. From the results, the maximum slope of the SI curve during the first 30 s was computed.

Statistical analysis

The sample size was estimated based on mean expected change of 15% with a standard deviation of 20%, aiming for 80% power. Continuous variables were assessed for normal distribution with the D'Agostino-Pearson test. Normally distributed variables are expressed as mean and standard deviation (SD); otherwise median and interquartile range (IQR) describe the variables with non-normal distribution. An independent *t*-test or a Mann–Whitney *U* test compared data between groups. OS-CMR results between the healthy control and OSAS group were assessed with a general linear model, using age as a covariate, to assess if age had a significant interaction at each time-point, using a Bonferroni multiple comparisons test if appropriate. For visualization of the response, SI during the breath-holds was fitted by a polynomial regression curve using the least-squares method. Readings of 12 patients were replicated by a second independent reader and inter-observer reliability was assessed using a two-way intraclass correlation (ICC) test. Tests were performed with GraphPad Prism version 6.0 for mac (GraphPad Software, La Jolla, CA, USA) and SPSS version 21 (SPSS, IBM, Armonk, NY, USA). Results were considered statistically significant with a p-value <0.05.

Results

Population characteristics

Twenty-nine patients with OSAS and 36 healthy volunteers successfully completed the study (Fig. 2, Table 1). One of the patients did not fulfill the predefined LVEF criterion (LVEF > 35%) and one healthy volunteer withdrew from the examination due to claustrophobia (Fig. 2). The data from these two subjects were not included in the analysis. All other participants were able to complete the breathing maneuvers and no procedure was stopped.

Group characteristics are described in Table 1. Patients with OSAS were significantly older than control subjects and had a higher body mass index (BMI). OSAS patients were followed mainly for symptoms not related to myocardial ischemia and stable coronary disease, but 83% also presented with at least one of the following co-morbidities: hypertension (55%), overweight with a BMI >30 kg/m^2 (69%), dyslipidemia (48%), and coronary artery disease (24%). Sixty-six percent of the patients were currently treated with nocturnal CPAP and had been followed for OSAS for 9.8 ± 7.1 years. LVEF and indexed myocardial mass were normal in both groups. Healthy volunteers had larger end-systolic and end-diastolic volumes (Table 1).

Table 1
Study participant characteristics.

	OSAS patients $n=29$	Healthy volunteers $n=36$	p-Value
Population			
Sex ratio (M/F)	28/1	17/19	<0.01
Age, years	60 ± 12	49 ± 12	<0.01
Weight, kg	93 ± 17	74 ± 10	<0.01
BMI (kg/m^2)	31.0 ± 5.5	25.5 ± 3.3	<0.01
Coronary disease	7/29 (24%)	0	<0.01
Atrial fibrillation	2/29 (7%)	0	<0.01
Heart failure	0	0	NS
Baseline heart rate, bpm	68 ± 12	64 ± 7	0.09
Sleep apnea syndrome			
Diagnosed OSAS	29/29 (100%)	0	NA
Treated OSAS (CPAP)	19/29 (66%)	0	NA
Duration of OSAS[a], years	9.8 ± 7.1	0	NA
CAD risk factors			
Hypertension	16 (55%)	0	<0.01
Overweight (BMI > 27)	20 (69%)	8 (22%)	<0.01
Dyslipidemia	14 (48%)	0	<0.01
Diabetes	6 (20%)	0	<0.01
Smoking	3 (10%)	0	<0.01
MRI baseline characteristics			
LVEF, %	70 ± 10	64 ± 6	<0.01
LVEDV index, ml/m	59 ± 22	91 ± 15	<0.01
LVESV index, ml/m	18 ± 9	33 ± 8	<0.01
Mass (systole) index, g/m	75 ± 24	71.2 ± 18.4	0.46

Data are mean ± SD or *n* (%)
[a] Years since the initial suspicion and diagnosis.
BMI, body mass index; bpm, beats per minutes; CAD, coronary artery disease; CPAP, continuous positive airway pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NA, not applicable; NS, not significant; OSAS, obstructive sleep apnea syndrome.

Reproducibility of results in patients with OSAS

A strong intraclass correlation coefficient (ICC) of 0.93 (95%CI: 0.90–0.95) indicated that the readers had a high degree of consistency in analyzing the images.

Effect of prolonged apnea on myocardial signal intensity

In both patients and healthy volunteers, myocardial oxygenation, as defined by changes of SI in OS-CMR, was significantly impacted by the breathing maneuver (Fig. 3). Non-linear best-fit regression curves of the change in SI over the breath-hold are presented in Fig. 4. Patients had a delayed and attenuated response. On the other hand, healthy volunteers had a rapid response from the beginning of the breath-hold, resulting in a greater slope of ΔSI[%] than the OSAS patients. At all three defined time-points during the breath-hold (15, 30, and 45 s), healthy participants had a significantly larger ΔSI[%] than OSAS patients (Fig. 4). By the end of the breath-hold in OSAS patients, SI decreased to 4.0 ± 11.0%, whereas healthy volunteers maintained a

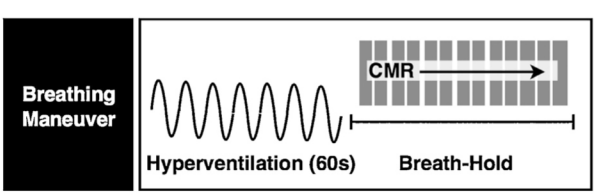


Fig. 2. Flow chart of patients. CMR, cardiovascular magnetic resonance imaging.

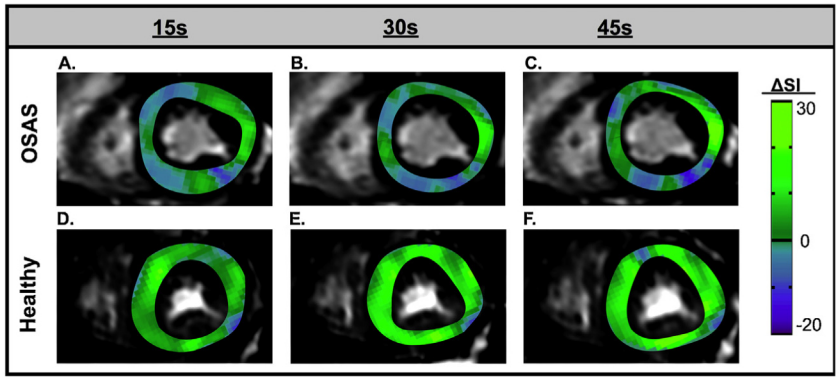


Fig. 3. Color maps of signal intensity changes in oxygenation-sensitive cardiovascular magnetic resonance images in a patient with obstructive sleep apnea syndrome (OSAS) and a healthy subject. Subtraction image of signal intensity changes from baseline to the three time points within the breath-hold (15 s, 30 s, and 45 s). The signal intensity increase is more pronounced in the healthy subject (top row) as compared to the patient with OSAS (bottom row).

higher SI ($8.8 \pm 8.0\%$; $p = 0.03$) by the time they needed to breathe. While at 15 and 30 s, age was not a significant factor, at the 45 s point near the end of the breath-hold, age did have a significant interaction ($p = 0.02$). Yet, even when accounting for this, the difference in OS-CMR results between groups was significant ($p = 0.01$).

Effect of CPAP treatment

OSAS patients without CPAP treatment ($n = 10$) did not differ from healthy controls (Fig. 4b), whereas patients under CPAP ($n = 19$) had a significantly attenuated mean oxygenation response at all time-points in comparison to healthy controls (15 s: 0.8 ± 9.3 vs. 6.8 ± 5.6; 30 s: 2.2 ± 7.1 vs. 9.8 ± 6.7; 45 s: 4.8 ± 2.1 vs. 11.3 ± 7.5, $p < 0.02$). Furthermore, OSAS patients receiving CPAP treatment had a significantly lower slope of ΔSI[%], and a lower response at 30 s (2.2 ± 7.1 vs. 8.6 ± 7.1, $p = 0.04$) in comparison to non-CPAP treated OSAS patients.

Discussion

Our data show that there is a blunted coronary vascular response in patients with OSAS, especially in those under positive airway pressure therapy. Furthermore, our study shows that oxygenation-sensitive CMR with breathing maneuvers is feasible in patients with cardiovascular or respiratory disease.

In order to be feasible for most patients, the most important time-points are data collected within the first 30 s and the slope value assessing the initial oxygenation response. After a proper period of hyperventilation, 86% of SAS patients and 94% of the controls maintained the breath-hold for 30 s, and all participants managed a breath-hold of at least 15 s. Of note, the attenuation of the coronary vascular/oxygenation response in patients with OSAS was already evident as early as 15 s after initiating a breath-hold following hyperventilation. This indicates a potential of this test to be used clinically, as it does not represent a significant challenge for patient compliance. The reduced vascular response does not support the hypothesis that repeated ischemic episodes lead to pre-conditioning and thus maintains vascular function and oxygenation.

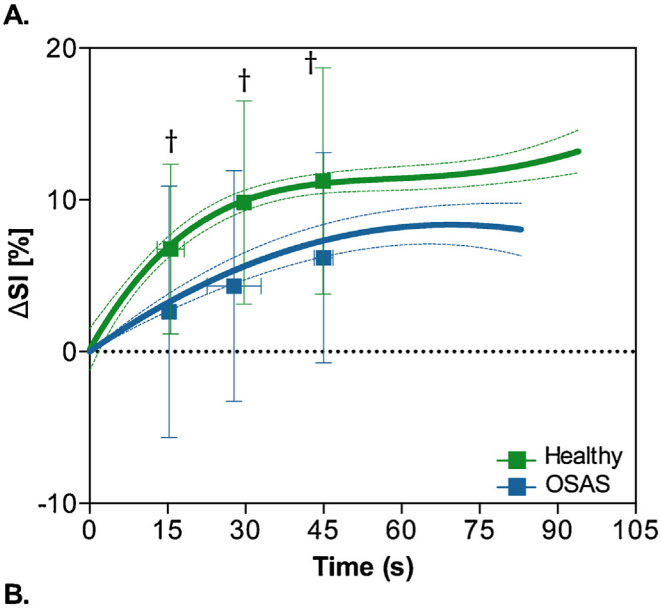
Patients with OSAS are known to suffer more frequently from co-morbidities, especially obesity [24]. This could be linked to higher oxidative stress [25–27], endothelial dysfunction [28–30], less nitric oxide production [31], and inflammation [32]. All of these pathophysiological aspects could contribute to a decreased myocardial adaptive response. Consistent with our findings, a study in 10 patients with hypertensive LV hypertrophy demonstrated an impaired ability to increase intra-myocardial oxygenation during vasodilatory stress [33].

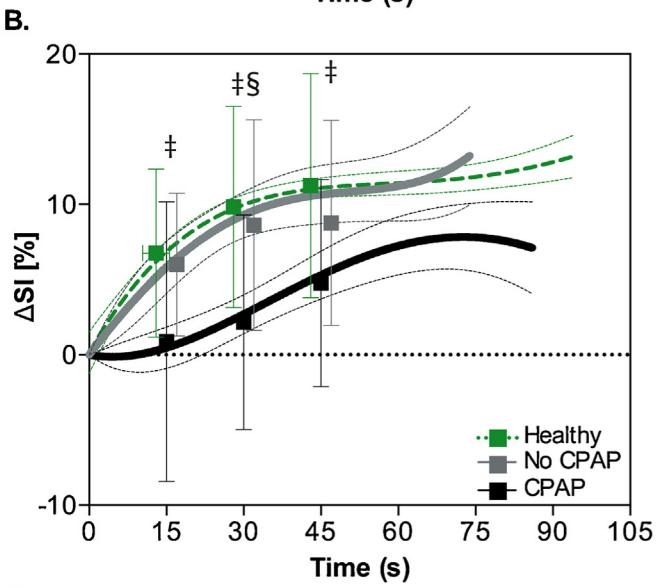
Most study participants were under treatment with CPAP, which may have improved their endothelial function [34–36]. In an observational study, CPAP treatment also significantly reduced cardiovascular event rates when compared to patients without CPAP [37]. In contrast, a randomized controlled study in 725 less severe patients failed to show a clinical benefit of CPAP on cardiovascular outcomes [38]. In our study, patients not on CPAP had a similar myocardial oxygenation response to healthy controls, whereas those on CPAP had a significantly reduced response. This may have been due to more severe and advanced disease and thus also more severe microvascular disease of the group under CPAP therapy. However, the numbers of patients are small; CPAP modalities are various as well as the observance, preventing from concluding in the present study. Further works are needed to investigate this question. This paradoxical result should also be interpreted as suggesting adverse effects of the CPAP. The various modalities for the treatment will have to be taken into account in further studies, particularly because of the SERVE-HF study [6] suggesting that servo-ventilation could exert deleterious effects – but not the other modalities for CPAP treatment.

Interestingly, whereas healthy volunteers had to breathe as soon as oxygenation signal started to decrease from the maximum value, OSAS patients could hold their breath until the oxygenation-related signal intensity decreased toward baseline values. This likely reflects a greater tolerance of the OSAS patients to hypercapnia and hypoxia.

These results pave the way for further basic research to better understand the physiological adaptations to repetitive hypercapnia and hypoxia. OS-CMR also may offer a powerful approach for assessing the myocardial response to short periods of ischemia as shown in animal models.

This new approach could address pathophysiological concerns such as those raised by the recent warnings in the SERVE-HF study [6]. Probably the pathophysiological mechanisms involved in cardiovascular disorders are not similar in patients with HF and predominantly central apneas when compared to patients without HF and predominantly obstructive apneas. Myocardial oxygenation response could be consistently compared in different groups of patients with various forms of SAS. In dedicated prospective trials, the impact of OSAS on the one hand, but on the other hand the impact of the CPAP as well as the various modalities of ventilations could be evaluated through these pathophysiological approaches. We could imagine that the most "physiological" response as regards myocardial response during the breathing





C.

	OSAS Patients	Healthy Volunteers	P
ΔSI[%]			
15s	2.6±8.3 (29)	6.8±5.6* (35)	0.02
30s	4.3±7.6* (24)	9.8±6.7* (34)	0.01
45s	6.2±6.9* (17)	11.3±7.5*(29)	0.03
End	4.0±11.0 (29)	8.8±8.0* (36)	0.01
Max Slope	0.44±0.56	0.76±0.50	0.02
Breath-Hold Duration (s)	52.1±29.6	66.5±27.7	0.04

Fig. 4. Change in myocardial oxygenation during long breath-holds after hyperventilation. (A) Non-linear regression curves (95% confidence bars) of the average signal intensity (SI) change in oxygenation-sensitive cardiovascular magnetic resonance images during a maximal voluntary breath-hold, performed immediately after a 60-s period of hyperventilation in 29 patients with obstructive sleep apnea syndrome (OSAS) (blue) and 36 healthy volunteers (green). The overall response is blunted in patients and the signal intensity is significantly different between the groups at the 15 s, 30 s, and 45 s time-points (square: mean ± SD, $^{\dagger}p < 0.05$ between healthy and OSAS results at each time-point). (B) Comparison of oxygenation changes within the OSAS patient group, divided into patients with (n = 19, black) and patients without (n = 10, gray) Continuous positive airway pressure (CPAP) treatment. Patients with CPAP treatment show a reduced vascular response to the breathing maneuver ($^{\ddagger}p < 0.05$ between healthy and OSAS patients on CPAP, $^{\S}p < 0.05$ between treatment with and without CPAP treatment). (C) Mean ± SD (n) change in oxygenation signal intensity from baseline at multiple time-points during the breathing maneuver in both groups ($^{*}p < 0.05$ for change from baseline within the breath-hold). At all time points, OSAS patients showed a blunted response.

manoeuvers could be considered as a valuable exploratory endpoint.

Limitations

This study was performed in a relatively small patient population. The confirmation of our findings in a larger population but also in other clinical settings is now warranted. Indeed, the confirmation of our results in animal models has just been recently provided [22] as well as application in healthy volunteers [23].

Confounders such as sex, age, body weight, co-existing coronary artery disease, arterial hypertension, and atrial fibrillation may have impacted our results. Indeed, as the populations (healthy volunteers versus patients with OSAS) are not similar, the impact of biases cannot be excluded. Nevertheless, patients with OSAS are well-known to present also more comorbidities. Because of the small sample size, we cannot take into account all the potential biases.

Finally, results regarding CPAP are surprising and we present above some likely explanations. One limitation is also the lack of details on the observance, previous treatments, type of CPAP, modalities of ventilations, etc.

Conclusion

The myocardial vascular response to combined breathing maneuvers of hyperventilation followed by voluntary apnea is blunted in patients with obstructive sleep apnea. Clinical studies should now further define the clinical role of oxygenation-sensitive CMR in patients with respiratory disorders.

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Author contributions

François Roubille was involved in the study design, performing the experiments, and in writing and editing the manuscript.

Kady Fischer was involved in the study design, performing the experiments, and in editing the manuscript.

Dominik Guensch was involved in the study design, the analysis, and in editing the manuscript.

Jean-Claude Tardif was involved in the study design and in editing the manuscript.

Matthias G. Friedrich was significantly involved in the study design and in writing and editing the manuscript.

All authors have read and approved the manuscript.

Conflict of interest

Matthias Friedrich is board member, advisor, and shareholder of Circle Cardiovascular Imaging Inc., the manufacturer of the software used for CMR image evaluation. Matthias Friedrich,

Dominik Guensch, and Kady Fischer have a pending U.S. patent regarding the use of breathing maneuvers for diagnostic purposes. There are no other conflicts of interest.

Acknowledgments

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