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Research paper

# miRNAs may change rapidly with thoughts: The Relaxation Response after myocardial infarction

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ABSTRACT

*Introduction:* Mental stress is potentially a major cardiovascular risk factor. Meditation and listening to music may be able to compensate by eliciting the Relaxation Response (RR) with a beneficial prognostic impact after myocardial infarction (MI), reducing the progression of the arteriosclerotic process and improving coronary blood flow. We aimed to study a possible epigenetic mechanism of the RR speculating that circulating microRNAs levels could change during relaxation.

*Methods:* We enrolled 150 consecutive patients after MI. 50 were trained to meditate, 50 given music appreciation and 50 served as controls. In addition, in order to rule out that the disease state could interfere with the possible movement of microRNAs, we enrolled 50 healthy volunteers (25 were trained to meditate and 25 had music appreciation). After training, and after 60 days of RR practice, we studied the individual variation, before and after the relaxation session, of some important cardiovascular circulating microRNAs: the microRNA-1, −16, −24, −33, −92, −144, −146, −155.

*Results:* As the RR appeared to be triggered in the same way irrespective of whether this was by music or meditation data was combined. After the RR, a reduction in microRNA-16, −33, −92, −144, −146, −155 ($p < 0.01$) and an increase in the levels of microRNA-1 and −24 ($p < 0.01$) from baseline was observed both at the first observation and after 2 months.

*Conclusions:* The RR modulates some microRNAs levels suggesting that psychic activity may be an important epigenetic and pathophysiological factor in the arteriosclerotic process and in ischemic heart disease. In particular, the analyzed microRNAs levels seems to vary in relation to the state of stress or relaxation of the subjects.

## 1. Introduction

Mental stress damages the brain [1] and the immune system [2,3] by affecting hormones and metabolism [4] and underlies many cardiovascular diseases [5–7], particularly myocardial infarction and its risk factors [8]. Many of the molecular mechanisms associated with such evidence are related to epigenetic markers that affect cellular activity in response to environmental or psychic stimuli [9]. These processes (DNA methylation, histone coding, chromatin conformation modification, non-coding RNAs) change cellular functioning in the absence of gene mutations or “defective” genes and can be stable, reversible, and inheritable [10]. Circulating microRNAs are key epigenetic elements that can convey significant physical or psychic stress signals at cellular level, modulating the adaptive response of each cell, tissue, organ, and of the whole individual to the environment [5]. Moreover, circulating microRNAs (miRNA) are at the center of research for their possible diagnostic and therapeutic ability in many cardiovascular diseases [11,12].

As we recently described [13], meditating and listening to classical or meditative music, are two techniques that are able to turn off the brain areas that carry stress signals [14–16] (the so called Default Mode Network, (DMN)) which evoke the Relaxation Response (RR) through specific neuronal circuits (called Attention Network, (AN)). 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 [17]. 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, correlates with a significant decrease of adverse cardiac events in patients with myocardial ischemia, stroke, atherosclerosis, hypertension and heart failure [18] and are

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recommended by the American Heart Association (AHA) [13] as "an adjunct to guideline-directed cardiovascular risk reduction by those interested in this lifestyle modification even if the benefits of such intervention remain to be better established"[19].

Therefore we wanted to study a possible mechanism, not yet described in literature, to the best of our knowledge, with the purpose to evaluate whether the stress axis activity downregulation related to the practice of meditation or music appreciation translates into a modification of some cardiovascular miRNAs, important in regulating cardiomyocyte function, vascular endothelial function and atherosclerotic process and lipid metabolism.

In fact, as described by Leung et al. [20], "*responding to stresses* −physical or psychological stressors trigger the same responses on the biological level [21,22]- *cells either choose to restore or reprogram their gene expression patterns. This decision is partly mediated by miRNA functions, in particular by modulating the amount of miRNAs, the amount of mRNA targets, or the activity/mode of action of miRNA-protein complexes. In turn, these changes determine the specificity, timing, and concentration of gene products expressed upon stresses. Dysregulation of these processes contributes to chronic diseases, including cancers*" and cardiovascular disease [11,12] and may be transmitted transgenerationally [23].

Is the movement and action of miRNAs a passive/automatic response to the stressor or can it be guided directly by mental activity?

This study aims to verify if the mental activity (which can only go either in the direction of stress or relaxation) is able to determine significant epigenetic variations related to some microRNAs chosen to explain the observations made in a previous work [13]. In other words, our aim is to see if the psychological activity (we have used meditation and music appreciation as two fairly reproducible examples of self- or stimulated relaxation-oriented psychological activity) could directly have an impact on microRNA levels. Our previous work [13] demonstrated that psychological activity associated with meditation and music appreciation results in a significant down regulation of neuroendocrine and inflammatory molecules and genes. In addition, Nuclear factor Kappa B (NfKB), and toll like receptor 4 (TLR4)) appears to improve the lipid profile of the atherosclerotic process and stimulation of a regenerative cardiovascular potential (increasing in circulating endothelial stem cells). The behavior of microRNA-1, −16, − 24, −33, −92, −144, −146 and −155, were selected on the basis of their mechanisms of action (see "discussion") as they may correspond and help to explain the results of our previous study.

## 2. Methods

### 2.1. Recruitment

In this paper we expanded the population studied previously [13], as follows. According to Professor Benson's work at Harvard [29], the RR is evoked in an equal way through a process of attention to a "internal" psychological (meditation) or a "external" stimulus (like music appreciation). So, on the one hand we wanted to confirm this aspect again (as happened in our previous study [13]) and thus we enrolled 150 patients post MI, creating three groups of 50 patients (meditation, music and "sick controls no intervention"-see below) based on the expected effect size (see statistical justification in the dedicated paragraph below). Once we had this confirmation, we also enrolled 50 more healthy subjects and taught them the RR (25 through meditation and 25 through music appreciation). This was to see if the state of the disease could alter or not the excursion of the analyzed markers during RR. Even in healthy subjects trained in RR we wanted to verify any potential difference between the methods used to elicit the RR itself.

For the comparison between groups, at least 50 subjects per group were needed (again, please see statistical justification in the dedicated paragraph below).

Finally, as the RR appeared to be triggered in the same way irrespective of whether this was by music or meditation (see below) data was combined and three groups were created (namely "INTERVENTION", group of post MI patients subjected to RR −nr. 100 subjects-, "CONTROL", group of "control patients-no intervention" −nr. 50 subjects- and "INTERVENTION HEALTHY CONTROLS", 50 healthy controls subjected to RR).

More in detail, between October 2015 to February 2017, 150 consecutive patients (116 males, mean age 52.7 ± 11.1) who had consulted in our Cardiologic Clinic for ST elevated (STEMI) or non ST elevated myocardial infarction (NSTEMI) and suffering from carotid atherosclerosis were enrolled in the study, after providing informed consent. All patients were free of cognitive deficit and had no other comorbidities. Patients over 65 years of age were excluded. In addition, in order to rule out that the disease could interfere with the possible movement of microRNAs, we also enrolled 50 healthy control subjects matched for age and gender of the MI patients. These healthy control participants were enrolled from amongst the acquaintances of the research group, and agreed to a medical examination in order to verify their "good state of health".

Of the 150 consecutive patients after MI, 50 were trained to meditation, 50 to music appreciation and 50 served as controls (no intervention, please see below). Of the 50 healthy subjects, 25 were trained to meditate and 25 had music appreciation.

After training, and after 60 days of RR practice, we studied the individual variation, before and after the relaxation session, of some important cardiovascular circulating microRNAs: the microRNA-1, −16, −24, −33, −92, −144, −146, −155.

### 2.2. Training and blood sampling time

These patients were consecutively trained as follows: 50 to Pneumomeditazione® and 50 to music appreciation. A brief description of each relaxation method is available below. Another 50 patients constituted the control group and were not subjected to any intervention. They were asked to relax in a way that felt more appropriate for a period of time corresponding to the relaxation session. Most people sat in the chair with eyes closed. None of the participants had practiced meditation or listened to music aimed at relaxation before the study. Each subject has expressed his free and autonomous choice to participate in the study giving a written informed consent.

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 partecipants during the two daily relaxation sessions. At 8:00 a.m. we performed blood samples before and immediately after the end of the session. We repeated the same scheme after 60 days of daily practice at home.

Thus, as the primary endpoint, measured was whether there had been any changes in the microRNAs (estimated effect size of at least 0.49 as described below). In blood samples we assessed the following molecules: microRNA-1, −16, −24, −33, −92, −144, −146 and −155.

The environmental conditions at the time of data collection were the same for all the subjects. In particular, the training, the relaxation sessions and blood withdrawals have taken place in the classroom of our clinic situated alongside our echocardiography laboratory. Patients had three days to decide whether or not to participate in the study and their enrollment occurred in the seventh day after infarction. The four days of training were held in our classroom before discharge. All patients received optimal medical therapy in accordance with European Society of Cardiology (ESC) and AHA guidelines for the treatment of ischemic heart disease and followed the same cardiac rehabilitation program (physical training and nutrition education).

The acute variation of the parameters studied can be attributed to the practice of relaxation according to the methods used because the precise timing of blood sampling (before and immediately after the end of the session) prevents any other influences. As previously described

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