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ORIGINAL ARTICLE

Adrenergic receptor polymorphisms in patients with stress (tako-tsubo) cardiomyopathy

Scott W. Sharkey (MD)[a,*], Barry J. Maron (MD)[a], Penny Nelson (PRA)[b], Mary Parpart (RN)[a], Martin S. Maron (MD)[c], Michael R. Bristow (MD, PhD)[b]

[a] *Hypertrophic Cardiomyopathy Center and Cardiovascular Research Division of the Minneapolis Heart Institute Foundation, Minneapolis, MN, USA*
[b] *Division of Cardiology, University of Colorado Health Science Center, Denver, CO, USA*
[c] *Division of Cardiology, Tufts-New England Medical Center, Boston, MA, USA*

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KEYWORDS
Cardiomyopathy;
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Summary
Background: Stress (tako-tsubo) cardiomyopathy (SC) is a newly reported condition afflicting older women, characterized by acute left ventricular (LV) systolic dysfunction, triggered by emotionally and physically stressful events, and occurring without significant coronary obstruction. Sympathetic nervous system hyperactivity has been implicated in the pathophysiology of SC. Single nucleotide polymorphisms involving the adrenergic receptors (AR) might result in susceptibility to SC.
Methods: Forty-one female SC patients were identified aged 34—89 years (mean 65) and were compared with 43 control females of similar age with respect to AR genotype frequencies for B1 receptor (amino acid positions 389 and 49) and alpha 2c receptor (deletion 322—325).
Results: For SC patients, initial LV ejection fraction was $32 \pm 10\%$ vs. $62 \pm 11\%$ in control patients, $p < 0.05$. Genotype frequencies for SC patients vs. controls were B1 389 Arg/Arg (0.49 vs. 0.51), B1 389 Arg/Gly (0.49 vs. 0.49), B1 389 Gly/Gly (0.02 vs. 0), B1 49 Ser/Ser (0.88 vs. 0.81), B1 49 Ser/Gly (0.12 vs. 0.16), B1 49 Gly/Gly (0 vs. 0.02), alpha 2c Wt/Wt (0.93 vs. 0.86), and alpha 2c Wt/Del 322—325 (0.07 vs. 0.14); p = ns for all comparisons.
Conclusions: Genotype polymorphism frequencies for B1 receptor (amino acid positions 389 and 49) and alpha 2c receptor (deletion 322—325) are not significantly different in SC patients compared to female controls. These data suggest that these

* Corresponding author at: Minneapolis Heart Institute Foundation, 920 E. 28th Street, Suite 620, Minneapolis, MN 55407, USA. Tel.: +1 612 863 3996; fax: +1 612 863 3875.
E-mail address: scott.sharkey@allina.com (S.W. Sharkey).

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AR polymorphisms do not mediate the sympathetic nervous system hyperactivity in SC patients.

Introduction

Stress (tako-tsubo) cardiomyopathy (SC) is a recently recognized acute cardiac syndrome characterized by the sudden onset of regional left ventricular (LV) systolic dysfunction typically triggered by an acute emotional or physical stress. The association of this syndrome with an acute stressful event, particularly in older women, has suggested to investigators a pathophysiologic role for the sympathetic nervous system [1—9]. Indeed, substantial elevations of plasma catecholamines (epinephrine, norepinephrine, and dopamine) have been reported in patients with stress cardiomyopathy [7].

Single nucleotide polymorphisms of the B1 and alpha 2c adrenergic receptors result in enhanced myocyte receptor function and enhanced synaptic norepinephrine release and theoretically could result in harmful sympathetic nervous system overactivity [10,11]. It is therefore reasonable to consider such genetic variation within the sympathetic nervous system as a predisposing factor for this cardiomyopathy. We postulated that unique single nucleotide polymorphisms involving the B1 adrenergic receptor (amino acid positions 389 or 49) and/or the alpha 2c adrenergic receptor (deletion 322—325) might result in susceptibility to SC.

Methods

Patient population

Between August 2001 and April 2006, 41 patients with SC presented to the Minneapolis Heart Institute and Abbott Northwestern Hospital and also consented to genetic analysis.

All patients were female and demonstrated the following features: (1) acute cardiac event typically presenting with substernal chest discomfort; (2) systolic dysfunction characterized by akinesia/hypokinesia of the mid and distal LV chamber associated with a hypercontractile basal LV segment (morphologic appearance of tako-tsubo cardiomyopathy); (3) absence of significant atherosclerotic coronary artery stenosis (i.e. $\leq$50% luminal narrowing) in the three epicardial coronary arteries at coronary angiography; (4) a stressful (emotional or physical) triggering event; and (5) no morphologic evidence of myocardial infarction (absent delayed hyperenhancement on cardiac MRI) with subsequent normalization of LV systolic function, consistent with myocardial stunning [4].

Genotyping

A 7-cm^3 blood sample was obtained from each SC patient and frozen for subsequent genetic analysis. Genomic DNA was extracted from the sample and adrenergic receptor polymorphisms were determined as previously described [12]. Samples were collected on an outpatient basis after hospital discharge. The genotypes are referred to as wild-type alpha 2c-adrenoreceptor (the more common variant), alpha 2c Del 322—325 (the variant with deletion of four amino acids), B1Arg389, B1Gly389, B1Ser49, and B1Gly49.

Control patients

For purposes of comparison, we used historical genotype data from 43 females whose hearts had been donated for purposes of cardiac transplantation. These patients were obtained from the database maintained at the University of Colorado (MRB and PN) and matched as closely as possible to SC patients with respect to age.

Statistical analyses

Continuous variables are reported as mean $\pm$ S.D. and assessed with paired or unpaired Student's *t*-test, as appropriate. Categorical variables were compared with standard chi-square test. Statistical significance was defined as $p \leq 0.05$. GB-STAT statistical software version 9.0 (Dynamic Microsystems, Silver Spring, MD, USA) was used in all analyses. The protocol and consent form for this study was approved 24 April 2006 by the Abbott Northwestern Hospital Institutional Review Board, Minneapolis, MN (IRB file number 2154-1E). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by this institution's human research board.