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Original research article

Elevated levels of miR-499 protect ischemic myocardium against uric acid in patients undergoing off-pump CABG

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ABSTRACT

Objective: This study screens the miR-499 differences in off-pump CABG and evaluates the relationship of miR-499 with heart ejection fraction% and uric acid (UA) levels.

Methods and results: 70 candidates undergoing CABG were selected and left ventricular EF, blood samples and hemodynamic data were taken at different time points. Statistically significant correlation was found between circulating levels of cardiac troponin I (cTnI), UA and miR-499, after off-pump CABG ($p < 0.001$). Furthermore, post-operative EF was strongly affected by pre-operative miR-499 expression levels vs. UA ($p < 0.005$).

Conclusion: Pressure overload and ischemia result in oxidative stress (OS) on the cardiovascular system. The elevated levels of miR-499 expression in ischemic myocardium protect it from OS, while declining protective effects were observed in decreased levels of miR-499 in UA concentrations.

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Introduction

Studies have demonstrated that there are significant expression profile changes in a bunch of miRNAs in both ischemic/normal heart tissues and peripheral blood. Some miRNAs

perform bold biological functions of protecting or damaging cardiac cells in myocardial ischemia through different pathways [1–4].

Evidence has indicated that miR-499 is produced almost exclusively in the heart. Plasma miR-499 concentrations are increased in all individuals with acute myocardial infarction

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but were below the limit of detection for all individuals in the other patient groups [2–4].

Also, in patients with heart failure, from plasma levels of heart-associated (miR-1, -133a, -208b, and -499) miRNAs, only miR-499 was significantly elevated (2-fold), whereas no significant changes in selected miRNAs were observed [5].

Remarkably, plasma levels of these miRNAs are reported to be not affected by a wide range of clinical confounders, including age, sex, body mass index, kidney function, systolic blood pressure, and white blood cell count [4,5].

On the other side, UA has been associated with adverse cardiovascular events in several settings. Its utility in patients undergoing surgical revascularization has, however, been associated with poorer survival after CABG [6–9]. Elevated serum UA levels have relationship with inflammatory markers and have deleterious effects on the endothelium [10]. Ischemia/reperfusion injuries can cause OS and can be monitored by using UA as a parameter of OS. During ischemia, there is a cascade of reactions due to a decrease in tissue blood flow, which results in increasing UA expression [11,12]. UA concentrations in patients undergoing CABG are a measure for ischemia/reperfusion injury [13].

We hypothesized that there is a relationship between UA and miR-499 levels with cardiac function in patients with coronary severe ischemia undergoing off-pump CABG, compared to their baseline. To testify this hypothesis, we analyzed the expression of miR-499 by using quantitative RT-PCR on samples at different time points in CABG candidates and then the clinical relevance of miR-499 levels with myocardial biochemical markers and hemodynamic changes was evaluated [1].

Materials and methods

Patients

In our procedure, 70 patients, aged 40–79 years, were elective for undergoing off-pump CABG surgery and were consecutively enrolled in a prospective observational setting. No exclusion criteria other than redo of CABG and a minimum of three anastomoses were defined. The study was conducted according to the recommendations by the Declaration of Helsinki on Biomedical Research Involving Human Subjects and also the study protocol was approved by the Medical Ethics Committee of Shahid Sadouqi University of Medical Sciences. Written informed consent was obtained from each individual [11,13].

Clinical samples

Baseline clinical data, including medical history, cardiac risk factors, operative details, New York Heart Association functional class, and the European System for Cardiac Operative Risk Evaluation (EuroSCORE), were collected prospectively by an experienced full-time data collector [9,11]. Blood samples were collected before CABG surgery and post-surgery, for determining the biochemical markers. All samples were immediately centrifuged for 10 min at 3000 × g, and stored

at –80 °C until analysis. Serum enzyme activities were measured at 37 °C [14,15].

Biochemical markers

CTnI levels as well as CK-MB activities in the serum were measured before and after operation. CTnI was assayed with the Stratus II system (Dade Behring, Marburg, Germany) according to the manufacturer's instructions. Activities of CK and CK-MB were measured with an immunoinhibitory assay at 37 °C, by means of an N-acetylcysteine-activated system (CK NAC-Method, Roche Diagnostics, Mannheim, Germany) [14]. UA was measured by using the same sample and ADVIA 1650 General Chemistry Analyzer (Siemens Diagnostics Solutions, Tarrytown, NY) [9].

Anesthetic technique

Premedication consisted of temazepam (10 mg), given orally 2–3 h before the procedure started. Anesthesia consisted of a balanced opiate-based general anesthesia technique. Induction took place by means of infusion of propofol (1.5–2 mg/kg), pancuronium (0.1 mg/kg) and fentanyl (7 mg/kg). Anesthesia was maintained with nitrous oxide in oxygen and continuous propofol infusion (10–20 ml/h), remifentanyl (0.25–1 mg/kg) and pancuronium as required. Hypertension was treated with vasodilators (nitroglycerin and nitroprusside). A mean arterial pressure of 60 mmHg or higher and a heart rate less than 70 beats per min was maintained. Heparin was administered at 150 IU/kg. After all anastomoses were completed, heparin was neutralized with protamine chloride 120 IU/150 IU. All patients received standardized postoperative care [16].

Surgical procedure

Median sternotomy and harvesting of the internal mammary artery were followed by full exposure of the coronary artery branches to be revascularized. The revascularization was performed on the beating heart using the Medtronic Octopus device (MedtronicW, Minneapolis, USA), while using intraluminal shunt during procedure to decrease the acute ischemic insult for myocardium. Most patients had at least one arterial graft (left internal thoracic artery, LITA). The left anterior descending (LAD) was revascularized first in all patients using the LITA. The left-sided grafts were performed followed by the right-sided grafts. Patients were fully heparinized at completion of harvesting of the conduits. Heparinized state was reversed using protamine and closure performed as routine [16].

Echocardiographic study to assess global LV function

Patients underwent a total of 4 contrast-enhanced echocardiographic studies: before, 1 day after, 4 days after, and 1 month after operation, as given in Ref. [15]. Global LV function and 5 anatomic regions (anterior, apex, lateral, inferior, and septum) were assessed with respect to regional LV function before and after contrast enhancement using the semi-quantitative methods recommended by the American Society of Echocardiography [15].

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