Reproductive History of Women With Takotsubo Cardiomyopathy

Elena Salmoirago-Blotcher, MD, PhD[a,b,*], Shira Dunsiger, PhD[b,c], Heather H. Swales, MD[d], Gerard P. Aurigemma, MD[e], Ira Ockene, MD[e], Lindsey Rosman, PhD[f], and Ilan S. Wittstein, MD[g]

Takotsubo cardiomyopathy (TC) occurs predominantly in postmenopausal women, suggesting a possible role of reproductive and hormonal factors in the pathophysiology of this condition. Yet reproductive characteristics of women with TC have received limited attention. This prospective case-control study sought to explore reproductive characteristics associated with TC. Incident TC cases and myocardial infarction (MI) controls were recruited among consecutive women presenting at the emergency departments of 2 large medical centers in Massachusetts and Connecticut. Female healthy controls were recruited from a registry of research volunteers. Information about reproductive history was collected 1 month after discharge using standardized questionnaires completed during phone interviews. Linear and logistic regression models were used to estimate associations with reproductive factors. From March 2013 to October 2015, 209 women were screened for eligibility and 107 (45 TC, 32 MI, and 30 healthy controls) were enrolled. Conditions uniquely associated with TC were a history of irregular menses (adjusted OR, TC vs MI 8.30; 95% CI 1.01 to 69.18), number of pregnancies (adjusted β coefficient 0.69; SE 0.35, p = 0.05), and use of post-menopausal hormone replacement therapy (OR 5.79; CI 1.20 to 28.02). We did not find associations with history of infertility, breastfeeding, hysterectomy or oophorectomy, oral contraceptive use, and age at menopause. In conclusion, our findings suggest that premenopausal reproductive factors may play an important role in the onset of TC at a later age. These results need to be confirmed in future studies with larger populations. **(Am J Cardiol 2016;■:■−■)**

Takotsubo cardiomyopathy (TC) is a syndrome characterized by acute left ventricular dysfunction accompanied by electrocardiographic changes and cardiac enzyme elevation in the absence of significant coronary artery disease.[1,2] A physical or emotional trigger precedes the occurrence of TC in 40% to 70% of cases[2−4] and 90% of cases are diagnosed in post-menopausal women.[3,4] This association suggests that low estrogen levels may play a role in the pathogenesis of this syndrome. Although there is a general consensus that an exaggerated sympathetic stimulation plays an important role in the development of TC,[5,6] the role of hormonal factors is still unclear. Studies conducted in animal models of TC have shown that estrogen supplementation reduces responses to emotional stress.[7−9] The few clinical studies examining reproductive characteristics of women with TC have yielded conflicting results.[10−13] The purpose of this study was to investigate whether the occurrence of TC is associated with specific reproductive characteristics. We expected that, consistent with laboratory evidence in animal models, conditions associated with low estrogen levels (i.e., a history of oophorectomy) would be more prevalent in TC women. In addition, we were interested in assessing whether conditions associated with a lifelong exposure to lower estrogen levels may play a role in the onset of this syndrome.

Methods

To study the reproductive history of women with TC, we conducted a prospective (i.e., enrolling incident cases and controls) case-control study. Inclusion criteria for TC cases were age ≥21 years, a first diagnosis of TC fulfilling Mayo Clinic diagnostic criteria,[14] English fluency, and access to a telephone. Exclusion criteria were inability or unwillingness to provide informed consent; a history of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy; dementia or severe cognitive impairment; and being clinically unstable. Women with TC associated with intracranial bleeding or head trauma were excluded because of cognitive and neurologic deficits impairing the ability to complete study interviews.

Controls were women admitted with a confirmed diagnosis of acute nonfatal myocardial infarction (MI) and a group of healthy controls (HC). Inclusion criteria for MI controls were age ≥21 years, a diagnosis of MI meeting

[a]Department of Medicine, Medical School, and [c]Department of Behavioral and Social Sciences, School of Public Health, Brown University, Providence, Rhode Island, USA; [b]Centers for Behavioral and Preventive Medicine, The Miriam Hospital, Providence, Rhode Island, USA; [d]Department of Medicine, Hartford Hospital, Hartford, Connecticut, USA; [e]Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, USA; [f]Department of Psychology, East Carolina University, Greenville, North Carolina, USA; and [g]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Manuscript received May 13, 2016; revised manuscript received and accepted August 19, 2016.

This work was supported by the American Heart Association (Dallas, Texas) award 13CRP1334001 to Dr. Salmoirago-Blotcher.

See page 6 for disclosure information.

*Corresponding author: Tel: (401) 793-8325; fax: (401) 793-8059.

E-mail address: elena_salmoirago-blotcher@brown.edu (E. Salmoirago-Blotcher).

0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.08.083

current diagnostic criteria,[15] English fluency, and access to a telephone. Women were excluded if they had a previous diagnosis of TC, were unable or unwilling to give informed consent, and if they were clinically unstable. Eligibility criteria for HC were age ≥21 years, English fluency, and access to a telephone. HC were excluded if they had a previous diagnosis of TC, a chronic condition (any cancer other than non-melanoma skin cancer, cardiovascular disease, liver failure, or renal failure), and a history of dementia or severe cognitive impairment. A trained physician abstractor blinded to the study outcomes confirmed eligibility for the study for all conditions.

TC and MI women were recruited among incident consecutive cases presenting at emergency departments of 3 large medical centers in the New England region from March 2013 to October 2015. Participants were identified through physician referral and daily reviews of computerized listings from cardiac catheterization laboratories, echo laboratories, and emergency departments. HC were recruited from a registry of research volunteers at the University of Massachusetts Medical School. All participants received a letter describing the study and inviting them to participate. To avoid selection bias (i.e., excluding women who were too ill or refused a coronary angiogram), TC cases that did not undergo an angiogram but otherwise met all other diagnostic criteria at discharge were also enrolled. A phone interview was scheduled for women expressing interest in study participation. After obtaining verbal informed consent and authorization to access medical records, research personnel conducted the study interview ∼1 month after discharge using a standardized script to elicit information consistently across participants. Both the interviewer and the study participants were blinded to the study outcomes and to participants' case or control status. The study was approved by the institutional review board at each participating institution.

Research Electronic Data capture technology was used to conduct computer-assisted interviews with direct data entry into electronic study surveys. Information about reproductive characteristics was collected using a survey modeled after the reproductive history questionnaire used for the Women's Health Initiative Observational Study.[16] The information collected included: age at first ("How old were you when you had your first menstrual period?") and last menstrual period (How old were you when you last had any menstrual bleeding?), history of menstrual irregularities ("during most of your life, were your periods regular, i.e., did they occur about once a month, not including any time when your were pregnant or taking birth control pills?"), history of ovarian dysfunction ("Between your first and your last period, did you go without any period for at least a year, not counting any time when your were pregnant or taking birth control pills?"), infertility ("Have you ever tried to become pregnant for more than one year without becoming pregnant?"), number of pregnancies, breastfeeding history ("Did you breastfeed any children for at least one month?"), history of menopausal symptoms ("Have you ever had menopausal symptoms such as hot flashes or night sweats?"), history of oophorectomy or hysterectomy and age at surgery, oral contraceptive use and duration of use ("Did you ever take birth control pills, diethylstilbestrol, or shots called Depo-Provera for birth control or any other reasons?"), use of hormone replacement therapy (HRT) ("Did you take hormone replacement therapy, that is, hormones that are taken around the time of menopause or after menopause, not including hormones used for birth control"), and duration of use.

Information about age, race/ethnicity, marital status, income, and education was collected directly from the participants using standardized questionnaires. Information about medical history (including coronary risk factors) was abstracted from the medical record with the exception of physical activity (frequency of walking outside the home for at least 10 minutes without stopping) and family history of coronary heart disease (CHD) (self-reported questionnaire). Body mass index was calculated from height and weight measurements at admission reported in the medical record.

Demographic and reproductive characteristics were compared using ANOVA (or nonparametric tests where applicable) for continuous measures and chi-square statistics for categorical variables. Generalized linear models and logistic regression models (adjusted for variables that were associated with the outcomes of interest with $p \leq 0.1$) were used to estimate associations with reproductive characteristics, with HC as the reference group. For all estimates, p values or 95% confidence intervals were calculated. All study analyses were performed using SAS, version 9.3, statistical software.

Results

From March 2013 to October 2015, 107 women (45 TC cases, 32 MI controls [STEMI, n = 24; non-STEMI, n = 8]) and 30 HC were enrolled in the study (Figure 1). HC had higher income and education and were slightly older compared with MI and TC, whereas other demographic characteristics were similar across groups (Table 1). Although diabetes and dyslipidemia, as well as a higher body mass index, were more common among MI controls, a history of smoking, a family history of CHD, and hypertension were also highly prevalent among TC cases. Clinical characteristics at admission were fairly similar between TC cases and MI controls with the exception of peak troponin levels, ejection fraction, and systolic blood pressure, which were lower in TC women. The diagnosis of TC was not angiographically confirmed in 15 women. These women, however, did fulfill all other diagnostic criteria for TC and received a final diagnosis of TC at discharge. Angiographically confirmed TC cases did not significantly differ from nonconfirmed cases in terms of baseline demographics and medical history (data not shown).

Unadjusted reproductive characteristic by case-control status are listed in Table 2, whereas findings from multivariable adjusted models are presented in Tables 3 (logistic regression) and 4 (linear regression).

Both TC cases and MI controls were younger than HC at their first menstrual period, with no significant differences between TC and MI. Women with TC were more likely to report irregular menses compared with HC and MI: in adjusted models, TC women were 8 times more likely than MI controls to have a history of irregular menses. The prevalence of a history of infertility was similar across