Distinctive Clinical Characteristics According to Age and Gender in Apical Ballooning Syndrome (Takotsubo/Stress Cardiomyopathy): An Analysis Focusing on Men and Young Women

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ABSTRACT

Background: Apical ballooning syndrome (ABS) predominantly affects postmenopausal women. There is a paucity of data regarding ABS in men and young women. The aim of this study was to compare the clinical characteristics and outcomes of men and young women (<50 y) to older women (≥50 y).
Methods & Results: We retrospectively reviewed the records of 224 patients and divided them into men (n = 12), young women (n = 12), and older women (n = 200). Older women were further subdivided into those who were and were not on hormone replacement therapy (HRT) at the time of presentation. Men were more likely to present after a physical trigger (100% vs 46%; $P = .009$), have lower ejection fractions (30.1 ± 8.0% vs 40 ± 13.9%; $P = .04$), and have greater need for mechanical ventilation (67% vs 17%; $P < .0001$) compared with older women. Younger women were more likely to have a history of psychiatric disorders (75% vs 24%; $P = .0001$) at presentation and a higher rate of recurrence (16% vs 3%; $P = .017$) compared with older women. Of the older women, 15 developed ABS while on chronic HRT. Those without HRT were more likely to require mechanical hemodynamic (7.7% and 0%; $P = .002$) and ventilatory (18.1% and 0%; $P = .017$) support compared with older women who were on HRT.
Conclusions: Men appeared to develop ABS as a consequence of a physical trigger, whereas young women had a higher rate of psychiatric comorbidities and a greater propensity for recurrence. Treatment with HRT in older women does not preclude the development of ABS. (*J Cardiac Fail 2013;19:306–310*)
Key Words: Apical ballooning syndrome, takotsubo cardiomyopathy, stress cardiomyopathy.

Apical ballooning syndrome (ABS) is a unique cardiomyopathy primarily characterized by depressed left ventricular systolic function, typically involving the midventricular and apical segments, and it frequently occurs following a physical or emotional stressor.[1,2] Commonly referred to as stress or takotsubo cardiomyopathy, the condition generally occurs in patients without obstructive epicardial coronary atherosclerosis, and by and large outcomes are characterized by improvement in left ventricular systolic function over time. As ABS has gained recognition as a clinical entity, it has become evident that, although it predominantly occurs in postmenopausal women, it may occasionally also be diagnosed in men and young women.[3] There is a paucity of data regarding these infrequent but important subsets of patients. Therefore, the aim of the present study was to describe the clinical characteristics and outcomes of men and young women and compare them with the typical older (''postmenopausal'') women who are at risk for ABS.

Methods

We conducted a retrospective analysis of the electronic medical records of patients who were prospectively identified with ABS during the time period from January 2002 to January 2012 at the Mayo Clinic. The diagnosis of ABS was based on the Mayo Clinic criteria[2]: 1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical

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involvement, the regional wall motion abnormalities extending beyond a single epicardial vascular distribution, and a stressful trigger often, but not always, present; 2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and 4) clinical absence of pheochromocytoma or myocarditis. Two-hundred twenty-four cases who met these criteria were divided into 3 groups: men (n = 12), women <50 years old (n = 12), and women ≥50 years old (n = 200). The women ≥50 years were further subcategorized into patients who were on systemic hormone replacement therapy (HRT) for >1 year at the time of the diagnosis (n = 15). The clinical, laboratory, electrocardiographic (ECG), and imaging data were obtained from the medical records. All subjects consented to the use of their medical records for research purposes, and the Mayo Clinic Institutional Review Board approved the study.

All continuous variables which demonstrated near-normal distribution are summarized as mean ± SD and were analyzed with the use of a 1-way analysis of variance. The between-group comparisons were tested with the use of a Student 2-sample *t* test. For continuous variables that did not demonstrate symmetric distribution, data are expressed as median and interquartile range and compared with the use of the Wilcoxon rank sum test. Categoric variables are represented as a frequency and tested with the use of the Pearson chi-square test. Kaplan-Maier analyses were done to compare recurrence-free survivals among the three cohorts. A P value of <.05 was considered to be statistically significant for comparison of men versus women. In Table 1, owing to multiple comparisons, $P < .025$ was considered to be statistically significant. Statistical analyses were performed with the use of JMP 9.0.

Results

Men Compared With Women ≥50 Years

Table 1 summarizes the baseline clinical characteristics, ECG findings, biomarker levels, echocardiographic features, left ventriculogram data, and clinical outcomes. There was no difference in the age and frequency of cardiovascular risk factors between the groups. Men were more likely to present after a physical trigger (100%) compared with women (46.5%; $P = .009$; Fig. 1). Physical triggers in males included acute exacerbation of chronic obstructive pulmonary disease (n = 5), invasive procedures (liver transplant, exploratory laparatomy, hepatic artery embolization, and bronchoscopy), dobutamine stress echocardiography, alcoholic pancreatitis with withdrawal symptoms and shoveling snow. There was no difference regarding history of psychiatric diseases, connective tissue/autoimmune disorders, irritable bowel syndrome, or fibromyalgia. ECG and cardiac biomarker profiles were similar between the groups except for peak B-type natriuretic peptide levels, which were significantly elevated in older women compared with men ($P = .0136$). Echocardiographically determined ejection fraction at admission was lower in men ($P = .02$). Linear regression analysis of initial ejection fraction by echocardiography correlated positively with age ($r = 0.75$; $P = .009$). A similar trend was observed with the ejection fraction derived by left ventriculography which was associated with significantly elevated end-systolic and -diastolic volumes compared with women. Men were more likely to require mechanical ventilation following the diagnosis of ABS compared with women ($P < .0001$).

Young Versus Older Women

Older females were more likely to have hypertension and coronary artery disease at presentation (P values .015 and .004, respectively; Table 1). Younger women were more likely to have a history of psychiatric disorders (75% vs 24%; $P = .0001$), such as anxiety (17% vs 8.0%; $P = .30$) and depression (75% vs 17%; $P < .0001$), and migraines (25% vs 4%; $P = .0006$) at presentation, but there was no difference in the frequency of Raynaud phenomenon, connective tissue/autoimmune diseases, irritable bowel syndrome, or fibromyalgia between the groups. There were no significant differences regarding findings on the ECG, biomarkers, echocardiography, and left ventriculography.

Older Women and Hormone Replacement Therapy

Diabetes mellitus was more prevalent in patients without HRT compared with those with HRT. The ECG, biomarker, echocardiographic, and left ventriculographic data were similar between these groups. Patients without HRT had a statistically non-significant trend toward lower ejection fractions (39.7% and 45.4%; $P = .19$), and they were more likely to require mechanical hemodynamic (7.7% and 0%; $P = .002$) and ventilatory (18.1% and 0%; $P = .017$) support.

Clinical Outcomes, Mortality, and Recurrence

The ejection fraction at follow-up (2.2 ± 3.7 mo) increased to a normal level in each of the 3 groups (Fig. 2). There were no deaths in women <50 years (mean follow-up 3.2 y). The in-hospital mortality in men was 17% (n = 2), and 3 additional deaths occurred during follow-up. All deaths were due to noncardiac causes. The in-hospital mortality in women ≥50 years was 6% (n = 11), and an additional 40 patients died during follow-up. Of those 51 deaths, 11 were due to cardiac causes. There was no significant difference between men and women ≥50 years regarding cause of death ($P = .36$) and mortality rates ($P = .35$). None of the men had a recurrence of ABS during a mean follow-up duration of 1.3 years (Fig. 3). Of the women <50 years, 2 (16%) had a recurrence over a mean follow-up of 3.5 years. In the women ≥50 years, 5 (3%) developed a recurrence of ABS over a mean follow-up duration of 3.3 years.

Discussion

Our study provides the most comprehensive evaluation of clinical phenotype of men and young women diagnosed with ABS to date, compared with women ≥50 years old (“the typical patient”). The major findings are: 1) Male

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