Clinical Characteristics, Sex Hormones, and Long-Term Follow-Up in Swiss Postmenopausal Women Presenting With Takotsubo Cardiomyopathy

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ABSTRACT

Background: The overwhelming majority of patients with stress cardiomyopathy (SC) are postmenopausal women, suggesting an important pathophysiologic role of the female sex hormones. Preliminary data suggest that myocardial stunning might be provoked by estrogen deficiency.

Hypothesis: We hypothesized that, compared with age- and gender-matched patients with myocardial infarction (MI) or patients with normal coronary arteries, patients with SC would exhibit altered levels of sex hormones. Furthermore, we aimed to describe the clinical course and the pattern of sex hormones of the SC patients during long-term follow-up.

Methods: Blood samples obtained on hospital admission were analyzed for estradiol (E2), progesterone (P), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in women with SC ($n = 17$), age-matched women with acute MI ($n = 16$), and women with normal coronary arteries ($n = 15$). Six years after the initial event, SC patients underwent a clinical and echocardiographic follow-up and reassessment of sex hormones.

Results: Estrogen concentrations at hospital admission were significantly higher in the SC group compared with the MI and the control groups, with no difference in P, FSH, and LH concentrations. Follow-up E2 after 6 years in SC patients was lower than during the acute SC episode. Follow-up P in these patients was lower than P in the MI and control groups during the acute event, with a similar trend for E2. After a median follow-up of 6.4 years, 1 sudden cardiac death occurred and 2 patients suffered from SC recurrence.

Conclusions: During the acute event, E2 concentrations are elevated in postmenopausal SC patients compared with women with acute MI or with normal coronary arteries. The higher E2 concentrations might have exerted atheroprotective effects and thus diverted the stress response to SC rather than MI. Recurrence and/or sudden cardiac death remains a potential risk of SC.

Introduction

Transient left ventricular apical ballooning syndrome, also known as stress cardiomyopathy (SC) or takotsubo cardiomyopathy, is an increasingly observed entity in clinical practice. Whereas the clinical features of SC have been well characterized over the last years, the underlying pathophysiology is still incompletely understood, and the long-term outcome beyond 2 years not well documented. Stress cardiomyopathy is associated with 2 striking epidemiological features that give rise to speculation about

its underlying mechanisms. First, the acute event is often precipitated by acute and extraordinary emotional stress, which led to the assumption that catecholamines play an important role. In fact, in some studies significantly elevated circulating catecholamine concentrations were found, and abnormalities of cardiac sympathetic innervation with evidence of sympathetic hyperactivity at the cardiac apex have been demonstrated.^{1,2} Perhaps even more important is the recent description of several cases of SC induced by exogenous adrenaline/dobutamine administration.³ The second striking feature is related to the fact that the overwhelming majority of patients with SC are postmenopausal women.⁴ This raises the possibility that a sex-hormone imbalance may play a role in the pathophysiology of SC. Interestingly, the hormonal status of these patients has never been characterized. In the present study, we therefore compared sex-hormone levels

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between SC patients and age- and sex-matched controls presenting with myocardial infarction (MI) and patients with normal coronary arteries. Furthermore, we assessed long-term prognosis of the cohort of patients presenting with SC.

Methods

All patients provided written informed consent. The local ethics committee of the Cantonal Hospital St. Gallen approved the study protocol. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Patients and Protocol

We prospectively identified a total of 23 patients with SC admitted to our cardiac catheterization laboratory from October 2003 to May 2005, defined as follows⁴: (1) transient apical or basal left ventricular (LV) wall-motion abnormalities in the initial ventriculography not attributable to a single coronary artery territory, (2) the absence of significant stenosis ($\geq 50\%$ of the luminal diameter) of epicardial coronary arteries, and (3) new electrocardiographic (ECG) abnormalities. Exclusion criteria were amenorrhea < 2 months or ongoing hormone-replacement therapy (HRT) to prevent confounding of hormone concentrations (primary endpoint). Six patients were excluded from further analysis due to cerebral hemorrhage (2 patients), persistent HRT (1 patient), and lack of blood samples (3 patients).

During the same period, we recruited 2 age- and sex-matched (women only) control groups consisting of 17 patients each, applying the same exclusion criteria as mentioned above. Patients in the first control group (MI group) were referred for percutaneous coronary intervention due to acute MI (ST-segment elevation MI or non-ST-segment elevation MI); 1 patient of this group was excluded due to HRT. Patients in the second control group (control) consisted of women who were referred to our hospital for coronary angiography because of chest pain without evidence of acute MI and who were finally shown to have no significant coronary artery stenosis. Two of these patients were on ongoing HRT and were excluded.

Laboratory Analyses

In all patients, troponin I, cardiac form (cTnI), creatine kinase (CK), creatinine, C-reactive protein (CRP), total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), hemoglobin, and leukocyte count were assessed at hospital admission. Serum samples drawn during cardiac catheterization were analyzed by a technician unaware of clinical data for estradiol (E2), progesterone (P), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) using the UniCel DxI 800 immunoassay system (Beckman Coulter, Chaska, MN).

Electrocardiography and Blood-Pressure Measurement

An ECG was recorded at hospital admission. Significant ST-segment elevation was defined as elevation of the J

point in 2 contiguous leads with the cutoff points ≥ 0.15 mV in leads V2 through V3 and/or ≥ 0.1 mV in other leads.⁵ T-wave inversion was defined as T-wave inversion ≥ 0.1 mV in 2 contiguous leads, and Q wave was defined as any Q wave in leads V2 through V3 ≥ 0.02 seconds or QS complex, and/or Q wave ≥ 0.03 seconds or ≥ 0.1 mV deep in 2 contiguous leads.⁵ The QT interval was measured using hand calipers and was corrected for heart rate using the Bazett formula. Two authors unaware of the clinical data measured the QT time and the R-R interval for calculating the corrected QT interval (QTc). If a difference between the measurements was present, the mean time was used for further calculations. Blood-pressure measurements also were recorded at hospital admission, using oscillometric devices.

Assessment of Left Ventricular Function and Wall-Motion Abnormalities

The initial left ventricular ejection fraction (LVEF) was assessed by ventriculography in all SC patients. According to the observed distribution of the wall-motion abnormalities, SC was categorized into 4 distinct types: (1) "typical" SC, for apical akinesia and basal hyperkinesias; (2) inverse SC, for basal akinesia and apical hyperkinesias; (3) midventricular type, for midventricular ballooning accompanied by basal and apical hyperkinesias; and (4) localized type, for any other segmental LV ballooning with clinical characteristics of SC-like LV dysfunction.⁶

Follow-Up Visits

All SC patients underwent follow-up echocardiograms 1 month after hospital discharge. Approximately 6 years after the index hospitalization, the patients were invited to another follow-up visit including a physical examination, echocardiography, and assessment of sex hormones.

Statistical Analysis

Data are expressed as mean $\pm$ SD or as median (interquartile range) as appropriate. The Kolmogorov-Smirnov test was used to test for normality. Analysis of variance (ANOVA) and Kruskal-Wallis test were performed for between-group comparisons. Post-hoc tests were done with Student Neuman-Keuls test for ANOVA and pairwise comparisons of subgroups according to Conover⁷ for the nonparametric ANOVA. For within-group comparisons, analysis was done by the Wilcoxon test and paired *t* test, respectively. A *P* value ≤ 0.05 was considered statistically significant. MedCalc software version 12.1.4.0 was used for statistical calculations.

Results

Clinical and ECG characteristics of the SC patients appear in Table 1. All 17 SC patients were female. Of these, 13 sought medical attention because of severe chest pain and additional dyspnea in 5 patients, and 2 patients were intubated due to respiratory failure. Three patients had significant mitral regurgitation. No patient had LV outflow tract obstruction. In 3 patients (18%), no distinct trigger for the SC was identified. In 6 patients (35%), a physical stressor

Table 1. Clinical and ECG Characteristics and Follow-Up of the 17 Patients With Stress Cardiomyopathy

Patient	Age, y	Symptoms	Trigger	Type of SC	ECG Abnormality ^a	Initial EF (%)	Cardiac Events During FU	EF FU (%)
1	68	CP + D	Heavy cycling	Typical	LBBB, TI	48	SC recurrence	65
2	58	CP + D	Nightmare	Typical	TI	47	None	60
3	84	Other	ND	Typical	LBBB	55	SC recurrence, SCD	NA
4	57	Other	Severe psychological problem	Typical	STE, TI, Q wave	58	None	60
5	85	CP	Heavy work in the garden	Typical	TI	65	None	55
6	65	Other	Hypoglycemia	Typical	STE, TI, Q wave	49	None	NA
7	73	CP	Cholecystectomy	Typical	TI, ST depression	70	None	NA
8	80	Other	ND	Typical	Q wave	36	None	60
9	84	CP	ND	Typical	TI	75	None	75
10	57	CP	Severe psychological problem	Typical	TI, Q wave	49	None	60
11	76	CP + D	Hemicolectomy	Typical	STE, RBBB	70	Aortic valve replacement	70
12	50	CP	Severe psychological problem	Typical	None	51	None	60
13	70	CP	Sawing a tree	Typical	TI, Q wave, LAFB	56	Hypertensive crisis	65
14	55	CP + D	Death of father	Typical	STE, ST depression	45	None	60
15	49	CP	Severe psychological problem	Typical	STE, ST depression, TI	75	None	75
16	50	CP + D	Accident	Inverse	ST depression, RBBB	33	None	55
17	70	CP	Severe psychological problem	Typical	ST depression, TI	40	None	60

Abbreviations: CP, chest pain; D, dyspnea; ECG, electrocardiographic; EF, ejection fraction; FU, follow-up at 1 month; LAFB, left anterior fascicular block; LBBB, left bundle branch block; NA, not available; ND, not determined; RBBB, right bundle branch block; SC, stress cardiomyopathy; SCD, sudden cardiac death; STE, ST-segment elevation; TI, T-wave inversion. ^aECG at hospital admission.

was identified, including recent surgery in 2 patients; and the remaining 8 patients (47%) reported an extraordinary emotional-stress situation prior to the cardiac event. The most common ECG features observed at hospital admission were T-wave inversion in 65%, ST-segment elevation and ST-segment depression in 33%, and Q wave in 29%. Two patients had left bundle branch block and 2 patients had right bundle branch block.

Coronary angiography and ventriculography were performed after a median of 1 day (0–4 days) after the onset of the clinical manifestations and showed a mean LVEF of $54\% \pm 13\%$. Fifty-six percent of patients had a reduced LVEF ($<55\%$). One patient had an inverse type of SC, whereas the other 16 patients had a typical apical ballooning pattern. All but 2 SC patients were on a β -blocker at hospital discharge.

Clinical Characteristics and Cardiac Biomarkers

Baseline clinical characteristics including cardiovascular risk factors and medications at hospital admission for all 3 groups are presented in Table 2. Hemodynamic and cardiac biomarker data are given in Table 3. Patients with MI were significantly more likely to have a history of dyslipidemia and had higher LDL concentrations compared with control patients and SC patients. The control group patients were more often treated with a β -blocker and thus had a lower heart rate than the other 2 groups, but there was no

statistically significant difference in systolic or diastolic blood pressure. The QTc time was longer in the SC group than in the MI and the control groups. Only 2 patients (13%) in the SC group had a peak CK level beyond the upper limit of 170 U/L, whereas 14 patients (82%) in the SC group were cTnI positive. Peak CK was higher in the MI group compared with the SC and control groups, whereas cTnI was elevated in both the SC and MI groups compared with the control group (Table 3).

Sex-Hormone Levels at Hospital Admission

The E2 concentration at hospital admission was significantly higher in the SC group compared with the MI and control groups, without significant differences between the 3 groups in P, FSH, and LH concentrations (Figure 1A–D, Table 4). The ratio of E2 to P was higher in SC patients compared with control patients ($7.45 [5.4–13.6]$ vs $0 [0–7.5]$; $P < 0.05$). Estradiol was positively correlated with P and inversely with CK (Spearman ρ 0.38, $P = 0.008$; and -0.31 , $P = 0.039$, respectively); in addition, both E2 and P were inversely correlated with age (Spearman ρ -0.29 , $P = 0.046$; and -0.35 , $P = 0.015$, respectively).

Compared with the lowest tertile, E2 concentrations in the highest tertile were associated with lower total cholesterol and lower LDL (5.0 ± 1.1 mmol/L vs 5.95 ± 0.8 mmol/L, $P = 0.035$; and 2.92 ± 1.0 mmol/L vs 3.93 ± 0.58

Table 2. Baseline Characteristics of the 3 Study Groups

	SC (n = 17)	MI (n = 16)	Control (n = 15)	P Value
Age (y)	66.6 ± 12.7	64.9 ± 12.6	64.1 ± 11.1	0.8
BMI (kg/m ²)	24.6 ± 3.3	24.2 ± 3.1	23.6 ± 1.8	0.56
Hemoglobin (g/L)	131 ± 8	129 ± 14	131 ± 9.9	0.82
WBC (g/L)	8 ± 4	10 ± 4 ^a	6.5 ± 1.7 ^a	0.04
CRP (mg/L)	3 (1.5–9.3)	5 (3–8)	3 (3–5)	0.18
Creatinine (μmol/L)	77 ± 23	77 ± 20	76.4 ± 13	0.99
Cholesterol (mmol/L)	5.1 ± 1.3	5.8 ± 0.7	5 ± 1.4	0.07
LDL (mmol/L)	2.9 ± 1.2 ^a	3.8 ± 0.6 ^{a,b}	3 ± 1.2 ^b	0.03
HDL (mmol/L)	1.7 ± 0.5	1.4 ± 0.3	1.7 ± 0.5	0.17
Smoker, n (%)	5 (29)	6 (41)	1 (7)	0.12
Hypertension, n (%)	9 (53)	9 (59)	8 (53)	0.98
Family history of CVD, n (%)	4 (24)	8 (47)	5 (33)	0.28
Dyslipidemia, n (%)	10 (59)	16 (100)	10 (67)	0.02
β-Blocker therapy, n (%)	2 (12)	5 (29)	10 (67)	0.01
Aspirin therapy, n (%)	3 (18)	7 (41)	10 (67)	0.02
Statin therapy, n (%)	0 (0)	2 (12)	4 (27)	0.08

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; SC, stress cardiomyopathy; WBC, white blood cells. Continuous variables are given as mean ± SD or median (IQR) as appropriate. ^a*P* < 0.05. ^b*P* < 0.05.

mmol/L, *P* = 0.02, respectively). A history of dyslipidemia or statin use was associated with lower E2 concentrations (dyslipidemia: 22.0 [0–35.5] ng/L vs 31.5 [29–94] ng/L, *P* = 0.018; statin use: 0.0 [0.0–0.0] ng/L vs 27.0 [22.0–32.0] ng/L, *P* = 0.043). No correlation between sex-hormone concentrations and the acute-phase protein CRP, heart rate, or blood pressure could be demonstrated.

Follow-Up and Hormone Levels at Follow-Up Visit

The first follow-up visit was scheduled 1 month after the acute episode, and a second long-term follow-up visit was performed after a mean time of 6.4 years (range, 5.4–7.7

years). Thirteen patients had a follow-up echocardiography 1 month after the index hospitalization, which showed normalization of LVEF in all patients (Figure 2). Clinical long-term follow-up data were available for 16 of the 17 SC patients. One patient whose QTc time at initial hospitalization was 454 msec experienced SC recurrence after 20 months while still on a β-blocker and died of sudden cardiac death (SCD) 26 months after the index episode. Another patient suffered from a SC recurrence 5 years after the initial episode and 2.5 years after stopping the β-blocker. None of the patients had significant arrhythmia during the follow-up period.

Table 3. Baseline Hemodynamic Characteristics, QTc Interval, and Cardiac Biomarkers in the 3 Study Groups. Variables are Given as Mean ± SD or Median (Interquartile Range) as Appropriate

	SC (n = 17)	MI (n = 16)	Control (n = 15)	P Value
SBP (mm Hg)	142 ± 27	137 ± 27	144 ± 25	0.56
DPB (mm Hg)	81 ± 13	80 ± 14	81 ± 12	0.94
Heart rate (bpm)	71 ± 10	73 ± 12	64 ± 11	0.06
QTc time (msec)	481 ± 44 ^{a,b}	449 ± 37 ^{a,c}	402 ± 26 ^{b,c}	<0.001
Peak CK (U/L)	92 (67–140) ^b	295 (96–665) ^{a,b}	81 (57–102) ^a	0.001
Peak Tnl (μg/L)	3.9 (1.7–16.5) ^b	24 (4.5–49.1) ^a	0.3 (0.3–0.35) ^{a,b}	0.001

Abbreviations: CK, creatine kinase; DBP, diastolic blood pressure; MI, myocardial infarction; QTc, corrected QT interval; SBP, systolic blood pressure; SC, stress cardiomyopathy; Tnl, troponin I. ^a*P* < 0.05. ^b*P* < 0.05. ^c*P* < 0.05.

Figure 1. Sex-hormone concentrations of (A) estradiol, (B) progesterone, (C) FSH, and (D) LH at hospital admission in the 3 study groups. Abbreviations: ANOVA, analysis of variance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MI, myocardial infarction; SC, stress cardiomyopathy.

At the long-term follow-up visit, 11 patients were free from dyspnea, whereas 2 patients had New York Heart Association class I dyspnea and 2 patients had New York Heart Association class II dyspnea. Sixty-two percent of patients had been on β -blocker therapy since the initial episode. Echocardiographic data were available for 13 patients, and all of them showed a normal LVEF without any significant mitral regurgitation.

Whereas both E2 and P concentrations in SC patients were significantly lower at the follow-up visit compared with the acute event (E2: 0.0 [0.0–0.0] vs 31.0 [26.0–49.5] ng/L, $P = 0.0005$; and P: 0.6 [0.32–0.95] vs 4.3 [2.3–5.8] nmol/L, $P = 0.0002$), gonadotropin levels did not change significantly over time (FSH: 90.0 ± 46.6 vs 71.9 ± 52.5 U/L, $P = 0.41$; and LH: 30.6 ± 10.9 vs 23.3 ± 15.6 U/L, $P = 0.29$) (Figure 3A–D). Follow-up P concentrations in the SC group were significantly lower than P concentrations of MI and control group patients during index hospitalization (Table 4), whereas E2 concentrations were not statistically different, although a trend toward lower levels in SC patients was evident.

Discussion

Although an increasing number of studies is being published, the exact pathophysiological mechanism of SC is still unknown. Possible mechanisms include

Figure 2. Ejection fraction of SC patients assessed at hospital admission and after 1 month. Abbreviations: FU, follow-up; SC, stress cardiomyopathy.

coronary vasospasm,^{8,9} widespread coronary microvascular dysfunction,^{4,9,10} and catecholamine toxicity.¹¹ A history of extraordinary emotional or physical stress prior to the event, which was present in 82% of our patients, supports this “catecholamine hypothesis.”^{8,9,12–15} Additionally, because there is a striking preponderance of postmenopausal women

Figure 3. Sex-hormone concentrations of (A) estradiol, (B) progesterone, (C), FSH, and (D) LH in patients with SC, assessed at index hospitalization and at a late follow-up visit after 6 years. Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; SC, stress cardiomyopathy.

presenting with SC,^{4,8,9,16} female sex hormones might play an important pathophysiological role. This was underpinned by the work of Akashi et al, who showed that estrogen supplementation in ovariectomized rats attenuated the stress-induced cardiac dysfunction and who thus suggested that reduced estrogen levels induced vulnerability to stress.^{17,18} Estrogen supplementation attenuated the exaggerated stress responses through sympathoadrenal activation and vagal inhibition,¹⁹ which is observed in SC.¹⁷ In addition to important regulatory effects on the release of epinephrine in the presynaptic cardiac sympathetic nerve fibers,²⁰ estrogen is involved in the adaptation of calcium metabolism in mammalian hearts.²⁰ Calcium entry into the sarcomere was shown to be influenced by estrogen-mediated regulation of several cascades, which play a critical role in the protection of the epicardium against “adrenergic storm” by shortening of phases 2 and 3 of the action potential.²⁰

In conclusion, postmenopausal status, which is characterized by decreased ovarian estrogen and P production compared with premenopausal status, is considered an important prerequisite for SC. Reflecting a possibly more pronounced physiologic ovarian insufficiency, we observed lower P and E2 levels in SC patients remote of the acute event compared with concentrations of the MI and control group

during the acute episode, respectively; although, given the weak correlation of sex-steroid concentrations with patient age, we cannot exclude that this finding might have been confounded due to the long follow-up duration. During the acute illness, however, we observed temporarily elevated E2 and P concentrations in the SC group compared with the MI and control group. This finding might be partly explained by the fact that as a consequence of stress such as critical illness, estrogens can increase due to increased peripheral aromatization of androgens to estrogens.^{21,22} Accordingly, this increase seems to be independent of the gonadotropins, which remained similar over time. However, it cannot be excluded that, after a fall in E2 in perimenopause, a certain critical E2 concentration is necessary to initiate a SC episode and that the higher E2 concentrations in SC compared with MI and control patients are of pathophysiological importance, because estrogen was shown to amplify stress response in an animal model.²³

Regarding the development of atherosclerosis and cardiovascular disease (CVD) in women, evidence exists that estrogen might be protective for the endothelium.^{24,25} Saltiki et al showed that postmenopausal women with a shorter lifetime (cyclic) exposure to endogenous estrogens were more likely to present with MI after menopause.²⁶ In postmenopause, however, higher endogenous estrogen

Table 4. Comparison of Sex-Hormone Concentrations Assessed at Different Time Points Between the 3 Groups. Variables are Given as Mean $\pm$ SD or Median (Interquartile Range) as Appropriate

	SC (IH)	MI (IH)	Control (IH)	P Value (ANOVA)
E2 (ng/L)	31 (26–49.5) ^{a,b}	21.5 (0–36) ^a	0 (0–41.5) ^b	0.03
Progesterone (nmol/L)	4.3 (2.3–5.8)	2.6 (1.9–4.9)	2.6 (1.3–2.9)	0.19
FSH (U/L)	71.9 $\pm$ 52.5	65 $\pm$ 36.3	60.3 $\pm$ 31.5	0.73
LH (U/L)	23.3 $\pm$ 15.6	20.7 $\pm$ 13.7	18.8 $\pm$ 9	0.62
	SC (FU)	MI (IH)	Control (IH)	P Value (ANOVA)
E2 (ng/L)	0 (0–0)	21.5 (0–36)	0 (0–41.5)	0.089
Progesterone (nmol/L)	0.6 (0.3–1) ^{a,b}	2.6 (1.9–4.9) ^a	2.6 (1.3–2.9) ^b	<0.001
FSH (U/L)	90 $\pm$ 46.6	65 $\pm$ 36.3	60.3 $\pm$ 31.5	0.1
LH (U/L)	30.6 $\pm$ 10.9 ^{a,b}	20.7 $\pm$ 13.7 ^a	18.8 $\pm$ 9 ^b	0.02

Abbreviations: ANOVA, analysis of variance; E2, estradiol; FSH, follicle-stimulating hormone; FU, follow-up; IH, index hospitalization; LH, luteinizing hormone; MI, myocardial infarction group; SC, stress cardiomyopathy group. ^a $P < 0.05$. ^b $P < 0.05$.

levels are not associated with a lower incidence of CVD²⁷ and exogenous estrogen substitution did not result in CVD prevention in recent randomized trials,^{28,29} although it might acutely increase ischemic threshold in coronary artery disease patients.³⁰ We observed significantly lower E2 concentrations in MI patients, who had similar E2 concentrations as patients in an age- and sex-matched control group, compared with SC patients during the acute event. Estrogens might increase during acute illness,²² and thus this difference is a remarkable finding considering similar concentrations of the acute-phase protein CRP, similar hemodynamic data, and a recent study showing that endogenous stress evidenced by copeptin levels is even lower in patients with SC compared with patients with MI.³¹ It might be speculated that patients with higher E2 concentrations after menopause might benefit from a protective vascular effect and thus have diverted the stress response to SC rather than MI. This protective effect of E2 might be partly be mediated by a more advantageous lipid profile,²⁴ which results in a decreased risk for acute coronary syndromes,³² and thus, the lower LDL levels in our SC patients compared with MI patients might be a reflection of these protective effects.

Stress cardiomyopathy is usually associated with full recovery³³ and infrequent major cardiovascular events in the long-term follow-up period. However, no study has assessed the long-term history beyond a mean follow-up time of 2 years.³⁴ Similar to other studies,³⁵ we observed an early recovery of the LVEF, with sustained normal values after several years. Accordingly, 73% of our patients were free from dyspnea at the follow-up visit. However, we found 2 patients (12%) with SC recurrence, with 1 of these suffering SCD, thus suggesting that the long-term prognosis might not be as benign as generally believed. Of concern is particularly the risk of disease recurrence and the prolonged QTc time in SC patients, which might predispose these patients to malignant ventricular arrhythmias.³⁶ However, despite significantly longer QTc times in SC patients compared with patients in our 2 control groups, we did

not observe any ventricular arrhythmia during the in-hospital period. One patient in our series with borderline prolongation of QTc time died of SCD during the follow-up time, but no ECG was available to determine if the death was due to arrhythmia.

Study Limitations

Our study has several limitations. A major limitation is the small study population, which did not allow for the detection of minor differences in hormone concentrations, particularly because correction for multiple testing was necessary examining 3 groups. Furthermore, it would be interesting to know the simultaneous concentrations of stress hormones to address the hypothesis of stress-induced elevation of sex hormones as a confounding factor. In addition, because the postmenopausal sex-hormone concentrations seem to be age related, the follow-up time of 6 years is rather long to assess short-term fluctuations.

Conclusion

During the acute event, E2 concentrations are elevated in postmenopausal SC patients compared with an age- and gender-matched control group with MI and another group with normal coronary arteries. The higher E2 concentrations might have exerted atheroprotective effects and thus diverted the stress response to SC rather than MI, which is associated with a more favorable prognosis. Recurrence and/or SCD remains a potential risk in SC patients.

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