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Original Article

Thoughts modulate the expression of inflammatory genes and may improve the coronary blood flow in patients after a myocardial infarction

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ABSTRACT

Background: Mental stress is one of the main risk factors for cardiovascular disease. Meditation and music listening are two techniques that are able to counteract it through the activation of specific brain areas, eliciting the so-called Relaxing Response (RR). Epidemiological evidence reveals that the RR practice has a beneficial prognostic impact on patients after myocardial infarction. We aimed to study the possible molecular mechanisms of RR underlying these findings.

Methods: We enrolled 30 consecutive patients after myocardial infarction and 10 healthy controls. 10 patients were taught to meditate, 10 to appreciate music and 10 did not carry out any intervention and served as controls. After training, and after 60 days of RR practice, we studied the individual variations, before and after the relaxation sessions, of the vital signs, the electrocardiographic and echocardiographic parameters along with coronary flow reserve (CFR) and the carotid's intima media thickness (IMT). Neuro-endocrine-immune (NEI) messengers and the expression of inflammatory genes (p53, Nuclear factor Kappa B (NFkB), and toll like receptor 4 (TLR4)) in circulating peripheral blood mononuclear cells were also all observed.

Results: The RR results in a reduction of NEI molecules ($p < 0.05$) and oxidative stress ($p < 0.001$). The expression of the genes p53, NFkB and TLR4 is reduced after the RR and also at 60 days ($p < 0.001$). The CFR increases with the relaxation ($p < 0.001$) and the IMT regressed significantly ($p < 0.001$) after 6 months of RR practice.

Conclusions: The RR helps to advantageously modulate the expression of inflammatory genes through a cascade of NEI messengers improving, over time, microvascular function and the arteriosclerotic process.

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1. Introduction

Mental stress is one of the major etiological aspects of ischemic heart disease and all its risk factors.^{1–7} The persistent activation of the stress axis determines a state of low-grade chronic

inflammation that feeds the atherosclerotic process and increases the risk of cardiovascular accidents.^{1–3}

Meditating and listening to classical music, are two techniques that are able to turn off the brain areas that carry stress signals (the so called Default Mode Network) which evoke the Relaxation Response (RR)⁸ through specific areas of the brain (called Attention Network).^{2,3} The RR is aroused when an individual focuses on a word, a sound or a song, a phrase, a repetitive prayer, or a movement, disregarding everyday thoughts.⁹ These two steps break the mind wandering and train of thoughts of everyday life. The practice of anti-stress methods (such as meditation or music appreciation)

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correlates with a significant decrease of adverse cardiac events in patients with myocardial ischemia, stroke, atherosclerosis, hypertension and heart failure¹⁰ and are recommended by the American Heart Association (AHA). Please visit: http://www.heart.org/HEARTORG/HealthyLiving/Stressmanagement/StressManagement_UCM_001082_SubHomePage.jsp.

The numerous studies conducted so far in the field of meditation and music appreciation have associated to their practice a reduction in plasma concentration of hormones related to stress response (such as cortisol and norepinephrine), some inflammatory cytokines and oxidative stress mediators.^{1–3} However, such research, focusing on individual neuro-endocrine-immune (NEI) mediators, do not offer an overview of how these biochemical messengers act in concert to determine the positive epidemiological effects related to the elicitation of the RR. Moreover, the final target of the NEI elements is cellular genome. We aimed to study some possible signals through which thought influences gene expression and many clinical, morphological, structural and functional cardiovascular parameters.

2. Methods

The design of our study follows what has already been published in literature⁸ and is shown in Fig. 1. Our study consists of two elements: a prospective and a cross-sectional aspect. Each subject served as its own control. The cross-sectional aspect of the research involved the comparison between groups.

From October to December 2015, we enrolled 30 consecutive patients (23 males, mean age 55.9 ± 6.1) who were hospitalized in our Cardiology Wards for ST elevated (STEMI) or non ST elevated myocardial infarction (NSTEMI) and who suffered also from carotid atherosclerosis. All patients were free of cognitive deficit and had no other comorbidities. These patients were randomly divided as follows: 5 to Transcendental Meditation®, 5 to Pneumomeditazione®, 10 to music appreciation. A brief description of each relaxation method is available in the online data supplements. Ten patients constituted the control group and were not subject to any intervention. They were asked to relax in a way that felt comfortable for them for a period of time corresponding to the relaxation session. Most of them chose to sit in their chairs with their eyes closed. Lastly, we enrolled 10 healthy control subjects matched for age and gender (5 of whom were trained in meditation and 5 in music appreciation). First of all these participants had to have a medical examination in order to verify their “good state of health”. None of the participants knew how to meditate or listen to music for

relaxation reasons before the study. Each person signed a consent form giving their permission to participate in the study.

All patients were assessed by the Service of Clinical Psychology of our hospital in order to certify the individual personality characteristics, their neuro-cognitive reserve and the degree of perceived stress, through questionnaires used routinely and available in Internet (Mini Mental State (MMS), Esame Neuropsicologico Breve (ENB-2), Cognitive Reserve Index questionnaire (CRIQ), Symptom Checklist Questionnaire-Revised (SCL-90-R) and Perceived Stress Scale by Sheldon-Cohen). The same questionnaires were repeated after 6 months.

The initial four days of training took place in our hospital before discharge and the rest of the relaxation sessions were carried out independently by the subjects at home for 20 min, 2 times a day. After four days of training, we studied participants during the two daily relaxation sessions. At 8:00 a.m. vital signs were measured and blood samples taken at the start and immediately after the end of the session. In the afternoon, at 16:00 vital signs were measured again, and an electrocardiogram and transthoracic echocardiography (TTE) with assessment of coronary flow reserve (CFR) were performed before and immediately after the relaxation session. This same scheme was repeated after 60 days of daily practice at home. An echoDoppler of the supra-aortic trunks (SAT) was done pre discharge and after 6 months of regular daily practice to assess intima media thickness (IMT) in the carotid district. Thus, as the primary endpoint, we have audited the lowering of mean arterial pressure and the reduction of the genetic and biochemical parameters of inflammation (estimated effect size of at least 1.8 as described below). As a secondary endpoint, we evaluated the performance of other molecules that, conveying messages of stress in the body, affects the endothelial function of coronary microcirculation. Then, we performed an echocardiogram with CFR estimation and an echo-Doppler SAT to assess heart and microcirculatory function and the progress of atherosclerosis associated with the molecular mechanisms explored.

In blood samples we assessed the following NEI molecules: stress mediators (cortisol, corticotropin (ACTH), copeptin, epinephrine, norepinephrine, insulin, thyroid-stimulating hormone (TSH), growth hormone (GH), testosterone, dehydroepiandrosterone (DEHA-S), prolactin (PRL)), inflammatory markers (erythrocyte sedimentation rate (ESR), fibrinogen, highly sensitive C-reactive protein (HS-CRP), interleukin-6 (IL-6), transforming growth factor beta-1 (TGFβ-1), galectin-3), markers of oxidative stress (malondialdehyde (MDA), asymmetrical dimethyl arginine (ADMA)), a cellular stress marker (high mobility group box1

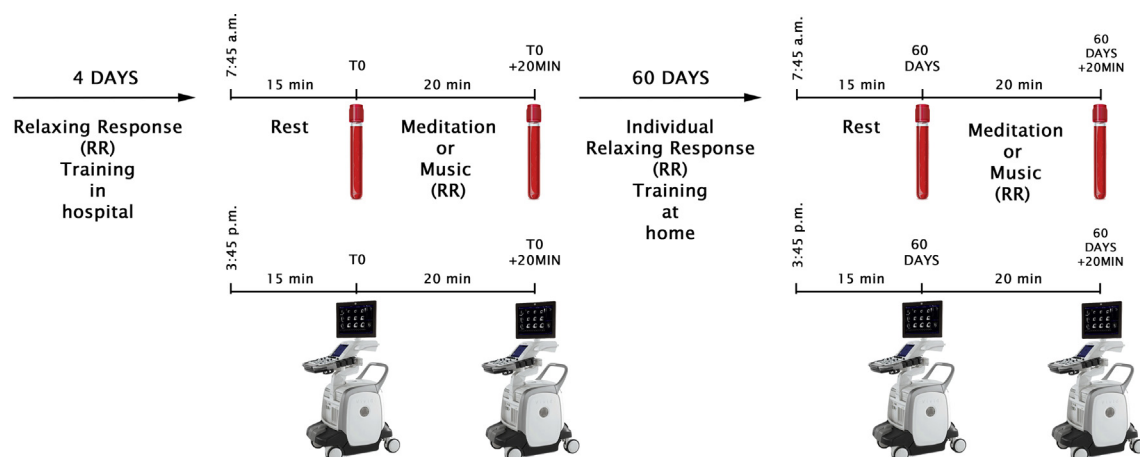


Fig. 1. Study design. Explanation in the text.

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