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ORIGINAL ARTICLE

The metabolically healthy but obese postmenopausal woman presents a favourable heart rate variability profile

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Abstract

Objective. The purpose of this study was to investigate the heart rate variability (HRV) profile in obese women displaying the metabolically healthy but obese (MHO) phenotype. *Design*. We studied 47 obese, sedentary postmenopausal women. Subjects were classified as MHO or at risk based on insulin resistance as assessed with the homeostatic model assessment (HOMA) index. Subjects were divided into tertiles according to HOMA values. Subjects in the lower tertile were categorised as MHO while subjects in the upper 2 tertiles represented at risk subjects. Outcome measures were heart rate variability factors (RR intervals, SDNN, LF, HF, pNN50, RMSSD), body temperature, body composition (DEXA) and a lipid profile as well as glucose and insulin. *Results*. MHO individuals had significantly lower resting heart rate, body temperature, lean body mass as well as fasting insulin and HOMA levels compared to at risk subjects ($p < 0.05$). In addition, RR intervals, SDNN and LF were significantly higher in MHO individuals ($p < 0.05$). Moreover, stepwise regression analysis showed that SDNN was an independent predictor of the variation in HOMA in our cohort. *Conclusion*. Results of the present study indicate that postmenopausal women displaying the MHO phenotype present a favourable HRV profile. Therefore, higher HRV could be associated, at least in part, in the protective profile of MHO individuals.

Key words: *RR intervals, resting heart rate, body temperature, postmenopausal women, HOMA, Polar S810*

Obesity is associated with an increased risk of developing cardiometabolic disturbances such as dyslipidemia, insulin resistance and hypertension, which could increased risk of type 2 diabetes and cardiovascular diseases (1). However, a unique subset of obese individuals has been well described in the medical literature that appears to be protected or more resistant to the development of metabolic complications associated with obesity (2). These individuals, now known as "metabolically healthy but obese" (MHO), despite having excessive body fatness, display a favourable metabolic profile characterised by high levels of insulin sensitivity, no hypertension, as well as a favourable immune, hepatic enzyme, lipid, inflammation and hormonal profiles (3). Evidence suggests that MHO individuals may account for as much as 30% of the obese population (4). Furthermore, a longitudinal study reported that the protective metabolic profile observed in MHO individuals was associated with lower incidences of type 2 diabetes and cardiovascular diseases (5) as well as mortality (6). Despite a general clinical awareness of the MHO individual, there is only a rudimentary understanding as to the constellation of factors or mechanisms underlying this "protective profile".

Several studies have shown that lower heart rate variability (HRV), which may reflect lower cardiac autonomic nervous system function/activity, could be associated with obesity, insulin resistance and the metabolic syndrome (7–9). In addition, decreased HRV has been reported to be associated with an increase risk of developing cardiovascular diseases and mortality (10,11). Based on the previous studies, evidence may suggest that MHO individuals may be associated with a favourable HRV profile. Therefore, the purpose of this study was to investigate the HRV

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profile in MHO and at risk subjects. We hypothesised that MHO individuals would present a more favourable HRV profile than at risk subjects.

Methods

Subjects

The study sample consisted of 47 obese postmenopausal sedentary women aged between 50 and 70 years old. This study was approved by the Institut de Recherches Cliniques de Montréal ethic committee. After reading and signing the consent form, each participant was invited to the Institut de Recherches Cliniques de Montréal for a series of tests. Methods for blood samples (fasting triglycerides, HDL-cholesterol, hsC-reactive protein, apo-lipoprotein B (ApoB), glucose and insulin) were determined as previously described (12). Women were included in the study if they met the following criteria: 1) body mass index between 30 kg/m^2 and 40 kg/m^2; 2) cessation of menstruation for more than one year and a follicle-stimulating hormone level $\geq$30 U/l; 3) sedentary ($<$2 hours a week of structured exercise); 4) non-smokers; 5) low to moderate alcohol consumers ($<$2 drinks/day); 6) no use of hormone replacement therapy and 7) free of known infection, thyroid and inflammatory disease. On physical examination or biological testing, all participants had no history or evidence of: 1) cardiovascular disease, hypertension, peripheral vascular disease or stroke; 2) diabetes (fasting glucose $<$ 7.0 mmol/L and 2-hours post 75 g OGTT $<$ 11.1 mmol/l); and 3) medications that could affect cardiovascular function, hypertension and/or metabolism.

Body composition

Body weight (BW), lean body mass (LBM) and fat mass were measured using dual energy x-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, USA). Standing height was measured using a wall stadiometer (Perspective Enterprises, Michigan, USA). Body mass index [BMI = body weight/height (m^2)] was calculated. Waist circumference was measured with a flexible steel metric tape at the nearest 0.5 cm.

Blood pressure

Sitting blood pressure was determined as the average of the last four readings of five (at 1/min) in the left arm after subjects rested quietly for 10 minutes using a Dinamap automatic machine (Welch Allyn Inc., San Diego, USA).

Heart rate variability and body temperature

Heart rate variability was measured after a 12-hour fasted state using a heart rate monitor (Polar S810, Oy, Finland). Subjects were in a lying position for 10 minutes, completely at rest, without talking. The laboratory room was semi-dark at a temperature of 19–21°C. Thereafter, heart rate variability was measured for 10 minutes. The last five minutes of recording were considered for analysis. Premature beats and artefacts were carefully eliminated with the software provided with the heart rate monitor (Polar Precision Performance SW, version 4.03.050, Polar Electro, Oy, Finland). Resting heart rate, RR intervals, standard deviation normal to normal (SDNN), the proportion derived by dividing NN50 by the total number of NN intervals (pNN50), root mean square of successive differences (RMSSD), low frequency (LF), high frequency (HF) and the ratio of LF/HF were then measured by the heart rate monitor software (Polar Precision Performance SW, version 4.03.050, Polar Electro, Oy, Finland). The frequency spectra were 0.040–0.150 Hz for the low frequency and 0.150–0.400 Hz for the high frequency. It should be noted that assessing HRV using the Polar S810 heart rate monitor has been validated (13). Body temperature taken orally was determined using an Electronic Thermometry (Welch Allyn, Mississauga, ON).

Identification of MHO individuals

MHO individuals were identified using the homeostatic model assessment (HOMA) index for insulin resistance. HOMA was calculated according to the formula: [fasting insulin (µU/ml) $\times$ fasting glucose (mmol/l)]/22.5. Subjects were divided into tertiles according to the HOMA values. Subjects in the lower tertile were categorised as MHO while subjects in the upper 2 tertiles represented at risk subjects. This method was based on two previous studies that used the HOMA index to identify MHO subjects (5,14).

Statistical analysis

Data are expressed as the mean $\pm$ standard deviation. We verified the normality of the distribution of variables with a Kolmogorov-Smirnov test and found that RMSSD, pNN50, LF, HF and LF/HF were not normally distributed. Therefore, we used the log transformed (base 10) for these variables in the analysis. An independent t-test was performed to compare MHO and at risk individuals. Moreover, a stepwise regression analysis was performed to identify predictors of HOMA. Using biologically plausible hypotheses, independent variables considered

in the final model for HOMA were percentage of body fat, waist circumference, triglycerides, HDL-cholesterol, ApoB, body temperature, resting heart rate, RR intervals, SDNN and LF. Statistical analysis was performed using SPSS 17 for Windows (Chicago, IL). Significance was accepted at $p < 0.05$.

Results

Physical and metabolic characteristics of MHO and at risk subjects are presented in Table I. Both groups were comparable for age, body mass index, percentage of body fat, waist circumference, blood pressure, triglycerides, HDL-cholesterol, hsC-reactive protein, ApoB and fasting glucose. By design, HOMA values were significantly lower in MHO individuals ($p < 0.05$). Lean body mass, fasting insulin and body temperature were also significantly lower in MHO subjects ($p < 0.05$).

The heart rate variability profile is shown in Table II. Resting heart rate was significantly lower in MHO women compared to at risk subjects (61.8 ± 6.7 vs. 67.1 ± 7.5 beats/min, respectively, $p < 0.05$). In addition, RR intervals (991.6 ± 111.5 vs. 903.6 ± 110.0 ms, $p < 0.05$), SDNN (53.4 ± 17.3 vs. 37.8 ± 13.5 ms, $p < 0.05$) and LF (875.1 ± 880.3 vs. 418.5 ± 384.5 ms^2, $p < 0.05$) values were significantly higher in MHO compared to at risk subjects. No differences were noted between groups for RMSSD, pNN50, HF and LF/HF. We also performed correlations between HRV measures with BMI and fasting glucose. Results show a significant correlation between LF and BMI ($r = -0.29$; $p < 0.05$) and a significant correlation between HF and fasting glucose ($r = -0.32$; $p < 0.05$).

Table I. Physical and metabolic characteristics of MHO and at risk individuals.

Variables	MHO (n = 16)	At risk (n = 31)
Age (years)	58.4 ± 3.5	60.4 ± 5.3
Body mass index (kg/m^2)	33.2 ± 2.8	34.8 ± 3.6
Waist circumference (cm)	101.7 ± 8.4	105.7 ± 11.1
% Body fat	47.5 ± 4.8	47.3 ± 3.2
Lean body mass (kg)	40.2 ± 3.4*	43.6 ± 4.9
Fasting insulin (μU/ml)	6.8 ± 2.1*	16.2 ± 6.6
Fasting glucose (mmol/l)	5.3 ± 0.6	5.5 ± 0.5
HOMA	1.5 ± 0.6*	4.0 ± 1.7
Total cholesterol (mmol/l)	5.44 ± 0.5	5.50 ± 0.8
LDL-cholesterol (mmol/l)	3.29 ± 0.5	3.33 ± 0.7
HDL-cholesterol (mmol/l)	1.61 ± 0.3	1.55 ± 0.3
Triglycerides (mmol/l)	1.20 ± 0.6	1.35 ± 0.5
ApoB (g/l)	0.90 ± 0.1	0.95 ± 0.2
hsC-reactive protein (mg/l)	2.9 ± 3.3	3.1 ± 3.0
Body temperature (°C)	36.2 ± 0.5*	36.4 ± 0.2
Systolic blood pressure (mmHg)	121.7 ± 11	121.1 ± 13
Diastolic blood pressure (mmHg)	73.9 ± 6.7	75.5 ± 6.8

*Significantly different from at risk individuals ($p < 0.05$).

Table II. Heart rate variability profile of MHO and at risk individuals.

Variables	MHO (n = 16)	At risk (n = 31)
Resting heart rate (beats/min)	61.8 ± 6.7*	67.1 ± 7.5
RR intervals (ms)	992 ± 112*	904 ± 110
SDNN (ms)	53.4 ± 17.3*	37.8 ± 13.5
RMSSD (ms)	37.0 ± 16.5	29.0 ± 16.4
pNN50 (%)	5.9 ± 5.9	3.6 ± 6.5
LF (ms^2)	875 ± 880*	419 ± 385
HF (ms^2)	556 ± 540	376 ± 480
LF/HF	238 ± 299	181 ± 167

*Significantly different from at risk individuals ($p < 0.05$).

Finally, we performed a stepwise regression analysis to identify independent predictors of HOMA. Table III illustrates the summary of the model. Our results show that the variables of ApoB and SDNN were independent predictors of HOMA, collectively explaining 21.2% of the variance ($p < 0.05$). We also performed stepwise regression analysis to identify independent predictors of HRV measures using the same independent variables as HOMA. Variables that predicted HRV measures in our cohort were resting heart rate and HDL-cholesterol.

Discussion

The concept of the MHO individual was first described in the 1980s (4) but little understanding has emerged to explain why MHO individuals seem to be protected from metabolic complications (4). MHO individuals have been shown to display a favourable metabolic profile, despite excessive body fatness (3). To add to the body of literature, we attempted to provide new information on cardiometabolic risk factors that characterise the profile of MHO postmenopausal women such as the HRV profile, which reflects cardiac autonomic nervous system function/activity. We hypothesised that MHO individuals would present a favourable HRV profile compared to at risk subjects. Results from the present study support our hypothesis. That is, we found that resting heart rate values were significantly lower by 7.9% and that RR intervals, SDNN and LF values were significantly higher by 9.7%, 41.3% and 109.1%, respectively, in MHO women compared to at risk obese women. This suggests that higher HRV and lower resting heart rate, despite high levels of body fat and normal blood pressure values, could contribute to the favourable metabolic profile observed in MHO individuals. In support of this concept, we showed that SDNN was an independent predictor of HOMA in our cohort. These findings are in line with previous studies which show that a favourable HRV profile such as lower resting heart rate and higher RR intervals may be associated with

Table III. Stepwise regression analysis regarding independent predictors of HOMA in obese postmenopausal women.

Dependent variable	Step	Independent variable	Partial r^2	Total r^2 cumulative	Beta coefficients	p-value
HOMA	1	ApoB	0.121	0.121	0.371	0.012
	2	SDNN	0.091	0.212	−0.302	0.038

insulin sensitivity (15,16). Moreover, no differences in RMMSD, pNN50 and HF (which may reflect vagal modulation) were observed between MHO and at risk individuals. In addition, results of the present study show significant correlations between LF and BMI as well as HF and fasting glucose. Similar results were observed in the study of Valensi et al. (17). This suggests that fasting glucose and/or BMI may contribute, at least in part, to lower HRV in at risk subjects.

Finally, we observed that body temperature was significantly lower in MHO subjects. This brings new insight as a potential metabolic risk factor for the identification and/or explanation of MHO individuals. However, future studies are needed to confirm this since a small difference (0.2°C) between groups was observed. Interestingly, body temperature and fasting insulin levels have been reported to be reduced after a restricted caloric diet in overweight sedentary men and women (18).

It should be noted that the strength of the present results is reinforced by the fact that the differences in the HRV profile between MHO and at risk subjects are present even in a relatively healthy homogenous population of obese postmenopausal women. It should also be noted that in the present study ApoB accounted for the greatest source of unique variance for insulin resistance and that percentage of body fat was not a predictor. This finding is in line with previous studies which suggest that ApoB levels could be an important factor associated with variations in insulin resistance compared to other metabolic risk factors (19,20).

What are the potential mechanisms that could explain, at least in part, the higher HRV in MHO individuals? It has been shown that carotid intima media thickness (CIMT) values, an early sign of atherosclerosis (21), were lower in MHO subjects compared to at risk individuals (22). However, Marini et al. (22) observed that MHO individuals had an intermediate CIMT between healthy non-obese women and at risk women. In addition, pulse wave velocity, which represents arterial stiffness and is an independent predictor of cardiovascular diseases, was reported to be significantly lower in MHO individuals compared to at risk subjects (23). Interestingly, it has been shown by several studies that lower HRV likely reflects atherosclerosis and/or arterial stiffness (24,25). Therefore, higher HRV in MHO individuals may involve, at least in part, a lesser intima thickness and arterial stiffness. However, we do not exclude the possibility that other factors could also be involved.

The present study has several limitations. First, our cohort is only composed of non-diabetic sedentary obese postmenopausal women. Therefore, our findings are limited to this population. Second, we used a cross-sectional approach, which does not allow us to conclude to any causal associations between insulin resistance and HRV in our cohort. Third, we did not include a control group of non-obese, metabolically healthy women, which could have confirmed that HRV does not differ between MHO subjects and non-obese healthy individuals. Despite these limitations, our results are strengthened by studying a well-characterised cohort. Furthermore, the results of the present study should be considered preliminary but they may hopefully stimulate interest in the need for greater participant characterisation in research protocols. Finally, HOMA and HRV were chosen because they are simple, inexpensive as well as non-invasive methods that may be used as clinical tools by health professionals to identify subjects who are at risk for metabolic complications.

In conclusion, results of the present study indicate that postmenopausal women displaying the MHO phenotype present a favourable HRV profile. That is, higher HRV, in particular a higher SDNN, could be associated, at least in part, in the protective profile of MHO individuals and in turn may be associated to a lower risk for the development of cardiovascular disease. Finally, the measurement of HRV is simple, inexpensive as well as non-invasive and may be used as a clinical tool by health professionals to identify MHO individuals.

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