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Modulation of vascular tone control under isometric muscular stress: Role of estrogen receptors

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ABSTRACT

Aims: The aim of this study was to evaluate isometric muscle contraction (handgrip) changes on key elements of cardiac afterload, before and after raloxifene administration in postmenopausal women.
Methods/results: 12 postmenopausal and 12 fertile women were studied. Postmenopausal women underwent raloxifene administration (60 mg/day for 30 days). We evaluated vascular reactivity in superficial palmar arterial arch during handgrip in postmenopausal women before and after (M + R) drug administration, and in controls. Blood flow was higher after raloxifene administration ($p<0.05$). Mean arterial pressure (MAP)/mean arterial flow (Fmed) and arterial pulse pressure (APP)/systolic maximum arterial flow (Fmax syst) were lower after raloxifene administration ($p<0.001$). Systolic blood pressure (SBP)/R-R ratio was higher in postmenopausal women than in the controls and M + R ($p<0.01$). End-handgrip systolic and diastolic blood pressure were higher in patients before raloxifene administration than in controls ($p<0.001$); diastolic and mean arterial pressure reduced after raloxifene administration ($p<0.001$). End-effort APP/Fmax syst-ratio before treatment was higher than baseline ($p<0.05$). Controls and no-treated patients showed a MAP/Fmed ratio at end-handgrip higher than M + R group and rest ($p<0.05$). Handgrip reduced R-R interval and increased SBP/R-R ratio were shown in all groups ($p<0.05$).
Conclusions: Raloxifene reduced the vascular effects of isometric muscle contraction by modulating the vasomotor tone of peripheral vessels in relation to exercise.

1. Introduction

After the beginning of menopause period, the decreased circulating estrogens concentrations had been associated with an impairment of arteriolar resistance (Mikkola and Clarkson, 2002). It has been demonstrated that estrogens can improve endothelial function and flow-mediated vasodilation in peripheral arteries (Bush et al., 1998; Lieberman et al., 1994; Koh et al., 1999; Herrington et al., 1999; Gerhard et al., 1998). Moreover, stiffness of large arteries, measured by mean of Doppler techniques (Penotti et al., 1996) or pulse wave analysis (Teede et al., 1999; Hayward et al., 1997), is lower in postmenopausal women in hormone replacement therapy (HRT), i.e. compounds endowed with estrogens' action, than in nonusers. It is well-established that hormone therapy can improve arterial compliance not only in normotensive but also in hypertensive postmenopausal women (Teede et al., 1999).

Furthermore, estrogens modulate the cardiovascular effects of catecholamines and other vasoactive substances (Cicinelli et al., 1997) resulting in cardiac afterload reduction induced by dynamic exercise (Pedersen et al., 1995).

Despite the benefic role on cardiovascular physiology, HRT is still under debate due to its possible negative influence on cardiovascular risk profile and overall mortality risk of patients (Sharpe et al., 2010). Recent meta-analyses (Magliano et al., 2006) reduced the concerns about such particular therapy by confirming the eventual protective role of HRT and estrogens in particular on cardiovascular risk and breast cancer incidence. Nevertheless, community scientific board tries to develop advanced drugs with a more sophisticated mechanism of action, such as selective estrogen receptor modulators (SERMs), able to increase estrogen receptors activity in peculiar tissues and diminish it in other body regions, in order to better target the action of outside drugs and reach the positive goal of the

Abbreviations: APP, arterial pulse pressure; BMI, body mass index; DBP, diastolic blood pressure; Fmax syst, systolic maximum arterial flow; Fmed, mean arterial flow; HRT, hormone replacement therapy; MAP, mean arterial pressure; SBP, systolic blood pressure; SERMs, selective estrogen receptor modulators.

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treatment (McDonnell and Wardell, 2010; Green et al., 2012). Raloxifene belongs to this pharmaceutical category.

SERMs preserve the estrogen favorable effects on vessels by directly influencing endothelium cell functions. It has been observed that raloxifene intake in rats determines a reduction in arterial resistances via calcium-dependent endothelial nitric oxide synthase activation (Chan et al., 2010); a similar event has been demonstrated in human endothelial cells (Simoncini and Genazzani, 2000).

As regard SERMs' role on cardiovascular response to exercise, to the best of our knowledge no data exists about cardiovascular effects of raloxifene during an isometric muscle stress and/or a static, sustained until exhaustion, muscle strain.

Daily life involved several examples of isometric muscle contractions (i.e., to lift weights and bags) that affect cardiac work and oxygen demand. In facts, isometric exercise reduces cardiac pre-load and is generally associated to a spontaneous Valsalva maneuver adopted during the exercise. As a result, arterial pressure and heart rate increase as well as peripheral resistance due to an alpha-adrenergic activation (Pedersen et al., 1995; Ulmer et al., 1989) which induces an increase in cardiac afterload.

The aim of this study was to evaluate the influence of an isometric stress on vascular structures in postmenopausal women and, consequentially, on the key elements of cardiac afterload, i.e. systolic and diastolic blood pressure, before and after raloxifene therapy. As a model of isometric stress we employed the isometric muscle contraction until exhaustion was achieved with a handgrip test.

2. Matherials and methods

2.1. Study population

The study involved two groups of healthy women volunteers: one formed by 12 postmenopausal women (group M) (aged between 49–63 years; mean age 57.7 ± 4.5 years), the other one composed by 12 fertile women (aged between 19–38 years; mean age 26.3 ± 4.9 years) (control group, named group C). All were outpatients attending the department of Obstetrics and Gynecology, Faculty of Medicine, University of Bari, Bari, Italy to check their gynecological status.

The patients were informed about the aim of the study and signed consent. The study was approved by the Institutional Review Board of Bari University General Hospital and carried out in accordance with the principles of the Helsinki Declaration.

Inclusion criteria were the following:

- according to postmenopausal women group, the menopause condition defined as an amenorrhea period of at least 12 months and laboratory findings of serum levels of estradiol <20 pg/ml and follicle-stimulating hormone >30 mIU/ml;
- anamnestic absence of angina pectoris, myocardial infarction, cerebrovascular disease, transient ischemic attacks, peripheral arterial disease, severe hypertension (i.e., systolic/diastolic blood pressure >160/100 mm Hg), thrombophlebitis, thrombosis or thromboembolic disease, diabetes, clinically significant liver (blood liver function parameters levels twofold the upper limit of normal range) or kidney (glomerular filtration rate <30 ml/min) disease;
- absence of overt or suspected estrogen-dependent cancers, neuro-ocular diseases, genital bleeding of uncertain origin, migraine or increase in frequency and severity of headaches during previous estrogen therapy, endocrine diseases;
- absence of neurodegenerative diseases related to menopause.

Women in childbearing age had been considered according to a normal cyclicity based on anamnesis, basal temperature of the last two months and ultrasound evaluation.

Exclusion criteria were:

- total cholesterol >220 mg/dl; triglycerides >200 mg/dl;
- obesity (body mass index [BMI] >30);
- smoking habits;
- excessive alcohol or drugs use;
- use of estrogens, progesterone, androgens or tibolone, dopamine or antidopaminergic drugs, clonidine or niacin in the six months before.

2.2. Study design

We chose the handgrip maneuver in order to reproduce a static muscle effort. The changes in autonomic nervous system determined by this movement concern all vascular districts innervated by the sympathetic system, due to a concurrent noradrenergic activation (Bini et al., 1980a, 1980b). We hemodinamically evaluated the vessels in front of the hand involved in handgrip maneuver. In this way, the counterpart of cholinergic control is not involved in vasomotor regulation of vessel. We considered superficial palmar arterial arch to evaluate the vascular reactivity because such zone is characterized by the following requirements: 1) not able to carry blood to muscles during handgrip maneuver; 2) be predominantly controlled by the sympathetic noradrenergic system; 3) not influenced by thermoregulation induced by handgrip maneuver (Vissing et al., 1991), but influenced by involuntary contractions due to handgrip (Williams et al., 1981); 4) be easily and non invasively studied during ambulatory controls.

2.3. Hemodynamic measurements

The hemodynamic changes induced by handgrip test were recorded in the control group (C) between the seventh and tenth day of the menstrual cycle. The same tests were performed in postmenopausal women before (M) and after 30 days of oral administration of raloxifene at a dose of 60 mg/day (M + R). All subjects reached the hemodynamic laboratory between 10.00 a.m. and 12.00 a.m., and 2 h after a light breakfast.

The subjects were asked not to take alcohol or caffeine within 24 h before the exam. The study was performed in a quiet air conditioned room (21–24 °C), the patients quietly lying on a bed for at least 20 min.

The maximum force developable by the left hand during voluntary contraction was determined at the beginning of the session on the average of three successive measurements. The patients were asked to collapse a special dynamometer for handgrip test, formed by a pressure gauge connected to the rubber bulbs filled with air, suitable for each patient's hand. Then, they should squeeze the rubber bulb with the strength necessary to maintain the pressure gauge at a level equal to 30% of the maximum basal value, stopping it due to muscular fatigue and exhaustion. All the patients showed no symptoms or signs of angina, ST segment elevation, T-wave abnormalities, high blood pressure or hypotension. A computerized poligraph Biopac MP100 measured the following parameters: EKG; skin electrical conductance (indicator of level activation of the sympathetic nervous fibers) and sphygmic wave recorded from a right hand finger through the photopletismografic system Finapres (Ohmeda, mod. 2300); Doppler velocimetry curve of the superficial palmar arterial arch of the right hand, using a 4 MHz probe connected to a flowmeter Cardioline, mod. DOP 2000, was calculated. A pneumogramma was recorded by mean of a band with strain-gauge transducer placed around the chest or abdomen.

During the relaxation period, the following parameter had been measured:

- systolic (SBP) and diastolic (DBP) blood pressure (in mmHg);
- arterial pulse pressure (APP, in mmHg), i.e. the oscillation of