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Influence of Heart Rate Variability and Psychosocial Factors on Carotid Stiffness, Elasticity and Impedance at Menopause

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Background and Aims. The risk for cardiovascular diseases (CVD) increases after menopause. Heart rate variability (HRV), a measure of autonomic control, is a strong predictor of CVD. We undertook this study to test the association of ultrasound indices of early carotid atherosclerosis with HRV, symptoms, hormonal conditions, metabolic state, indicators of stress, and psychosocial factors in women at peri- and postmenopause, registering ambulatory R-R interval monitoring.

Methods. In a cross-sectional design we studied 100 women at peri- and early postmenopause collecting anthropometry, symptoms, stress-related measurements, metabolic variables, cortisol, FSH and estradiol. We evaluated carotid ultrasonographic indices, and HRV was recorded for 4 h calculating time (SDNN, pNN50, rMSSD) and frequency domains (LF, HF, LF/HF) in women according to menopausal stage, estradiol levels, body mass index and waist circumference.

Results. Carotid indices were similar in peri- and postmenopausal women. For HRV measurements, SDNN was increased at postmenopause. Women with estradiol levels <109.2 pmol/L had increased intima-media thickness (IMT), resistive index, and systolic diameter. Using multivariate analysis, we found the associations of IMT positively with non-HDL-cholesterol, resistive index positively with LF-HRV, but negatively with effort/reward imbalance, carotid β stiffness index inversely with estradiol, and arterial distensibility positively with HF-HRV and creatinine concentrations, but negatively with non-HDL-cholesterol.

Conclusions. Carotid thickness was related mainly with lipid alterations. Indices of early carotid damage were related with various components of HRV as a manifestation of autonomic imbalance, indicating CVD risk. Other factors involved were time since last menses and psychological stress. Low creatinine was associated with diminished carotid distensibility. This suggests that estrogen, lifestyle, behavior and autonomic regulation participate in vascular damage.

Key Words: Arterial stiffness, Sympathetic predominance, Body mass index, Non-HDL-cholesterol, Creatinine, Cardiovascular risk, Menopause.

Introduction

Women at postmenopause have progressive risk for cardiovascular diseases (CVD) and bone mass loss (1–3). Several factors besides estrogen decrease have been proposed to explain CVD risk, such as increased weight, altered lipid and glucose metabolism (4), and low-grade chronic inflammation that may account for endothelial dysfunction (5,6). Perimenopause is a critical stage for CVD risk. However, few studies have addressed the interaction of estrogen decrease with other factors that may enhance artery damage.

Early cardiovascular damage may be evaluated with the ultrasound measurement of the carotid intima-media

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thickness (IMT) (7), which describes structural changes in vessel and arterial wall. Furthermore, the evaluation of arterial elasticity is highly correlated with pathologic changes in the common carotid artery and is accepted as an important predictor for CVD, considering that it is an early step in the process of atherosclerosis (8).

Arterial elasticity includes vascular properties such as distensibility, resistivity, and stiffness (8) and may be altered by aging, diabetes, atherosclerosis, and chronic renal disease.

Resistive index is related to artery function and systemic circulatory adaptations; therefore, it is a hemodynamic measure considered to reflect vascular impedance (8). β stiffness index is a common clinical marker derived from regional diameter and blood pressure change. In contrast, distensibility is a better indicator of the artery's elasticity that decreases with age, whereas diameter increases (9). Therefore, endothelial dysfunction reduces compliance (increases arterial stiffness), especially in the smaller arteries. Increased arterial stiffness is an important component of CVD risk (10).

Early vascular damage at menopause is associated with complexly related factors such as estrogen deprivation through pathways not well defined (11). The stress response is also involved in CVD (12). Physical and emotional symptoms, mainly hot flashes and depressive mood, have been related to vascular damage (3,13). Because vasomotor symptoms are accompanied by autonomic changes, its possible association with decreased cardiac autonomic regulatory function has been suggested (14). Thus, menopause may have a negative effect on the elastic properties of the vessels (15) and time since menopause is inversely related to the pulsatility index of the carotid (16). Recently, preclinical carotid artery abnormalities have been associated with obesity at postmenopause (17).

The autonomic nervous system (ANS) contributes to maintain the homeostatic responses to environmental changes (18). Recent findings show altered sympathovagal activity after menopause, with a shift to sympathetic tone (19), but there is insufficient information about the role of the autonomic regulation on cardiovascular risk at postmenopause. Aging is also associated with deterioration in cardiac ANS and with other changes in autonomic nervous control, for example, to baroreceptor output, afferent neural conduction and sinoatrial node responsiveness.

HRV represents the cyclic changes of the RR interval of heart activation and is an indicator of autonomic nervous system (ANS) modulation. Spectral analysis of HRV, analyzing time and frequency domains, evaluates cardiovascular risk (20). HRV decreases with age, obesity, hypertension, insulin resistance, dyslipidemia, and smoking (21) and increases with exercise (22). HRV may also be associated with inflammation, implicated in obesity and CVD (23). Reduced cardiac parasympathetic activity increases the risk for atherosclerosis and coronary artery disease. In the Framingham study the reduced HRV in short-term recordings (2 h) predicted new cardiac events, hypertension, and hyperglycemia (24). In addition, reduced carotid artery elasticity interferes with baroreceptor function and could lead to a low vagal tone (25).

The aim of this work was to investigate the interaction of US carotid indices with HRV in a 4-h period, psychosomatic symptoms, and hormones, adjusting by age, menopausal status, body composition, and metabolic factors in women at peri- and early postmenopause to identify early vascular damage in women at midlife.

Subjects and Methods

Volunteers

In a cross-sectional design we studied women at peri- ($n = 50$) and postmenopause ($n = 50$) from urban and suburban areas of León, Mexico.

We considered women at perimenopause if they were >45 years of age with menstrual irregularities and previously regular cycles. Women at postmenopause had at least 1 year since the last spontaneous cycle and were non-hysterectomized, non-pregnant, non-lactating women.

We included women who did not have clinical evidence of chronic infectious or cardiovascular diseases or antecedents of arrhythmias. They did not receive anxiolytics, antidepressants, β-blockers, Ca-channel blockers, anti-hypertensives, statins, fibrates, anti-arrhythmics, hypnotic medication or hormone replacement therapy in the previous 6 months.

The Institutional Bioethics Committee approved this study. The nature of the study and possible risks were explained to all participants. Those who accepted participation signed informed consent.

Anthropometric Data

We collected the following data: age, height, weight and waist circumference, which were measured without shoes and with indoor clothing. Body mass index (BMI) was calculated as the body weight divided by height squared (kg/m^2) and represented a measure of overall adiposity. Women with $18.5 < BMI \leq 24.9$ were considered with normal weight, overweight and obese with BMI ≥ 25. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest as a measure of central adiposity (normal values for women <88 cm). Blood pressure was measured with a random zero sphygmomanometer in sitting position after a 5-min rest.

Years of education, exercises at least 1 day/week (yes or no), smoking habit (yes or no), as well as alcohol consumption at least one drink/week (yes or no) were also registered.