



ELSEVIER

ORIGINAL ARTICLE

JOURNAL of
CARDIOLOGY

Official Journal of the Japanese College of Cardiology

www.elsevier.com/locate/jjcc

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

Received 8 July 2008; received in revised form 20 August 2008; accepted 22 August 2008
Available online 9 October 2008

KEYWORDS

Cardiomyopathy;
Heart failure;
Sympathetic nerve;
Stress

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); $p = \text{ns}$ 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).

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

© 2008 Japanese College of Cardiology. Published by Elsevier Ireland Ltd. All rights reserved.

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-cm³ 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.

Results

The 41 SC patients ranged in age from 34 to 89 years (mean 65 ± 11 years) with a racial distribution of Caucasian ($n=40$, 98%) and Hispanic ($n=1$, 2%). The 43 control patients ranged in age from 51 to 75 years (mean 59 ± 6 years, $p < 0.05$) with a racial distribution of Caucasian ($n=35$, 82%), Hispanic ($n=3$, 7%), African American ($n=1$, 2%), and unknown ($n=4$, 9%). In SC patients, initial LV ejection fraction was mean $32 \pm 10\%$ vs. mean $62 \pm 11\%$ in control patients, $p < 0.05$.

In SC patients, the inciting stressor was emotional in 31 (76%) and physical in 10 (24%) patients. ST-segment elevation was present on initial electrocardiogram in 20 (49%) SC patients. Troponin T or I was elevated at admission or during hospitalization in 40 (98%) SC patients.

In SC patients, the wild-type alpha 2c adrenoreceptor genotype was present in 93% of patients, while the heterozygous genotype (Wt/Del 322–325) was present in 7% of patients (no SC patients were homozygous for Del 322–325). For the B1 adrenoreceptor (amino acid position 389), the genotype was homozygous Arg/Arg in 49%, heterozygous Arg/Gly in 49% and homozygous Gly/Gly in 2% of SC patients. For the B1 adrenoreceptor (amino acid position 49), the genotype was homozygous Ser/Ser in 88%, and heterozygous Ser/Gly in 12% of SC patients (no SC patients were homozygous for Gly).

The genotype frequency of polymorphisms (alpha 2c Del322–325, B1Arg389, and B1Ser49) in SC patients is compared with those of control patients in Table 1. No significant differences were present in the polymorphism frequencies between the two groups.

Discussion

The sudden onset of SC, virtually always triggered by a stressful event, intuitively suggests a pathophysiologic role for the sympathetic nervous system in this condition. Indeed, plasma catecholamines (epinephrine, norepinephrine, and dopamine) are substantially elevated in patients during the acute phase of this condition, often to levels exceeding those observed in patients with acute myocardial infarction and similar degrees of LV dysfunction [7]. In addition, case reports document the occurrence of the SC syndrome in patients with pheochromocytoma or paraganglioma [13,14]. Catecholamine excess could mediate a direct cardiomyopathic effect via overstimulation of the B1 cardiac receptor [15]. Alternatively, over-stimulation of the alpha-1 and

Table 1 Genotype frequencies of alpha 2c, B1-389, and B1-49 adrenoreceptors in stress cardiomyopathy and control patients

	Alpha 2c Wt/Wt	Alpha 2c Wt/Del 322–325	B1 389 Arg/Arg	B1 389 Arg/Gly	B1 389 Gly/Gly	B1 49 Ser/Ser	B1 49 Ser/Gly	B1 49 Gly/Gly
SC ($n=41$)	0.93*	0.07*	0.49*	0.49	0.02*	0.88*	0.12*	0*
Control ($n=43$)	0.86	0.14	0.51	0.49	0	0.81	0.16	0.02

SC, stress cardiomyopathy.

* Not significant compared with control patients.

alpha-2 adrenoreceptors of the small coronary arteries and arterioles (<300 μm diameter) could result in non-physiologic vasoconstriction leading to myocardial ischemia [16]. Single nucleotide polymorphisms within the alpha and beta adrenergic receptors have been proposed as a basis for physiologic variability within the sympathetic nervous system in humans [10,11]. Two common polymorphisms of human B1-adrenergic receptor result in either an arginine (B1Arg389) or a glycine (B1Gly389) at amino acid position 389 [10]. Experimentally, the Arg type B1 receptor displays increased coupling to the stimulatory G protein resulting in increased adenylyl cyclase activity when compared to the Gly variant [10]. Another known B1-adrenergic receptor polymorphism involves substitution of Gly for Ser at amino acid position 49 (B1 49) and may also enhance B1 receptor function [17,18].

In addition, sympathetic nervous system activity is modulated by inhibitory pre-synaptic alpha 2-adrenoreceptors [19]. The alpha 2c receptor controls norepinephrine release from cardiac sympathetic nerves. In humans, a 4-amino acid deletion polymorphism exists (alpha 2c Del 322–325) and is associated with decreased G-protein coupling which could lead to increased norepinephrine release and consequently sympathetic over-stimulation [19].

This study demonstrates no significant differences in the frequencies of these adrenoreceptor polymorphisms in patients with SC when compared to female controls. The SC patients reported in this study are predominantly Caucasian and the polymorphism frequencies for other racial groups with SC (including Asian in whom this cardiomyopathy was first reported) is unknown. Nonetheless, these observations effectively exclude single nucleotide polymorphisms of these particular adrenoreceptors as operative in the sympathetic nervous system over-activity observed in SC. Currently unrecognized polymorphisms may emerge for future genetic analysis. Further studies of SC should also consider alternative hypotheses such as regional differences in myocardial adrenergic receptor density, asymmetry in myocardial sympathetic innervation, or variability in those areas of the brain which modulate cardiac sympathetic activity.

References

- [1] Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, et al. Systematic review—transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004;141:858–65.
- [2] Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* 2003;41:743–8.
- [3] Owa M, Aizawa K, Urasawa N, Ichinose H, Yamamoto K, Karasawa K, et al. Emotional stress-induced ‘apical cardiomyopathy’: discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. *Jpn Circ J* 2001;65:349–52.
- [4] Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472–9.
- [5] Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol* 2001;38:11–8.
- [6] Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoreceptors: a possible animal model of ‘tako-tsubo’ cardiomyopathy. *Circ J* 2002;66:712–3.
- [7] Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenbligh G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539–48.
- [8] Tagawa M, Nakamura Y, Ishiguro M, Satoh K, Chinushi M, Kodama M, et al. Transient left ventricular apical ballooning developing after the Central Niigata Prefecture Earthquake: two case reports. *J Cardiol* 2006;48:153–8.
- [9] Cheng TO. Takotsubo cardiomyopathy represents a stress-induced myocardial stunning. *J Cardiol* 2007;49:106–7.
- [10] Small KM, Wagoner LE, Levin AM, Kardias SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med* 2002;347:1135–42.
- [11] Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005;111:2837–49.
- [12] Small KM, Rathz DA, Liggett SB. Identification of adrenergic receptor polymorphisms. *Methods Enzymol* 2002;343:459–75.
- [13] Spes C, Knape A, Mudra H. Recurrent tako-tsubo-like left ventricular dysfunction (apical ballooning) in a patient with pheochromocytoma—a case report. *Clin Res Cardiol* 2006;95:307–11.
- [14] Van Spall HG, Roberts JD, Sawka AM, Swallow CJ, Mak S. Not a broken heart. *Lancet* 2007;370:628.
- [15] Mann DL, Kent RL, Parsons B, Cooper 4th G. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 1992;85:790–804.
- [16] Heusch G, Baumgart D, Camici P, Chilian W, Gregorini L, Hess O, et al. Alpha-adrenergic coronary vasoconstriction and myocardial ischemia in humans. *Circulation* 2000;101:689–94.
- [17] Börjesson M, Magnusson Y, Andersson B. A novel polymorphism in the gene coding for the beta 1-adrenergic receptor associated with survival in patients with heart failure. *Eur Heart J* 2000;21:1853–8.

- [18] Levin MC, Marullo S, Muntaner O, Andersson B, Magnusson Y. The myocardium-protective Gly-49 variant of the beta 1-adrenergic receptor exhibits constitutive activity and increased desensitization and down-regulation. *J Biol Chem* 2002;277:30429–35.
- [19] Small KM, Forbes SL, Rahman FF, Bridges KM, Liggett SB. A four amino acid deletion polymorphism in the third intracellular loop of the human alpha 2C-adrenergic receptor confers impaired coupling to multiple effectors. *J Biol Chem* 2000;275:23059–64.

Available online at www.sciencedirect.com



ScienceDirect