Experimental and Molecular Pathology 100 (2016) 469–475

Contents lists available at ScienceDirect

Experimental and Molecular Pathology

journal homepage: www.elsevier.com/locate/yexmp

Altered mitochondrial expression genes in patients receiving right ventricular apical pacing

Haiyan Xu [a,b], Jianshu Gao [a,c], Fang Wang [a,*]

[a] Department of Cardiology, Shanghai General Hospital of Nanjing Medical University, Shanghai, PR China
[b] Department of Cardiology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, PR China
[c] Department of Cardiology, Yancheng First People's Hospital, Nantong University, Yancheng, Jiangsu, PR China

ARTICLE INFO

Article history:
Received 20 February 2016
and in revised form 9 May 2016
Accepted 9 May 2016
Available online 10 May 2016

Keywords:
Gene expression
Mitochondria
Right ventricular apical pacing
Microarray

ABSTRACT

Left ventricular mechanical dyssynchrony from right ventricular apical (RVA) pacing may lead to heart failure. Mitochondrial dysfunction has been observed in the failing heart; however, whether RVA pacing may alter the underlying mitochondrial dynamics at an early stage in patients with preserved ejection fraction is not well understood. RNA was isolated from peripheral whole blood samples of 13 patients. The differentially expressed mRNA profiles from 58 samples (13 experimental subjects; 35 control subjects) were performed using Affymetrix array. Finally, a five-gene signature was identified. DAVID was performed to explore the biological functions of target genes with altered gene expression between two groups. The gene signature (OPA1, CTSA, NDUFA1, STK10 and PRDX1) was able to identify patients post-implant with an area under receiver operating characteristic curve of 0.90 in this study. Our test showed that the gene signature had a sensitivity of 91% with a specificity of 86% in discrimination between post-implant group and healthy controls. In the cellular component category, four genes of the five-gene signature except STK10 were related to mitochondrion. The five-gene signature was associated with oxidative phosphorylation, mitochondrial ATP synthesis and apoptosis in biological process analysis. Pathway analysis indicated that a significant enrichment of candidate genes involved in the calcium signaling and glycosphingolipid biosynthesis pathways. The expression changes observed in this study reflect a profound effect of ventricular mechanical dyssynchrony caused by RVA pacing on the transcriptome at an early stage. RVA pacing alters cellular energy metabolism may have association with mitochondrial dynamics.
© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Sick sinus syndrome (SSS) is the most common bradycardiac arrhythmia in the elder requiring implantation of permanent pacemaker (PPM). Changes in cardiomyocyte structure and function occur with age and precede anatomical and functional changes in the heart. Right ventricular apical (RVA) pacing, a commonly selected pacing site, provides an adequate electrical impulse to the right ventricular myocardium, thus restoring a physiological excitation–conduction of the heart. It is well known that pacing-induced remodeling could be detrimental in the long term, causing electro-mechanical dyssynchrony, developing a pacemaker induced cardiomyopathy and congestive heart failure in some patients (Sweeney et al., 2003; Olshansky et al., 2007; Wilkoff et al., 2002). The incidence of heart failure is about 3.3% in patients with high-grade atrioventricular block during the 3 years after pacemaker implantation (Toff et al., 2005). In MOST trail, the incidence of heart failure is 9.6% in pacemaker recipient with sick sinus syndrome during the 6-year follow-up period (Sweeney et al., 2003).

The molecular mechanisms underlying electrophysiological and structural remodeling triggered by altered activation is not well defined. Alterations in mitochondrial energy metabolism have been observed in a variety of heart disease, such as heart failure and ischemic heart disease (Rosca et al., 2008; Disatnik et al., 2013). Even though the electrophysiological and mechanical aspects of pacemaker induced dyssynchrony have been well studied (Marrus et al., 2012; Matsushita et al., 2009), how dyssynchrony affect mitochondrial dynamics and mitochondrial mitophagy remains unknown. Identification of pathways involved in mitochondrial dynamics will provide insights into mechanisms that regulate cardiac energy metabolism and novel ways to improve heart function. Gene expression profiling has emerged as a powerful tool for the comprehensive investigation of the pathophysiology of heart disease (Margulies et al., 2009; Gao et al., 2008). Several lines of evidence suggest that unique gene expression patterns in

Abbreviations: CI, confidence interval; CTSA, cathepsin A; DAVID, Database for Annotation, Visualization and Integrated Discovery; DDDR, dual chamber rate modulated; ECG, electrocardiogram; GCOS, GeneChip Operating System; IMM:, inner mitochondrial membrane; LV, left ventricular; NDUFA1, NADH ubiquinone oxidoreductase subunit A1; OPA1, optic atrophy 1; PPM, permanent pacemaker; PRDX1, peroxiredoxin 1; ROC AUC, area under the receiver receiver-operating characteristic curve; RVA, right ventricular apical; SSS, sick sinus syndrome; STK10, serine/threonine kinase 10; VVI, single chamber ventricular rate modulated.

* Corresponding author at: Department of Cardiology, Shanghai General Hospital of Nanjing Medical University, No. 650 New Songjiang Road, Songjiang District, Shanghai 200080, PR China.
E-mail address: wangfang_201309@163.com (F. Wang).

http://dx.doi.org/10.1016/j.yexmp.2016.05.005
0014-4800/© 2016 Elsevier Inc. All rights reserved.

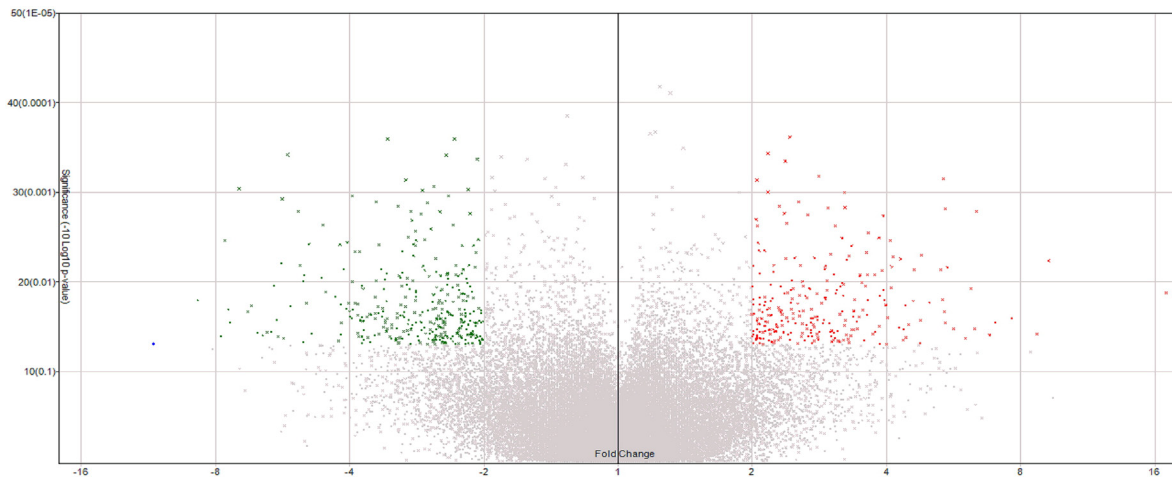

Fig. 1. The expression profiles of mRNAs were compared between 10 patients pre-implant and their post-implant samples. Red dots represent mRNAs with more than 2-fold increase; green dots represent mRNAs with more than 2-fold decrease (log 10 scaled, $P < 0.05$).

peripheral blood could reflect changes occurring within the cells and tissues of the disease state (Aziz et al., 2007; Shi et al., 2014).

Given the importance of abnormal mechanoenergetics in dyssynchronous heart, we hypothesized that RVA pacing may alter the underlying mitochondrial dynamics responsible for energy supply. In this report, we used blood samples by microarray technology and identify gene expression signatures unique to experimental subjects' exposure to short term RVA pacing.

2. Materials and methods

2.1. Patients and blood samples

The investigation protocol was approved by the Institutional Review Board and the Ethic committee of Shanghai General Hospital. Consent forms were obtained from all study participants. Between September 2013 and December 2013, thirteen patients with sick sinus syndrome or atrioventricular block were recruited. The patients with sick sinus syndrome or atrioventricular block were confirmed by electrocardiogram (ECG) or Holter. All subjects had cardiac pacemakers implanted for either sick sinus syndrome ($n = 8$) or atrioventricular block ($n = 5$). Only one patient had persistent atrial fibrillation. Enrollment criteria included normal cardiac function, no history of left or right bundle branch block and no history of coronary, valvular, or other structural cardiac disease. Most of the patients (84.6%) received dual chamber rate modulated (DDDR) pacing systems. Pacemaker implantation was performed under local anesthesia. Atrial leads were placed in the right atrial appendage or right atrial septum. Ventricular leads were placed in the right ventricular apex. All patients who received DDDR pacing systems had single chamber ventricular rate modulated (VVIR) pace mode with the lower rate programmed to ≥60 and the upper rate to ≤ 110 beats per minute for one week. Pacemaker check-ups were performed one week after implantation and percent RVA pacing was determined from stored pacemaker diagnostic data. The percent RVA pacing measured varied from 22% to 100%.

Whole blood RNA samples from 13 patients, including 10 patients before and after pacemaker implant (one week later), two separated patients before pacemaker implant and one patient with ICD battery depletion were collected. To obtain gene signatures specific to cardiac pacemaker implant, we included 35 healthy subjects as controls who have no history of bradycardiac arrhythmia and cardiac pacemaker implantation.

2.2. Blood collection, RNA isolation and RNA quality control

Peripheral whole blood (2.5 mL) was collected using PaxGene tubes (PreAnalytix, Hombrechtikon, Switzerland), and whole-blood RNA was then isolated as described previously (Marshall et al., 2010). Isolated RNA integrity was validated by means of a 2100 Bioanalyzer RNA 6000 Nano Chip (Agilent Technologies, California, USA). Samples were excluded for subsequent microarray analysis that did not meet the following quality criteria: RIN ≥ 7.0; 28S:18S rRNA ≥ 1.0. RNA quantity was verified by absorbance at 260 nm in a DU1000 Spectrophotometer (Beckman-Coulter, California, USA).

2.3. Microarray hybridization

Two hundred nanograms of RNA from each sample was used for cDNA synthesis and hybridization onto Affymetrix Human Genome U133 Plus 2.0 GeneChip oligonucleotide arrays in accordance with the standard protocol (Affymetrix, CA, USA). Gene expression profiles of RNA samples were imported into Affymetrix the GeneChip Operating System1.4.1 (GCOS) software, using a scaling factor that adjusted the global trimmed mean signal intensity value to 500 for each array. Expression data were normalized by MAS 5.0 algorithm included in the Affymetrix GCOS software.

2.4. Gene Microarray Data Analysis

To identify candidate genes for pacemaker implant, we first selected probe sets from 54,675 probe sets on the Affymetrix Gene Profiling cGMP U133 Plus 2.0 microarray, according to criteria of reliability, repeatability and linearity. A few thousands of probe sets were picked out for further analysis, which presented in all samples with intensities ranging from 100 to 10,000. These probe sets were also present in the MAQC list for Affymetrix U133 Plus 2.0 microarray and were proved

Table 1
Final panel of 5 genes.

Probe set ID	Gene symbol	Fold change(linear)	P-value
203047_at	STK10	1.03	0.78
200661_at	CTSA	1.10	0.18
202298_at	NDUFA1	1.05	0.31
208680_at	PRDX1	−1.04	0.67
212213_x_at	OPA1	1.05	0.07

Download English Version:

https://daneshyari.com/en/article/2774862

Download Persian Version:

https://daneshyari.com/article/2774862

Daneshyari.com