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Voluntary breath-holding duration in healthy subjects with obesity: Role of peripheral chemosensitivity to carbon dioxide

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ABSTRACT

Objective: The present study aimed to explore the peripheral chemoreflex sensitivity in healthy subjects with high body mass index (BMI).

Methods: We studied 26 healthy men with obesity and 23 healthy men without obesity. All participants performed the breath-holding test in the morning, and the single-breath carbon dioxide (SB-CO_2) test on the next day.

Results: The sensitivity of peripheral chemoreceptors to CO_2 did not differ between two groups (P = .47). In contrast, the duration of breath-holding was significantly lower in participants with elevated BMI (40.6 ± 10.5 s *versus* 47.2 ± 8.7 s; P < .05). In the multifactor regression model, only differences in waist-to-hip ratio (WHR) and SB-CO_2 remained statistically significant (R^2 for the model = 0.62, P < .001).

Conclusions: The sensitivity of peripheral chemoreflex to CO_2 was preserved in healthy men with obesity. The higher sensitivity of peripheral chemoreflex to CO_2 and higher WHR were associated with a decrease in the duration of voluntary apnea in subjects with obesity.

1. Introduction

The role of peripheral chemoreflex sensitivity in the pathogenesis of various pathological conditions has garnered much attention in recent years. Changes in a level of activity of the receptors of carotid sinus increase the tone of the sympathetic nervous system (Kara et al., 2003) and decrease the sensitivity of the arterial baroreflex (Halliwill et al., 2003; Ponikowski et al., 1997). This consequently leads to the progression of chronic diseases and worsens the prognosis by increasing the risk of adverse cardiac events (Giannoni et al., 2009). Thus, the sensitivity of peripheral chemoreflex is a marker of disturbances in reflex regulation of cardiorespiratory system. Obesity is associated with chronically elevated sympathetic activity that negatively affects the cardiovascular system (Esler et al., 2006). Thus, we predicted impaired reflex responses from peripheral chemoreceptors in participants with obesity.

Most previous studies investigating the sensitivity of the peripheral chemoreflex, including studies in patients with obesity, typically performed a hypoxic test (Cormack et al., 1957; Edelman et al., 1973; Weil et al., 1970). However, persistent hypoxia may occur when employing certain techniques that can increase the risk of adverse events related to hypoxia, especially in high-risk patients. The single-breath carbon dioxide (SB-CO_2) test, designed by McClean et al. (1988), is an alternative method for evaluating the sensitivity of peripheral chemoreflex, and is relatively safe compared to hypoxic tests. In addition, the SB-CO_2 test has been validated in practice. To date, there are no reports on the peripheral chemoreflex sensitivity to CO_2 in participants with normocapnic obesity. Despite its relative safety, the SB-CO_2 test has been associated with impaired gas exchange, and requires sophisticated equipment, which limits its application in routine practice. On the other hand, the test has been demonstrated to be a useful tool in the assessment of peripheral chemosensitivity in healthy participants (Ilyukhina and Zabolotskikh, 2000). In contrast, disturbances of respiratory biomechanics and metabolism can potentially affect the duration of voluntary apnea in participants with obesity.

Therefore, the present study aimed to explore the peripheral chemoreflex sensitivity in healthy participants across a broad range of body mass index (BMI). More specifically, we attempted (1) to compare chemosensitivity between two groups of participants, one group with normal and the other group with high BMI, and (2) to explore the relationship between chemosensitivity and the duration of voluntary breath-holding in the entire sample studied.

2. Methods

2.1. Study protocol

We studied 26 healthy men with obesity class 1–2 (BMI 25–39.9 kg/m^2) and 23 men without obesity (BMI < 25 kg/m^2) matched for age

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(mean age, 39 ± 4.5 years). The mean BMI was 36.7 ± 3.0 kg/m^2 for the participants with obesity and 22.5 ± 1.4 kg/m^2 for the participants without obesity. All participants were non-smokers and normotensive, and none of them were under any medications or had a history of acute/chronic illnesses or alcohol/drug addictions. Patients with obstructive sleep apnea were also excluded. Informed written consent was obtained from all participants. The study was approved in 2017 by the institutional Ethics Committee of Kuban State Medical University.

2.2. Measurements and procedures

All participants were instructed to refrain from caffeine and alcohol for at least 12 h before study. Anthropometric characteristics, including height (cm), weight (kg), waist circumference (cm), and hip circumference (cm) were measured using standard methods. The BMI (kg/m^2) and waist-to-hip ratio (WHR) were calculated according to the standard formulae [BMI = weight (kg)/height (m^2); WHR = waist circumference (cm)/hip circumference (cm)], while the respiratory function was evaluated using spirometry.

In all participants, breath-holding test was performed in the morning before breakfast. The SB-CO_2 test was performed next day.

The single-breath carbon dioxide test was performed as follows (McClean et al., 1988; Chua and Coats, 1995). The participant's nose was clamped using a soft grip. Breathing through the mouth was monitored using a mouth-piece connected to a pneumatic respiratory valve separating the inhaled gas mixture from the exhaled air. The inspiratory port was connected to a T-shaped valve in such a way that ventilation was carried out from either a rubber bag or a 2-L tank, which was filled after each inhalation with a gas mixture containing 13% CO_2 or atmospheric air. After a brief period of eupnoea (approximately 5 min) in the expiratory phase, the T-shaped valve was switched to breathing a mixture with high CO_2 content; the next breath was taken using this mixture. Subsequently, the valve was switched to atmospheric air. On average, 10 breaths of the hypercapnic mixture were taken with intervals of 2-min of breathing room air. The respiratory rate and tidal volume were estimated breath-to-breath with the calculation of minute ventilation (MV). The CO_2 fraction in the exhaled mixture was measured using a sidestream gas analyser (Nihon Kohden, Japan). As a control, the average MV was calculated from the data of the last five breaths before breathing the hypercapnic mixture. Similarly, the average feedback of end-tidal CO_2 fraction ($FetCO_2$) was determined during these breaths and used as the control $FetCO_2$. The ventilation response to a hypercapnic stimulus was determined as the average of the two highest rates of MV (during the first 20 s after the stimulus; breaths beyond this time-point were excluded to minimize the contribution of central chemoreception). Poststimulus $FetCO_2$ was also assessed during these cycles. The ventilation response to breathing a hypercapnic mixture was calculated using the following formula: [poststimulus MV − control MV]/[(poststimulus $FetCO_2$ − control $FetCO_2$) × (Patm − 47)], where *Patm* represents the atmospheric pressure in mmHg and 47 is the saturated water vapour pressure in mmHg. The median of all 10 episodes was considered as the sensitivity of the peripheral chemoreflex, and was expressed in L/min/mmHg.

The breath-holding test was carried out as follows (Ilyukhina and Zabolotskikh, 2000). The voluntary breath-holding duration was assessed three times, with 10-min intervals of normal resting breathing. After inspiration of an atmospheric air volume equal to 2/3 of the vital lung capacity ± 15% (under spirometry control), the participant was instructed to hold his breath and the duration of voluntary apnea was measured from the beginning of the voluntary inspiration until reflex contractions of the diaphragm were noted by palpation. Subsequently, the mean value of three samples was calculated. The test was performed at a constant room temperature (22 °C).

2.3. Statistical analysis

Data showed normal distribution (Kolmogorov–Smirnov test) and were thus presented as mean ± standard deviation. The Student's *t*-test was used to evaluate differences between groups. The correlations between the variables were tested using univariate models (Pearson's linear correlation coefficients) and multivariate models. Statistical significance was set at $P < .05$.

3. Results

3.1. Clinical characteristics in participants with normal versus high BMI

The participants with obesity were characterized by higher body weight, higher BMI, and higher WHR (all $P < 0.001$). In contrast, these participants had lower values of vital capacity, forced vital capacity, and forced expiratory volume in the first second (all $P < .05$). The respiratory rate was significantly lower in participants with lower BMI. There were no statistical differences in other respiratory parameters between the two groups (Table 1).

3.2. Peripheral chemoreflex sensitivity in participants with normal versus high BMI

Although the sensitivity of peripheral chemoreceptors to CO_2 did not differ between the two groups ($P = .47$), the duration of breath-holding was significantly lower in participants with obesity ($P < .05$; Table 2).

We found a significant inverse correlation between the results of two tests. This correlation was greater in participants with lower BMI than in participants with obesity ($r = -0.83$, $R^2 = 0.69$, $P < .001$ *versus* $r = -0.57$, $R^2 = 0.32$, $P = .003$).

3.3. Correlations between BHD and selected variables

To investigate the possible determinants of decreased BHD in participants with obesity, we performed correlation analysis. The BHD was negatively correlated to several anthropometric variables in participants with obesity (Table 3), including BMI ($P = .06$), WHR ($P < .05$), initial $PetCO_2$ ($P < .05$), and SB-CO_2 test ($P < .05$).

3.4. Multivariate regression

The multivariate regression model included all the variables that appeared to correlate significantly with BHD in the univariate models. There were no highly interrelated (arbitrary cut-off: $r = 0.70$)

Table 1
Basic parameters in patients with normal and high BMI.

Parameter	Normal BMI	High BMI	P Value
Age, years	39.4 ± 4.4	38.6 ± 4.7	.55
Weight, kg	73.6 ± 4.0	108.7 ± 9.3	< .0001
WHR	0.86 ± 0.06	1.02 ± 0.06	< .0001
BMI, kg/m^2	22.5 ± 1.4	36.7 ± 3.0	< .0001
Height, cm	1.77 ± 0.06	1.74 ± 0.05	.11
SpO_2, %	98.6 ± 1.1	98.4 ± 1.1	.5
$PetCO_2$, mmHg	35.8 ± 1.5	35.8 ± 1.7	.97
VC, % predicted	97.7 ± 3.3	93.5 ± 6.0	.0037
FVC, % predicted	95.0 ± 2.6	89.8 ± 7.0	.012
FEV_1, % predicted	95.0 ± 2.3	89.8 ± 6.2	< .0001
FEV_1/FVC, % predicted	0.98 ± 0.05	0.99 ± 0.04	.48
MV, L/min	6.02 ± 0.83	6.27 ± 0.88	.33
Breathing rate, min^{-1}	11.3 ± 2.1	12.7 ± 2.5	.03

BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MV, minute ventilation; $PetCO_2$, end-tidal carbon dioxide partial pressure; SpO_2, oxygen saturation; VC, vital capacity; WHR, waist-to-hip ratio.