Clinical Research in Cardiology (2019) 108:1226–1233
https://doi.org/10.1007/s00392-019-01454-6

ORIGINAL PAPER

Epicardial fat accumulation is an independent marker of impaired heart rate recovery in obese patients with obstructive sleep apnea

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Received: 14 September 2018 / Accepted: 13 March 2019 / Published online: 18 March 2019

Abstract

Background Sympathetic nervous system activation plays a pivotal role in obese patients with obstructive sleep apnea (OSA), contributing to increased cardiovascular risk. Epicardial adipose tissue (EAT) activates cardiac autonomic nervous system. Our main study objective was to investigate effects of these autonomic dysfunction factors on post-exercise heart rate recovery (HRR).

Methods 36 patients, referred for clinical assessment of obesity (BMI > 30 kg/m^2), underwent overnight polysomnography, transthoracic echocardiography and cardiopulmonary exercise testing.

Results Compared to non-OSA patients, OSA patients were older and displayed reduced body weight-indexed peak VO_2. Cardiac output at peak exercise was similar among groups. Peak exercise arterio-venous oxygen content difference D[a-v]O_2 was lower in OSA patients. In univariate linear analysis, age, AHI, EAT thickness, peak VO_2 and diabetes were associated with blunted HRR. Multiple linear regression analysis showed that increased EAT thickness, AHI and diabetes were independently associated with lower HRR. For identical AHI value and diabetes status, HRR significantly decreased by 61.7% for every 1 mm increase of EAT volume ($p = 0.011$). If HRR was treated as a categorical variable, EAT [odds ratio (OR) 1.78 (95% confidence interval [CI] 1.19–2.66); $p = 0.005$], and type 2 diabetes [OR 8.97 (95% CI 1.16–69.10); $p = 0.035$] were the only independent predictors of blunted HRR.

Conclusions Aerobic capacity and peak exercise D[a-v]O_2 are impaired in obese OSA patients, suggesting abnormal peripheral oxygen extraction. EAT thickness is an independent marker of post-exercise HRR, which is a noninvasive marker of autonomic nerve dysfunction accompanying poor cardiovascular prognosis in obese patients.

Keywords Obstructive sleep apnea · Epicardial adipose tissue · Exercise testing · Heart rate recovery

Introduction

Increasing adiposity is associated with neuroendocrine and metabolic abnormalities, including renin-angiotensin system activation, autonomic nervous system dysfunction, hyperleptinemia, inflammation, and deregulation of growth factors [1]. Among these perturbations, activation of the sympathetic nervous system plays a pivotal role, possibly contributing to increased cardiovascular risk [1]. Chronic intermittent hypoxia elicited by recurring obstructive sleep apnea (OSA) episodes represents a key event that potently activates autonomic reflexes [2]. During obstructive apneic and hypopneic events, activation of peripheral and central chemoreflex by hypoxemia and hypercapnia results in persistent increased chemoreflex sensitivity with consequent activation of the sympathetic nerve [2, 3]. Subsequent

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sympathetic nervous system hyperactivity is believed to be an integral intermediate mechanism of cardiovascular disease morbidity and mortality in obese patients with OSA [4–11].

Cardiopulmonary exercise is considered a simple and reliable test for the identification of autonomic nervous dysfunction [12]. Exercise is associated with increased sympathetic and decreased parasympathetic activity, resulting in an acceleration of heart rate caused by vagal withdrawal and adrenergic discharge [12]. The decline in heart rate during recovery (HRR) is principally due to a reactivation of the parasympathetic nervous system, mostly in the early recovery period. Sympathetic withdrawal also contributes to HRR, as evidenced by brisk HRR even after atropine administration at maximal exercise 126.

As blunted HRR is a powerful predictor of cardiovascular disease and all-cause mortality, extensive evaluation of HRR has been performed in several pathological conditions such as coronary artery disease, heart failure, hypertension, type 2 diabetes, metabolic syndrome and obesity, rheumatologic cancer and diseases [13, 14]. In untreated OSA patients, HRR is inversely related to OSA severity as expressed by apnea-hypopnea index (AHI), independently from peak heart rate and parameters of body composition [15, 16].

Growing evidence suggests that epicardial adipose tissue (EAT), the visceral fat depot in the heart, plays a critical role in the activation of the cardiac autonomic nervous system [17]. EAT is the anatomical site of intrinsic adrenergic and cholinergic nerves that can adversely influence the autonomic nervous system of the heart through derangements of extrinsic cardiac sympathetic and parasympathetic activity [17]. In patients with metabolic syndrome, increased EAT thickness has been associated with blunted HRR [18, 19] and further identified as a novel independent cardio-metabolic risk factor [20].

Interestingly, previous studies have reported that EAT and OSA are related. Chronic intermittent hypoxia could impair EAT homeostasis [21, 22]. In line, continuous positive airway pressure therapy reduces EAT thickness and significantly ameliorates cardiovascular parameters in obese OSA patients [22]. Alternatively, chronic intermittent hypoxia can stimulate adiposity increasing further fat accumulation in the neck that contributes to upper airway narrowing, thus to the severity of OSA. Hence, there may be a bidirectional relationship between EAT accumulation and OSA severity.

Post-exercise HRR is typically blunted in patients with OSA [15, 16] and recent reports suggest that excessive accumulation of EAT also affects HRR in patients with metabolic syndrome [18, 19]. Whether overlap of both conditions may further impair HRR has not been previously reported. Considering that OSA and increased EAT thickness can induce sympathetic over activation, we sought to investigate the effect of this autonomic dysfunction on HRR. The main objective of our study was to test whether post-exercise HRR in severely obese OSA patients (BMI > 30 kg/m^2) would be independently associated with EAT thickness after adjusting on OSA status. First, we tested whether OSA would influence aerobic capacity and cardiopulmonary parameters in a population of severely obese patients. Second, we tested whether EAT thickness would be independently associated with HRR in severely obese patients, after having adjusted on several factors including OSA status.

Patients and methods

Study design and population

All patients received information regarding study protocol and main objectives. Oral and written consents were obtained from all patients and were notified in their medical file record. This study was conducted in accordance with the Declaration of Helsinki and approved by appropriate local Ethics authorities. The study is also registered in the Australian New Zealand Clinical Trials Registry, (ANZCTR) under the following allocation number ACTRN12618001487202. In this cross-sectional study, participants with body mass index (BMI) > 30 kg/m^2 were recruited at the out-patient clinic of the Department of Metabolic Disorders and Obesity of the University Hospital of Martinique, located in the French Caribbean overseas department of Martinique. Subjects having heart valve disease, coronary heart disease, heart failure, chronic obstructive pulmonary diseases, asthma and other lung diseases, endocrine and acute or chronic inflammatory processes, rheumatologic diseases, and having more than 5% change of body mass within the last 3 months were excluded. Subjects were also excluded from the study if they were taking medications for lipid disorder or taking anti-inflammatory drugs, nutritional supplements, tobacco products (cigarettes, cigars, chewing tobacco, vapors), or if they consumed an average of more than ten alcoholic beverages per week. The patients had to have been physically inactive as defined by the American College of Sports Medicine's (ACSM) guidelines (less than 60 min of structured or planned physical activity per week) within the last 6 months. A medical examination of each participant was done prior to study inclusion revealing no contra-indications for cycling exercise. Evaluations were performed on different days with a 1-week interval between each evaluation.

Transthoracic echocardiography

Echocardiograms were performed using EPIQ 7C machine (Philips Healthcare, Suresnes, France) according to standard technique. Transthoracic echocardiography was performed

according to the American Society of Echocardiography guidelines. The biplane method was used to measure LVEF. Measurements of EAT thickness were obtained from a parasternal long axis view. EAT thickness was measured perpendicularly to the free wall of the right ventricle, at end systole, in three cardiac cycles as previously reported [21, 22]. Measurements of EAT thickness were performed offline by two independent medical doctors. The average value from three cardiac cycles was used for statistical analysis. Intra- and inter observer reproducibility for echocardiographic EAT thickness assessment were excellent (0.96 and 0.94, respectively).

Polysomnography

A full-night diagnostic polysomnography (Nox A1, ResMed Corp, San Diego, CA, USA) was performed on each subject. To determine the stages of sleep, electroencephalogram, electro-oculogram and electromyogram of the submentalis were continuously recorded. Oral and nasal airflow, electrocardiogram, abdominal and thoracic movements, and pulse oximetry (SpO_2) were also continuously recorded. Airflow and electrocardiographic recordings were monitored by an oro-nasal thermistor placed in front of the nostrils and the mouth and an online 12-leads electrocardiogram, respectively. Thoraco-abdominal excursions were measured qualitatively, using respiratory effort sensors placed over the ribcage and abdomen (2 channels). In addition, snoring was detected with a vibration snore sensor (1 channel) and body posture with a body position sensor (1 channel).

Sleep stage and respiratory event scoring were performed according to standard criteria by a registered polysomnographic technician blinded to participant status (Noxturnal, ResMed Corp, San Diego, CA, USA). EEG arousal, AHI and ODI scoring followed the latest American Academy of Sleep Medicine Scoring Rules (version 2.2.0). Apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were calculated as total number events per hour of sleep. Cumulative time percentage with $SpO_2 < 90\%$ (CT90) was defined as the cumulative time spent with $SpO_2 < 90\%$ during sleep (10:00 p.m.–7:00 a.m.). Moderate to severe OSA was characterized by an apnea/ hypopnea index (AHI) ≥ 15 events/h by polysomnography.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed according to standardized procedures using an electromagnetic braked cycle ergometer. Exercise protocol involved an initial 3 min of rest, followed by 2 min of unload cycling with a progressive increment every minute (10 W/min) until exhaustion, at a pedaling frequency of 60–65 rate/min. Subjects were continuously monitored using 12-lead ECG (Case, GE Healthcare, France). Blood pressure was recorded every 2-min. Throughout the exercise session, subjects breathed through an oro-nasal mask (Hans Rudolf 7450 SeriesV2™ Mask, CareFusion, France).

Breath-by-breath cardiopulmonary data (PowerCube-Ergo, Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) were measured at rest, warm up and incremental exercise testing. Before each test, oxygen (O_2) and carbon dioxide (CO_2) analyzers and flow mass sensor were calibrated using available precision gas mixture and a 3-L syringe, respectively. Minute ventilation (V_E), oxygen uptake (VO_2), carbon dioxide output (VCO_2) were recorded as concurrent 10-s moving averages, as was determined ventilation anaerobic threshold by the V-slope method. Ventilatory reserve was calculated as (MVV − peak V_E)/MVV × 100, where MVV is maximal voluntary ventilation estimated as FEV_1 multiplied by 35. Peak values were averaged over the last 30 s of exercise. Patient effort was considered to be maximal if two of the following occurred: predicted maximal work is achieved, predicted maximal heart rate (HR) is achieved, $V_E/VO_2 > 45$ and RER > 1.10, as recommended by the statements of the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) in 2013. At peak exercise, subjects were assessed for Borg-perceived exertion ratings for both respiratory and leg discomfort. During the study period, mean values between qualified replicate tests performed weekly on control subjects were $3.1 \pm 4.2\%$, $3.4 \pm 3.2\%$, $2.1 \pm 2.2\%$, for peak VO_2, VCO_2 and V_E, respectively. Peak oxygen pulse (O_2 pulse) was calculated and was expressed in ml per beat and as percentage of predicted value by dividing the predicted peak VO_2 by predicted peak HR. V_E/VCO_2 slope was calculated off-line as a linear regression function using 10-s averaged values and excluding the non-linear part of the relationship after the respiratory compensation point (where non-linear rise in V'_E occurred relative to VCO_2 in the presence of decreasing end-tidal pressure of CO_2).

Cardiac output was estimated using thoracic bioimpedance (Physio Flow, Manatec Biomedical, Paris, France) during the submaximal exercise tests. Arterio-venous oxygen content difference ($D[a\text{-}v]O_2$) was calculated from cardiac output and VO_2 using the Fick Principle. The percentage of HR reserve used at peak exercise referred to $[(HR_{stage} - HR_{rest})/(220 - \text{age in years} - HR_{rest})] \times 100$, where HR is heart rate. Heart rate recovery (HRR) was defined as the change in heart rate from peak exercise at 1 min (HRR-1) and 3 min (HRR-3).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (SPSS, Inc., Chicago, IL). Data are presented

as mean ± standard deviation for continuous variables and percentages (%) for categorical variables. Normality of the data was tested using the Kolmogorov–Smirnov test. The differences among the groups were evaluated using either unpaired *t* test or Mann–Whitney test, as the data were normally distributed or not. Chi-square test was used for categorical data. The role of key variables associated with HRR-1 was tested by univariate and multivariate linear regression. Interaction terms were also tested. Variables with a p value < 0.20 after univariate analysis were included in the multivariate model (backward stepwise technique). In addition, HRR-1 was dichotomized according to a cut-off set at 12 bpm. The new binary variable was coded '0' for < 12 bpm and '1' for ≥ 12 bpm. Univariate and multivariate logistic regression was carried out to identify independent predictors. After univariate analysis, variables with significant association ($p < 0.20$) with the binary variable were considered for multivariate analysis (backward stepwise procedure). The level of statistical significance was set at p value < 0.05.

Results

For study purposes, 96 obese patients were screened prospectively from January 1st 2017 to December 31st 2017. Among these 96 initial patients, 36 obese adults met inclusion criteria and were enrolled in the study. Most of the participants were women (80.6%). Mean age was 41.7 ± 6.5 years and BMI was 41.7 ± 6.5 kg/m^2. According to nocturnal polysomnography, moderate-severe OSA (AHI > 15 events/h) was diagnosed in 47.2% of patients, whereas none had mild OSA (AHI < 15/h). Type 2 diabetes and hypertension were present in 36.1% and 19.4% of patients, respectively. Mean ventricular ejection fraction was 71.4 ± 6.8% and EAT thickness was 8.5 ± 3.1 mm.

Baseline characteristics and cardiopulmonary exercise test measurements of non-OSA and OSA obese patients are shown in Table 1. Whereas OSA patients were older compared to non-OSA patients, sex, type 2 diabetes and hypertension were similar among groups. Despite similar BMI, obese OSA patients had higher EAT thickness compared to non-OSA patients. Cardiopulmonary exercise testing data are shown in Table 2. Respiratory exchange ratio at peak exercise was > 1.0 in all patients. Heart rate at rest, peak exercise heart rate, age-predicted maximal heart rate, and percent heart rate reserve used did not differ between non-OSA and OSA patients. The proportion of patients not achieving age-predicted peak heart rate of at least 85% ($p = 0.74$) and a heart rate reserve of at least 80% ($p = 0.48$) was similar in both groups. Anaerobic threshold was achieved at 67 ± 8% and 70 ± 10% of peak VO_2 ($p = 0.34$) in non-OSA and OSA patients, respectively. Changes in HRR at 1 min and at 3 min were significantly lower in patients with OSA compared to non-OSA patients. Body weight-indexed peak VO_2 was lower in OSA patients. Exercise blood pressure response was higher in patients with OSA compared to non-OSA patients. Non-OSA and OSA obese patients achieved similar rise of cardiac output from baseline to peak exercise. D[a-v]O_2 were lower in patients with OSA compared to non-OSA patients (Table 2). As shown in Table 3, in univariate analysis by linear regression, lower HRR-1 was associated with higher age, increased AHI, ODI and CT90, increased EAT thickness (mm), reduced peak VO_2 and type 2 diabetes. No significant interaction was found between independent predictors. In the multivariate linear regression model, only increased EAT thickness, increased AHI and type 2 diabetes were independently associated with lower HRR-1. For identical AHI value and type 2 diabetes 2 status, HRR significantly decreased by 61.7%

Table 1 Characteristics of obese patients according to obstructive sleep apnea status ($n = 36$)

	Non-OSA patients ($n = 19$)	OSA patients ($n = 17$)	p value
Age (year)	38.9 ± 10.1	47.1 ± 12.0	0.03
Female sex (%)	84.2	76.5	0.68
BMI (kg/m^2)	41.5 ± 5.2	41.9 ± 7.8	0.85
LVEF (%)	73.3 ± 7.2	69.3 ± 5.9	0.08
LVM (g/m^2)	75.9 ± 12.9	76.6 ± 17.6	0.88
SWTd (mm)	9.7 ± 1.5	10.9 ± 3.1	0.14
PWTd (mm)	9.3 ± 2.0	10.2 ± 2.4	0.23
E/*e*′ ratio	8.7 ± 2.3	9.7 ± 2.6	0.24
EAT thickness (mm)	6.6 ± 1.6	10.7 ± 2.8	< 0.0001
Hemoglobin (gm/dL)	15.1 ± 1.7	14.8 ± 1.2	0.16
AHI (events/h)	3.1 ± 1.0	33.5 ± 25.2	< 0.0001
Arousal index (events/h)	9.8 ± 3.1	38.0 ± 13.1	< 0.0001
ODI (events/h)	13.1 ± 8.7	50.1 ± 15.3	< 0.0001
CT90 (%)	0.1 [0–0.2]	2.5 [1.4–7.8]	< 0.0001
Hypertension (%)	15.8	23.5	0.68
Type 2 diabetes (%)	21.1	52.9	0.08
Cigarette smoking (%)	5.2	11.8	0.59
ACE inhibitors (%)	26.3	17.6	0.69
β-blocker (%)	10.5	17.6	0.65

Values are either given as counts and percentages, as means ± standard deviation or median [25–75% percentile]

OSA obstructive sleep apnea, *BMI* body mass index, *LVEF* left ventricle ejection fraction, *LVM* left ventricle mass, *SWTd* end-diastolic septum wall thickness, *PWTd* end-diastolic posterior wall thickness, *E* early diastolic transmitral flow velocity, *e′* early diastolic mitral annular velocity, *EAT* epicardial adipose tissue, *AHI*: apnea hypopnea index, *ODI* oxygen desaturation index, *CT90* cumulative time percentage with SpO_2 < 90%, *ACE* angiotensin-converting-enzyme

Table 2 Results from cardiopulmonary exercise testing in obese patients according to obstructive sleep apnea status ($n=36$)

	Non-OSA ($n=19$ patients)	OSA ($n=17$ patients)	p value
Peak heart rate (bpm)	156.0 ± 13.0	151.0 ± 17.0	0.34
Peak heart rate (% predicted)	86.0 ± 5.0	89.0 ± 9.0	0.22
Heart rate reserve used (%)	71.0 ± 12.0	76.0 ± 19.0	0.29
HRR 1 min (%)	14.8 ± 4.0	6.5 ± 1.9	< 0.0001
HRR 3 min (%)	26.0 ± 5.6	19.4 ± 5.9	< 0.0001
Peak systolic BP (mmHg)	186.0 ± 25.0	206.0 ± 25.0	0.06
Peak diastolic BP (mmHg)	84.0 ± 18.0	99.0 ± 16.0	0.02
RER at peak exercise	1.2 ± 0.1	1.2 ± 0.1	0.86
Peak VO_2 (ml/kg/min)	16.1 ± 2.7	14.3 ± 1.9	0.03
Peak VO_2 (% predicted)	73.0 ± 14.0	70 ± 12	0.09
Oxygen pulse (ml/beat)	12.2 ± 2.9	10.6 ± 2.6	0.11
Peak cardiac output (l/min)	16.9 ± 1.5	17.2 ± 1.9	0.63
Peak D[a-v]O_2 (ml/100 ml)	11.4 ± 3.0	8.9 ± 2.8	0.02
Peak breathing reserve (%)	26.8 ± 16.5	39.5 ± 12.4	0.01
VE/VCO_2 slope	31.4 ± 5.1	31.5 ± 5.4	0.98

Values are given as counts and percentages or as means ± standard deviation

OSA obstructive sleep apnea, bpm: beat per minute, *HRR* heart rate recovery, *BP* blood pressure, *RER* respiratory exchange ratio, *VO_2* oxygen uptake, *VE* expired ventilation, *VCO_2* carbon dioxide pulmonary output, *D[a-v]O_2* arterio-venous oxygen content difference

for every 1 mm increase of EAT volume ($p=0.01$). In line, for identical AHI and EAT values, HRR was significantly impaired, by a factor of 5, for a diabetic obese patient with obstructive sleep apnea as compared to a non-diabetic one ($p<0.01$).

If HRR was treated as a categorical variable, EAT [odds ratio (OR) 1.78 (95% confidence interval [CI] 1.19–2.66); $p=0.005$], and diabetes [OR 8.97 (95% CI 1.16–69.10); $p=0.035$] were the only independent predictors of blunted HRR after multivariate logistic regression.

It is to be further noted that no significant interaction was described between EAT and AHI or between EAT and nocturnal hypoxemia (ODI or CT90) for both linear and logistic regression models.

Discussion

New findings of our study are twofold. First, we found that peak exercise VO_2 and arterio-venous oxygen content difference D[a-v]O_2 were reduced in obese OSA patients, suggesting impaired peripheral oxygen extraction. Second, our results suggest that blunted post-exercise HRR in patients was related to increased EAT thickness (mm) as evaluated by trans-thoracic echocardiography. The latter information is important as both increased EAT thickness and attenuated HRR are associated with increased risk of cardiovascular events and all-cause mortality.

Main characteristics of cardiopulmonary exercise testing in obese patients with OSA were reduced peak VO_2, narrower D[a-v]O_2 and higher peak diastolic blood pressure compared to non-OSA patients. Previous studies have yielded contrasting results, with some studies showing no impairment in peak exercise capacity in OSA patients and others showing reduced peak exercise capacity compared to non-OSA patients [23]. In our study, mean difference of peak VO_2 between non-OSA and OSA patients was ~ 2 ml kg^{-1} min^{-1}. This is an important observation as increase of one metabolic equivalent (1-MET is approximately 3.5 ml kg^{-1} min^{-1}) has been associated to ~ 10–25% improvement in survival [23]. A novel finding in this study is that D[a-v]O_2 was lower in OSA patients compared to non-OSA ones, suggesting tissue oxygen extraction and utilization defects at peak exercise. Factors that may affect D[a-v] O_2 during exercise in OSA have not been studied in detail. Of note, patients with OSA display abnormal endothelial function, owing to decreased nitric oxide bioavailability, increased oxidative stress, systemic inflammation and sympathetic over-activity [24, 25]. Endothelial dysfunction can in turn inhibit peripheral vasodilation and impair regional blood distribution, which may lead to peripheral oxygen extraction deficit [24]. Abnormal capillary density, mitochondrial dysfunction and oxidative stress, induced by intermittent hypoxia episodes in the skeletal muscle, may also impair tissue oxygen extraction and/or oxygen utilization in OSA patients [26]. Overall, we speculated that increased blood pressure response and oxygen extraction/utilization deficits could be attributed at least in part to endothelial dysfunction that characterizes OSA patients.

Table 3 Association of key variables with HRR-1 in obese patients

	Univariate regression*		Multivariate regression**	
	β	*p* value	*β*	*p* value
Age (years)	− 0.24	0.17		
Male gender	− 2.31	0.31		
Body weight (kg)	− 0.01	0.80		
Waist circumference (cm)	− 0.08	0.35		
BMI (kg/m^2)	− 0.17	0.31		
LVEF (%)	0.13	0.45		
LVM (g/m^2)	− 0.01	0,81		
SWTd (mm)	− 0.39	0.30		
PWTd (mm)	− 0.34	0.41		
E/*e*′ ratio	− 0.37	0.31		
EAT (mm)	− 0.60	< 0.001	− 0.62	0.01
AHI (events/h)	− 0.54	0.001	− 0.07	0.03
ODI (events/h)	− 0.16	< 0.001		
CT90 (%)	− 0.53	0.016		
Peak VO_2 (ml/kg/min)	0.39	0.02		
Peak heart rate (bpm)	− 0.15	0.38		
Hypertension	0.84	0.71		
Type 2 diabetes	− 5.50	0.001	− 4.59	< 0.01

Results of univariate and multivariate linear regression analysis

HRR-1 heart rate recovery at 1 min, *BMI* body mass index, *LVEF* left ventricle ejection fraction, *LVM* left ventricle mass, *SWTd* end-diastolic septum wall thickness, *PWTd* end-diastolic posterior wall thickness, *E* early diastolic transmitral flow velocity, *e′* early diastolic mitral annular velocity, *EAT* epicardial adipose tissue, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *CT90* cumulative time percentage with $SpO_2 < 90\%$, VO_2 oxygen uptake, *HbA1c* glycated hemoglobin

*Variables with significant association in univariate analysis ($p < 0.2$) were considered for multivariate analysis

**Variables entered into the initial multivariate linear model for HRR-1: age, EAT, AHI, peak VO_2 and type-2 diabetes. Several interactions were also tested, such as between EAT and AHI

Statistical significance level set at $p < 0.05$

Consistently with most previous studies [15, 16, 27], post-exercise cardiovascular characteristics of obese patients with OSA also included blunted HRR, despite similar age-predicted maximum heart rate and maximal heart rate reserve utilization. In OSA patients, mechanisms for attenuated HRR include impaired parasympathetic tone reactivation as well as slower withdrawal of sympathetic influence after exercise [15, 16, 27]. On the other hand, OSA often co-exists with obesity and metabolic syndrome, which are conditions also known to induce autonomic dysfunction and impaired HRR. It has become evident that anatomical distribution of adipose tissue at the epicardial site (EAT) is crucial for the development of deleterious implications of obesity, predisposing to cardiovascular diseases [17]. Specifically, several studies have demonstrated a close relationship between EAT and cardiac autonomic function [19, 28]. Accumulation of EAT has been shown to determine cardiac autonomic dysfunction through additive production of catecholamines within EAT and derived from the sympathetic nervous system [29]. Consistently with previous reports [28, 29], we found that blunted HRR-1 in patients was related to EAT thickness as evaluated by trans-thoracic echocardiography. Interestingly, after multivariate linear regression, we found that increased EAT thickness and AHI, as well as type 2 diabetes, were independent predictors of blunted HRR in obese patients, suggesting that both EAT and AHI participate in cardiac autonomic dysfunction.

In obese individuals, fat deposits in any part of the upper airway, increasing the total volume of soft tissue within the maxilla-mandibular enclosure, narrowing the pharynx and increasing the collapsibility of the upper airways, thereby predisposing to OSA. Chronic intermittent hypoxia, elicited by OSA episodes, represents a key event that has been shown to influence function of adipocytes and appears to be a key factor in adipocyte dysfunction, proliferation and hypertrophy [30]. As such, adiposity is stimulated increasing further fat accumulation in the neck that contributes to upper airway narrowing, and thus to OSA severity. Nevertheless, while the causal link between EAT accumulation and cardiac autonomic dysfunction is clear, it remains unknown whether nocturnal hypoxemic burden contributes to the generation of epicardial fat in OSA patients.

Our study suggests that HRR at the first minute is blunted in obese patients with severe OSA. Previous studies that have examined HRR in OSA also concluded that only obese patients with OSA have an attenuated HRR [15, 16, 27]. A key question is hence whether HRR in OSA is of any clinical value. Clinical significance of HRR-1 is supported by findings showing that attenuated HRR-1 is a powerful independent predictor of cardiovascular and all-cause mortality both in health and patient populations [13]. Overall, HRR-1 should be considered as a clinical tool to evaluate global risk in OSA.

Study limitation

This study has several limitations. Our study is first limited by a small sample size of obese participants. Second, there are several limitations to the measurement of EAT thickness by transthoracic echocardiography, technique which only partially measures EAT. In contrast, both EAT thickness and volume can be more precisely and accurately measured by cardiac computed tomography and magnetic resonance imaging than by echocardiography. However, EAT measurement by echocardiography has the advantage of being an easy and readily available technique in our local setting, all while being a validated technique

with excellent reproducibility. High fidelity of EAT with measurements obtained from magnetic resonance imaging have been reported. These characteristics are welcome regarding the purely observational purpose of our clinical study. Third, echocardiography as applied technique to assess fat tissue surrounding the heart may not be able to distinguish epicardial adipose tissue that adheres to the outside of the myocardium and pericardial fat adhering to the pericardium. Likewise, distinction between atrial and ventricular epicardial fat deposits was not made during our study. Owing to their local (direct) cardiac effects, atrial and ventricular epicardial fat can differentially impact atrial and ventricular structure and function. In particular, elective accumulation of EAT surrounding the atria, instead of the entire heart, may be responsible for autonomic dysfunction and atrial fibrillation. Fourth, we did not include a group of control patients. Furthermore, autonomic measurements and power spectrum analysis of HR variability during exercise and post-exercise recovery period were not performed in our study. It was, however, our objective to use noninvasive and relatively simple procedures such as HRR to evaluate cardiac autonomic dysfunction in our patients. Finally, our study was performed at a single tertiary-care health-screening center. As such, potential biases with respect to study population sampling may have existed.

Conclusion

Aerobic capacity and peak exercise D[a-v]O2 are impaired in obese OSA patients, suggesting abnormal peripheral oxygen extraction. Thickness of EAT is an independent marker of post-exercise HRR, which is a noninvasive marker of autonomic nerve dysfunction accompanying poor cardiovascular prognosis in obese patients. Consistently with what is described in medical literature, AHI and type 2 diabetes were also significantly associated to post-exercise HRR in our study.

Our report may set precedence for the use of HRR following sub-maximal exercise and EAT (measured by echocardiography) as index of autonomic nerve activity derangement. This may help determine noninvasive prognosis for obese patients with OSA.

Acknowledgements This work was supported by a grant from the Clinical Research and Innovation Unit (DRCI) of the University Hospital of Martinique (2016).

Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

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