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Inspiratory muscle metaboreflex increases blood pressure in eutrophic and obese individuals

Metaborreflexo inspiratório eleva a pressão arterial em indivíduos obesos e eutróficos

Metaborreflejo inspiratorio aumenta la presión arterial en individuos obesos y eutróficos

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Abstract

Introduction: Metaboreflex, activated by the accumulation of metabolites during exercise, leads to peripheral vasoconstriction, increasing the blood pressure. Obese individuals have decreased inspiratory muscle endurance, which suggests an early accumulation of metabolites and, consequently, alterations in inspiratory muscle metaboreflex. **Objective:** To compare the hemodynamic responses mediated by the inspiratory muscle metaboreflex in obese and eutrophic individuals. **Method:** Twenty obese (31 ± 6 years old, ten males, 37.5 ± 4.7 kg/m^2) and twenty eutrophic individuals (29 ± 8 years old, ten males, 23.2 ± 1.5 kg/m^2) were included in this study and submitted to respiratory muscle strength evaluation through manovacuometry. Inspiratory muscle metaboreflex was induced by resistive exercise at 60% maximal inspiratory pressure sustained until exhaustion. The control protocol consisted of breathing without inspiratory resistance (zero cmH_2O) sustained for 30 minutes. Blood pressure and heart rate were measured throughout the

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protocols, on different days and in a randomized order. **Results:** The inspiratory muscle metaboreflex activation induction protocol led to a similar increase in systolic, diastolic and mean blood pressures, as well as heart rate in obese and eutrophic individuals. As expected, the hemodynamic variables remained unaltered in the control protocol. **Conclusion:** Inspiratory muscle strength did not differ (p = 0.814) between obese and eutrophic individuals. This study suggests that obese individuals present hemodynamic responses induced by the inspiratory muscle metaboreflex, similar to eutrophic individuals.

Keywords: Obesity. Respiration. Blood Pressure.

Resumo

Introdução: *O metaborreflexo, ativado pelo acúmulo de metabólitos durante o exercício, ocasiona vasoconstrição periférica, resultando em elevação da pressão arterial. Indivíduos obesos apresentam redução da endurance muscular inspiratória, sugerindo um acúmulo precoce de metabólitos e, consequentemente, alterações no metaborreflexo inspiratório.* ***Objetivo:*** *Comparar as respostas hemodinâmicas mediadas pelo metaborreflexo inspiratório em indivíduos obesos e em eutróficos.* ***Método:*** *Participaram do estudo vinte indivíduos obesos (31 ± 6 anos, dez homens, 37,5 ± 4,7 kg/m^2) e vinte eutróficos (29 ± 8 anos, dez homens, 23,2 ± 1,5 kg/m^2) submetidos a avaliação da força muscular respiratória através de manovacuometria. O metaborreflexo inspiratório foi induzido através de exercício resistido a 60% da pressão inspiratória máxima mantido até a exaustão. O protocolo controle consistiu na respiração sem resistência inspiratória (zero cmH_2O) mantida durante 30 minutos. A pressão arterial e a frequência cardíaca foram mensuradas ao longo dos protocolos, realizados em dias distintos e em ordem randomizada.* ***Resultados:*** *O protocolo de indução do metaborreflexo inspiratório induziu aumento das pressões arteriais sistólica, diastólica e média, bem como da frequência cardíaca semelhante em indivíduos obesos e eutróficos. Conforme esperado, no protocolo controle as variáveis hemodinâmicas permaneceram inalteradas.* ***Conclusão:*** *A força muscular inspiratória não variou (p = 0,814) entre indivíduos obesos e eutróficos. Este estudo sugere que indivíduos obesos apresentam respostas hemodinâmicas, induzidas pelo metaborreflexo inspiratório, semelhantes aos indivíduos eutróficos.*

Palavras-chave: *Obesidade. Respiração. Pressão arterial.*

Resumen

Introducción: *El metaborreflejo, activado por el acúmulo de metabolitos durante el ejercicio, lleva a la vaso constricción periférica resultando en aumento de la presión arterial. Individuos obesos presentan menor resistencia muscular inspiratoria, lo que sugiere un acúmulo precoz de metabolitos y, consecuentemente, alteraciones en el metaborreflejo inspiratorio.* ***Objetivo:*** *Comparar las respuestas hemodinámicas mediadas por el metaborreflejo inspiratorio en individuos obesos y eutróficos.* ***Método:*** *Se incluyeron en este estudio veinte individuos obesos (31±6 años, 10 hombres, 37,5 ± 4,7 kg/m2) y veinte individuos eutróficos (29 ± 8 años, 10 hombres, 23,2 ± 1,5 kg/m2), los cuales se sometieron a evaluación de la fuerza muscular respiratoria mediante manovacuometría. El metaborreflejo inspiratorio se indujo mediante ejercicio resistido al 60% de la presión inspiratoria máxima sostenida hasta el agotamiento. El protocolo de control consistió en respirar sin resistencia inspiratoria (cero cmH2O) mantenida durante 30 minutos. La presión arterial y la frecuencia cardíaca se midieron a lo largo de los protocolos, que se realizaron en días diferentes y en orden aleatorio.* ***Resultados:*** *El protocolo de inducción del metaborreflejo inspiratorio llevó a un aumento similar en las presiones sistólica, diastólica y media, así como a la frecuencia cardíaca en individuos obesos y eutróficos. Como esperado, las variables hemodinámicas permanecieron inalterables en el protocolo de control.* ***Conclusión:*** *La fuerza muscular inspiratoria no difirió (p = 0,814) entre individuos obesos y eutróficos, lo que apunta que los individuos obesos presentan respuestas hemodinámicas inducidas por el metaborreflejo inspiratorio similares a los individuos eutróficos.*

Palabras clave: *Obesidad. Respiración. Presión arterial.*

Introduction

Metaboreflex, activated by the accumulation of metabolites during exercise, stimulates chemosensitive afferents, mainly type III and IV, which cause peripheral vasoconstriction, by increasing sympathetic nerve activity, resulting in elevated blood pressure (BP) [1, 2] and blood flow redistribution from inactive muscles to exercising muscles [1], which is a determining factor in exercise tolerance [3].

Induction of metaboreflex in peripheral muscles in normotensive obese women produces a lower increase in muscle sympathetic nerve activity than in normotensive eutrophic women [4]. In contrast, obesity associated with metabolic syndrome seems to induce exaggerated vasoconstriction during metaboreflex activation in peripheral muscles, while obese patients with adequate metabolic control have unchanged metaboreflex [5]. Interestingly, Limberg et al. [6] reported that young adults with metabolic syndrome showed sympathetic and BP responses during peripheral muscle metaboreflex activation, similarly to healthy subjects. In addition to the possible changes in cardiovascular responses during metaboreflex activation, obesity could lead to respiratory changes [7-10]. In an animal model study, greater susceptibility to acute lung injury was found in obese rats [11]. In addition, there seems to be a higher prevalence of pulmonary hypertension in obese individuals, probably due to inflammatory responses in obesity [12].

Pulmonary capacity may be influenced by fat deposition in the abdominal cavity wall, which results in reduced lung function and respiratory muscle dysfunction [7], leading to adaptive ventilatory strategies during exercise, such as increased metabolic demand and respiratory work [13]. These changes in inspiratory muscle function could influence circulatory responses during fatiguing resistive inspiratory work by induction of inspiratory muscle metaboreflex activation, as observed in congestive heart failure [14, 15] and diabetes mellitus [16]. However, hemodynamic responses to inspiratory muscle metaboreflex activation have not been studied in obese individuals. In a recent study, it was shown that obese individuals have reduced inspiratory muscle endurance assessed by a progressive increase in workload [17], which could suggest an early accumulation of metabolites, leading to changes in inspiratory muscle metaboreflex [14, 18, 19]. Accordingly, the objective of this study was to compare hemodynamic responses mediated by inspiratory muscle metaboreflex activation in obese and eutrophic individuals.

Methods

Sample

Twenty obese individuals (31 ± 6 years old, ten men, 37.5 ± 4.7 kg/m^2) and twenty lean individuals (29 ± 8 years old, ten men, 23.2 ± 1.5 kg/m^2) were recruited by convenience sampling. All subjects were sedentary non-smokers and free of cardiovascular, pulmonary, neuromuscular and infectious diseases. Obese individuals with body mass index (BMI) > 30 kg/m^2 and eutrophic individuals with BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2, aged 18 to 46 were included. Lean subjects were matched for gender and age in relation to the obese ones. The study was approved by the ethics committee of the University of Cruz Alta (Unicruz) and registered in the Clinical Trials Database under no. NCT03056937. All individuals signed an informed consent formulary.

Study protocol

All subjects were in fasting and were instructed to avoid caffeinated and alcoholic beverages for at least 12 hours and to refrain from exercise for at least 48 hours prior to the protocols. The protocols were performed in the morning, in a temperature-controlled room at 22 °C (Figure 1).

Protocols for inducing inspiratory muscle metaboreflex activation and the control protocol (no inspiratory load) were performed on separate days and in order according to simple randomization using envelopes containing the names of the protocols on folded papers, which were opened immediately before the protocol. Firstly, with the individual in a sitting position, maximal inspiratory pressure (MIP) was determined using a vacuum manometer (Famabras, Brazil), as previously established [18]. Predicted MIP and MEP (maximal respiratory pressure) values for gender and age were calculated using the equation of Neder et al. [19]. Subsequently, the individuals were placed in a semi-sitting position (Fowler, 45°), resting for 15 min. Next, BP, respiratory rate (RR), heart rate (HR) and peripheral oxygen saturation (SpO_2) were

determined during 5 min of spontaneous breathing. The protocol for induction of inspiratory muscle metaboreflex was performed with subjects using a nose clip, while continuously breathing through a two-way valve (Model 2600; Hans Rudolph, Shawnee, KS, USA) connected to an inspiratory muscle trainer (Powerbreathe, Southam, UK) in the inspiratory pathway, adjusted to 60% MIP. The inspiratory pressure in the mouth was continuously evaluated using a vacuum manometer. Subjects were instructed to maintain a RR of 15/min and an inspiratory time/total time ratio of 0.75 following a light and auditory signal from a metronome [18, 20, 21]. The test was stopped when the inability to generate the target inspiratory pressure was detected in three consecutive inspiratory efforts [18]. Inspiratory effort was assessed using a Borg scale of 6 to 20 points. Blood pressure, HR, SpO_2 and RR were measured every minute at baseline and during the protocol. The control protocol adopted the same procedures as the protocol for induction of inspiratory muscle metaboreflex activation, but inspiration was performed without resistance (zero cmH_2O) and for 30 min.

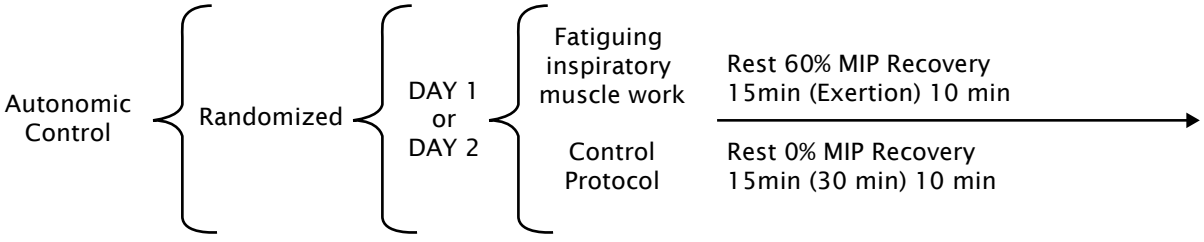

Figure 1 – Illustrative representation of the study design.

In both protocols, CO_2 was added when the end-tidal carbon dioxide pressure ($PetCO_2$) dropped above 2 mmHg in relation to baseline values.

Variables analyzed

RR was determined by calculating the respiratory flow integral at a sampling rate of 1 kS. HR was measured noninvasively (Bio Amp ML132; Adinstruments, Sydney, Australia), $PetCO_2$ via capnography (CO_2 Gas Analyzer-17630, Vacumed, Silver Edition, USA), systolic (SBP) and diastolic (DBP) blood pressure by means of a mercury sphygmomanometer positioned on the forearm [22], and SpO_2 through a middle-finger pulse oximeter (Contec CMS50C). All signals were recorded, digitized and digitally stored at 500 Hz using LabChart 8 acquisition software (Adinstruments, Bella Vista, Australia). The variables were presented as a mean of 5 minutes of baseline, a mean of 60 seconds for the first and second minutes of exercise and the last minute of failure to maintain the task [18].

Statistical analysis

A sample size of 40 individuals was calculated to detect changes in SBP of 10 mmHg and standard deviation of 12 mmHg with statistical power of 90% and alpha error of 0.05. Data were expressed as mean and standard deviation. Analysis was performed using SPSS version 22 software. Data were normally distributed as determined by the Shapiro-Wilk test. Two-way analysis of variance was used to determine the effects of inspiratory muscle metaboreflex activation in obese and lean individuals; $p < 0.05$ was considered significant.

Results

Obese individuals were similar to the eutrophic ones in relation to age ($p = 0.38$). BMI was significantly higher in obese subjects ($p = 0.001$), as expected. Inspiratory muscle strength expressed as absolute values of MIP was similar in obese (121 ± 118 cmH_2O) and lean (118 ± 31 cmH_2O, $p = 0.81$) individuals. The percentage of MIP predicted for gender and age did not differ between obese ($105 \pm 26\%$) and lean ($104 \pm 26\%$, $p = 0.67$) individuals.

SBP, DBP, MBP (mean blood pressure) and HR increased similarly in the two groups during the protocol to induce inspiratory muscle metaboreflex activation. SpO_2 remained unchanged in both groups. As expected, there was an increased perceived

effort (Borg scale), which was similar in obese and lean subjects (Table 1). The duration of inspiratory muscle metaboreflex activation in obese individuals was reduced (338 ± 236 seconds) compared to lean individuals (631 ± 468 seconds), p = 0.019.

During the control protocol there was no change in SBP, DBP, MBP and HR in either group. SpO_2 showed an increase during the protocol in both groups. Perceived effort increased similarly in both groups (Table 1).

Table 1 – Hemodynamic responses to protocols to induce inspiratory muscle metaboreflex activation and control protocol

Induction of inspiratory muscle metaboreflex activation (60% MIP)					
	Groups	**Baseline**	**1 min**	**2 min**	**Final**
SBP (mmHg)	Obese	129 ± 22†	131 ± 25	132 ± 26*	132 ± 25*
	Lean	114 ± 10	118 ± 10	121 ± 12*	122 ± 11*
DBP (mmHg)	Obese	85 ± 15†	91 ± 21*	88 ± 20*	89 ± 20*
	Lean	76 ± 7	82 ± 11*	84 ± 13*	85 ± 9*
MBP (mmHg)	Obese	114 ± 19	118 ± 23*	117 ± 23*	118 ± 22*
	Lean	102 ± 8	106 ± 9*	109 ± 11*	109 ± 9*
HR (bpm)	Obese	78 ± 11	87 ± 12*	87 ± 10*	86 ± 12*
	Lean	71 ± 13	84 ± 14*	84 ± 13*	85 ± 10*
SpO2 (%)	Obese	98 ± 1	98 ± 1	98 ± 1	97 ± 3
	Lean	98 ± 1	98 ± 2	98 ± 2	97 ± 3
Borg scale (effort)	Obese	2.9 ± 4.8	4.3 ± 4.1*	5.2 ± 5.5*	7.2 ± 6.5*
	Lean	3.1 ± 3.9	4.3 ± 2.8*	4.5 ± 2.4*	7.4 ± 4.8*
Control protocol (zero cmH2O)					
	Groups	**Baseline**	**1 min**	**2 min**	**Final**
SBP (mmHg)	Obese	130 ± 22	128 ± 26	129 ± 26	131 ± 29
	Lean	116 ± 11	117 ± 11	120 ± 12	115 ± 12
DBP (mmHg)	Obese	86 ± 15†	86 ± 12	87 ± 12	88 ± 22
	Lean	77 ± 8	73 ± 18	80 ± 9	80 ± 8
MBP (mmHg)	Obese	115 ± 19†	114 ± 21	115 ± 20	117 ± 26
	Lean	103 ± 9	102 ± 10	106 ± 11	103 ± 10
HR (bpm)	Obese	77 ± 13	78 ± 16	80 ± 16	78 ± 16
	Lean	79 ± 13	70 ± 20	75 ± 12	75 ± 12
SpO2 (%)	Obese	98 ± 1	99 ± 0,7*	99 ± 0.7*	99 ± 1*
	Lean	99 ± 0,7	99 ± 1*	99 ± 0.5*	99 ± 1*
Borg scale (effort)	Obese	3.4 ± 4.6	2.8 ± 4.1	3.5 ± 3.8	4.4 ± 4.7*
	Lean	3.5 ± 3.7	2.8 ± 3.2	3.3 ± 2.7	4.4 ± 3*

Note: MIP: maximal inspiratory pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; HR: heart rate; SpO_2: peripheral oxygen saturation; *$p < 0.05 \times$ rest; †: $p < 0.05 \times$ lean.

Discussion

This pioneering study suggests that obese individuals have similar hemodynamic responses to inspiratory muscle metaboreflex activation as lean individuals. Fatiguing resistive inspiratory muscle work, performed with a constant load of 60% MIP, leads to the accumulation of metabolites that stimulate the metaboreceptors to induce sympathetic activation and peripheral vasoconstriction, increasing BP [2], suggesting that the increase in BP found in our study was mediated by inspiratory muscle metaboreflex.

Although hemodynamic responses during fatiguing inspiratory muscle work were similar to obese and lean individuals, the physiological mechanism may differ between the groups. In a previous study, handgrip exercise increased MAP in obese and lean children similarly, but the increase in BP in lean children was mediated by increased peripheral vascular resistance, while it was induced

by increased systolic volume in obese children [23]. In addition, the manner in which muscle metaboreflex activation is induced (during or after handgrip) determines the mechanism of BP elevation [24], and body position may also influence the cardiovascular responses to muscle metaboreflex induction, which have shown to be attenuated in the supine position compared to the sitting position [25]. In our study, the semi-sitting position (Fowler, 45°) was used according to previous studies [5, 21], but there are no studies demonstrating the influence of body position in relation to the induction of inspiratory muscle metaboreflex. Obesity, when associated with metabolic syndrome, could influence hemodynamic responses during fatiguing inspiratory muscle work. This issue is reported in the literature only in relation to peripheral muscle exercise. In adult subjects [5], the presence of metabolic syndrome induces exaggerated vasoconstriction during peripheral metaboreflex activation; however, metabolically healthy obese individuals appear to have unchanged peripheral metaboreflex compared to healthy non-obese subjects. In contrast, another study [6] demonstrated that young adults with metabolic syndrome have sympathetic and BP responses during peripheral metaboreflex activation, similar to healthy subjects. In this study, only nine obese individuals had metabolic syndrome, precluding sufficient statistical power to determine the effects of metabolic syndrome on hemodynamic responses to inspiratory muscle metaboreflex activation induced by exercise. Future studies could investigate the influence of metabolic syndrome on inspiratory muscle metaboreflex-induced hemodynamic responses.

Recent studies indicate that both inspiratory [26, 27] and peripheral muscle [4, 28] metaboreflex may be influenced by gender and age. In young individuals, women have a lower inspiratory metaboreflex in relation to men [26, 27]. In obese women, peripheral muscle metaboreflex appears to be attenuated [4], while in postmenopausal sarcopenic and presarcopenic women it may be exacerbated due to increased arterial stiffness [28]. Age seems to influence hemodynamic responses mediated by inspiratory metaboreflex only in women, as shown in the study by Smith et al. [29], in which postmenopausal women had a greater increase in MAP and peripheral vascular resistance, as well as a greater reduction in peripheral blood flow during resistive inspiratory exercise than premenopausal women. In a study comparing healthy young men (mean age of 24) with older men (mean age of 59), it was concluded that the neural interaction between the arterial baroreflex and peripheral muscle metaboreflex in the regulation of sympathetic activity was preserved in older individuals [30]. Another study with overweight and obese men found an exacerbated cardiovascular response, with greater afterload and systemic arterial stiffness, to induction of the muscle metaboreflex associated with a cold exposure test [31]. The findings of this study cannot be attributed to gender or age, as there was a homogeneous distribution between obese and lean individuals.

Future studies could investigate the physiological mechanisms related to inspiratory muscle metaboreflex activation by measuring peripheral blood flow and muscle sympathetic nerve activity, as well as the implications of inspiratory muscle metaboreflex for physical performance in obese individuals.

Conclusion

This study suggests that obese individuals with preserved inspiratory muscle strength have similar hemodynamic responses induced by inspiratory muscle metaboreflex to lean individuals.

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