ABSTRACT. Takotsubo cardiomyopathy (TCM) is generally a reversible cardiomyopathy with a favorable prognosis. Because of a risk of sudden cardiac death (SCD), a wearable cardioverter-defibrillator (WCD) is occasionally prescribed, although its utility is unknown. We reviewed a national database of TCM patients who were prescribed a WCD. The database collected baseline demographics, left ventricular ejection fraction (EF), usage compliance, documented arrhythmias, and final survival status. One-hundred and two patients with mean age 63 ± 12 years, 11% men, had an initial EF of 27 ± 7% at the time of WCD prescription. The mean days of use was 44 ± 31 days, with an average daily hours used of 20 ± 4 hours. The average follow-up period was 440 ± 374 days and 95% of patients wore the WCD >90% of prescribed days. Two patients (2%) experienced shocks for ventricular arrhythmias (VAs) and survived; two patients (2%) experienced significant bradyarrhythmias; one patient received two inappropriate shocks due to signal artifact; no patients experienced a detection failure; two patients died during the prescription period; one with asystole, and one while not wearing the WCD; five patients died after discontinuing WCD usage, two of whom had an EF ≥35% at the time of WCD discontinuation. The WCD was used with a compliance of >90%. The device detected VAs reliably with a low risk of inappropriate shocks. TCM may be associated with a significant risk of death due to tachy- or bradyarrhythmias and the risk of SCD may persist even if the EF improves.

KEYWORDS. LifeVest, sudden cardiac death, Takotsubo cardiomyopathy, wearable cardioverter-defibrillator.

Introduction

Takotsubo cardiomyopathy (TCM) is a unique, reversible cardiomyopathy of unclear etiology and favorable prognosis, often associated with stress. However, ventricular arrhythmias (VAs) and sudden cardiac death (SCD) have been reported in these patients. While the risk of SCD in TCM with low left ventricular ejection fraction (EF≤35%) is unknown, defibrillation is the definitive treatment for ventricular tachycardia (VT) and ventricular fibrillation (VF), and its success depends primarily on time to therapy. The implantable cardioverter-defibrillator (ICD) is an effective treatment for patients at risk of SCD due to sustained VAs, but it is not indicated for patients with suspected reversible cardiomyopathies. The wearable cardioverter-defibrillator (WCD) is often used in patients who are thought to be at risk of SCD or in patients with clinical features suggestive of risk of SCD, but are not candidates for ICDs. The WCD provides constant monitoring and immediate treatment for life-threatening VAs without the need for bystander intervention. We reviewed a national database of TCM patients prescribed a WCD to gain further insight on detection...
and treatment of VAs in this population. This study is the largest analysis to date of patients with TCM referred for WCD therapy.

Methods

The LifeVest (Zoll Medical Corporation, Pittsburgh, PA) consists of seven non-adhesive electrodes: four sensing electrocardiogram (ECG) leads and three defibrillation electrodes. A motor designed to deliver a vibratory alert to the patient before shock delivery and the monitoring and defibrillation electronics are housed in a unit, which is carried on a waist belt or shoulder strap. The monitoring electrodes are positioned circumferentially around the chest and held in place by an elastic strap. Sensing electrodes provide two channels of ECG oriented front to back and right to left. The defibrillator electrodes are positioned in the apex-posterior direction. If an arrhythmia is detected, an alarm sequence starts with a silent vibration and is followed by escalating audible alarms. The alarms serve as a “responsiveness test,” allowing conscious patients to prevent defibrillation by holding a “response button” prior to shock delivery. If a response button is not pressed, the device delivers defibrillation shocks. Before shock delivery, gel is released from the electrodes, and a voice warns bystanders to stand clear. The WCD database included all patients who wore a LifeVest after market release in the United States. This database was maintained by the manufacturer (ZOLL, Pittsburgh, PA) for regulatory, reimbursement, and tracking purposes. The database contains indicators, baseline demographics (age and sex), compliance, reasons for ending use (patient or physician reported), and event data. Additional demographic and medical data were retrieved from medical records for the purpose of reimbursement. All patients signed consent for use of their de-identified data for quality monitoring, healthcare operation activities, and/or research. All data were anonymized before they were given to the investigators. Patients in the United States who wore a LifeVest from August 2007 through February 2012 were included in this study.

TCM patients were identified by searching the database for ICD-9 code 429.83, or physician’s medical order notes, indicating a diagnosis of TCM. The diagnosis of TCM was based on identification of characteristic wall motion abnormalities (apical hypokinesis and basal hyperkinesis) by two-dimensional (2D)-echocardiography and/or cardiac catheterization. The patients included in the study had normal coronary arteries or mild CAD with no hemodynamically significant stenoses on coronary angiogram. The WCD recorded any ECGs prior to and during treatment or near treatment events and total wear time. A WCD shock was adjudicated to be appropriate if delivered for sustained VT/VF and inappropriate if occurring for arrhythmias other than VT/VF. These data were stored in the database, and ECGs were further reviewed by two blinded electrophysiologists. Inappropriate shocks were further investigated for causes of inappropriate detection from ECG recordings and reasons for lack of response button use from patient call reports. Mortality outcomes in patients after discontinuation of WCD use were determined from the Social Security Death Index (SSDI). Raw count of days worn was defined as total days that the device recorded actual use. Average daily hours worn was equal to total hours worn divided by raw count of days worn. A non-compliant patient was one who reported stopping WCD use because of discomfort or unwillingness to wear prior to discontinuation of therapy by a physician.

Statistical analysis

Data are reported as mean ± 1 standard deviation and range, from minimum to maximum. To compare means between groups, one-way ANOVA was used for continuous variables. Data were considered significant at a two-sided p-value <0.05. All analyses were conducted using SPSS version 20 (IBM SPSS Statistics 20, Austin, TX).

Results

Baseline characteristics

The demographics of the study population are shown in Table 1. One hundred and two patients with diagnosis of TCM were included in our study. There were 11 men (11%) and 91 women (89%). Races included Caucasian (63%), African American (2.9%), Hispanic (1.9%), and unspecified (32%). The mean age was 63 years. The mean EF at the time of referral for a WCD was 27%. The reason for WCD prescription was primary prevention in 93

<table>
<thead>
<tr>
<th>Variables</th>
<th>TCM (total patients = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 12 (ranging 22–88)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Female</td>
<td>91 (89%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64 (63%)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>33 (32%)</td>
</tr>
<tr>
<td>EF</td>
<td>27 ± 6% (range 7.5–45)</td>
</tr>
<tr>
<td>Troponin T (µg/l)</td>
<td>3 ± 4 (range 0.03–21.04)</td>
</tr>
<tr>
<td>NT-BN P (pg/ml)</td>
<td>2636 ± 3533 (range 118–11733)</td>
</tr>
<tr>
<td>Physical stress</td>
<td>9 (8.8%)</td>
</tr>
<tr>
<td>Emotional stress</td>
<td>34 (33%)</td>
</tr>
<tr>
<td>CAD</td>
<td>23 (23%)</td>
</tr>
<tr>
<td>DM</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>HTN</td>
<td>56 (56%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>42 (41%)</td>
</tr>
<tr>
<td>Previous TCM</td>
<td>4 (3.9%)</td>
</tr>
<tr>
<td>Mean days worn</td>
<td>44 ± 31 (range 1–138)</td>
</tr>
<tr>
<td>Mean average hours worn</td>
<td>20 ± 4 (range 3–24)</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; DM: diabetes mellitus; HTN: Hypertension; TCM: Takotsubo cardiomyopathy.
patients (91%); the remaining nine patients (9%) were prescribed the WCD for secondary prevention. Fifty-six patients had coronary artery disease (CAD) or at least one CAD risk factor, which included hypertension, diabetes mellitus, or smoking. Four patients had a previous history of TCM; one was taking a β-blocker at the time of recurrent TCM. The data regarding medication use were available in 79 patients. The list of medications at the time of the initial presentation, either alone or in combination, included β-blockers in 19%, aspirin (ASA) in 17.7%, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers in 24%. Discharge medications, either alone or in combination, included β-blockers in 61%, ASA in 32%, ACE inhibitors or angiotensin receptor blockers in 50%, and aldactone in 7.8%. Improvement of EF was observed in 74% of patients who were prescribed β-blockers at discharge. The remaining patients on β-blockers received an ICD, died or had no reported EF at the end of WCD use.

Clinical manifestation

Among the 102 TCM patients, stressful events preceding the presentation of TCM were documented in 43 patients. These events were classified as psychologically mediated in 34 patients and physically triggered in six patients. The most common cardiovascular symptom at presentation was chest pain (49%). Other symptoms included: shortness of breath (27%), syncope (20%), cardiac arrest (5.8%), and palpitations (4.9%). One patient was incidentally found to have non-sustained ventricular tachycardia on a Holter monitor, and the diagnosis of TCM was made during investigation, on cardiac catheterization. The most common presenting ECG finding was ST elevation (27.4%). The other features included T-wave inversion (22.5%) and QT prolongation (14.7%). Cardiac arrhythmias at presentation included VAs (6.8%), non-sustained VT (11.7%), atrial fibrillation (10.7%), and advanced atrioventricular block (1.9%). Initial troponin level was elevated in 94% of patients with documented troponin values. The mean of peak troponin was 3 μg/L. Brain natriuretic peptide (BNP) values were elevated in 96% of patients with documented BNP values (N=20), with a mean of 2,636 pg/ml.

Adherence data

Compliance data were calculated directly from the device, based on the information stored regarding the exact time and duration the device was worn each day. The mean number of days of use was 44 days (Figure 1a) and the average number of hours worn per day was 20 hours. Patients who wore the WCD less than a month tended to wear fewer hours per day (Figure 1b). Ninety-five percent of patients wore the WCD >90% of prescribed days and 99% wore it >80% of prescribed days. Over the duration of WCD prescription, compliance was 83 ± 18% of prescribed hours with a median of 91%. Seventy-two percent of patients wore the WCD >90% of total prescribed hours and 77% wore it > 80% of total prescribed hours.

Outcomes

Seventy-one patients (70%) reported improvement of EF beyond 35% as the reason for discontinuing WCD use; five of these patients had improved EF after 90 days from the day of diagnosis. Improvement in EF was the most common reason for discontinuing WCD use; other reasons for end-of-use are shown in Table 2. Potentially fatal arrhythmias, including asystole and VA, are recorded by the WCD. However, only sustained VAs
are treated with shock therapy. Events, outcomes and death data are shown in Figure 2, and Table 3. Two sustained VAs occurred in two patients. A 60-year-old woman with an EF of 35% was successfully treated with a single 150-J shock, 42 s after detecting VT on day 37; the patient was conscious but felt unwell. Another patient (female, 71 years old), with an EF of 45% was prescribed a WCD for “secondary” prevention after a brief VF episode in the hospital. On day 3, she received a single 150-J shock for VF while asleep, 49 s after detection.

Three bradyarrhythmia episodes were detected in two patients. One patient (male, 55 years old) with an EF of 23% experienced asystole and died on the seventh day of WCD use; β-blockers had been prescribed at the time of discharge. Another patient (female, 66 years old) with an EF of 23% had two episodes of transient complete heart block on day 8 and 26 of WCD use.

Two inappropriate shocks (150 J) were delivered to one patient (female, 58 years old) with an EF of 30% on the tenth day of WCD use. The reason for inappropriate detection was signal artifacts. The patient briefly pressed the response button early during the false detection and vibratory alert; however, the response button was not pressed long enough to prevent shocks. There were no cases of failure to treat VAs in our study.

The average follow-up period was 340 ± 374 days. Seven patients with TCM, mean age 65 years, died. Average days of WCD use in deceased patients was 31 days. Two of the seven deaths occurred during the period of WCD prescription: one had asystole, as reported above; the other patient wore the WCD for only 12 days, and died on the thirteenth day while not wearing the WCD. The remaining five deaths occurred after discontinuation of the WCD. Death information post-WCD use was obtained from Social Security Death Index but the causes of death could not be ascertained. Of these, two patients had documented EF improvement beyond 35%. One patient (female, 75 years old) presented with chest pain and an EF of 32%; she was found to have normal coronary anatomy on cardiac catheterization. After 22 days, she was found to have improved EF and the WCD was discontinued. Another patient (male, 82 years old) presented with complete heart block with an EF of 20%. He received a permanent pacemaker, and his follow-up on day 32 showed EF improvement. Of the remaining three deaths, two patients were non-compliant with WCD usage and one ended use for unknown reasons.

Course after WCD use

Six patients had an ICD implanted immediately after terminating WCD use. An ICD was implanted in two patients with sustained VAs, as mentioned above, treated by the WCD. Two patients (both female, 21 and 60 years of age, with an EF of 23% and 18%, respectively) received ICDs due to non-improved EF at day 90. One patient (female, 66 years old) with an EF of 23% had two episodes of complete heart block without EF improvement on day 52 of WCD use, and an ICD was implanted. One patient (male, 65 years old) presented with cardiac arrest with an EF of 8%. ICD was implanted for secondary prevention at day 48 because the EF had not improved significantly.

Discussion

TCM is a non-ischemic, reversible cardiomyopathy with a favorable prognosis. It is an unusual condition in clinical practice, and management experiences are varied. In general, a newly diagnosed non-ischemic cardiomyopathy is managed with maximal medical therapy for at least 3 months and if the EF does not improve beyond 35%, ICD implantation for primary prevention may be considered. Since TCM is reversible, the utility of a WCD for primary prevention in patients with EF ≤35% is unknown, although a WCD is sometimes prescribed in these patients presenting with syncope, non-sustained VT, or other clinical features that heighten concern about the risk of SCD. We report our observations on 102 patients based on a national database. The main observations from this cohort include 1) compliance with WCD usage exceeded 90%; 2) two patients (1.9%) experienced appropriate shocks and survived; 3) two patients (1.9%) experienced significant bradyarrhythmias meeting criteria for pacing; 4) while one patient received two inappropriate shocks due to signal artifact, none showed detection failure; 5) two patients (1.9%) died during the prescription period—one with asystole and one while not wearing the WCD; and 6) five patients (4.9%) died after discontinuing WCD usage, two of these patients had an EF >35% at the time of WCD discontinuation.

Takotsubo cardiomyopathy, or apical ballooning cardiomyopathy, was first described by Sato et al. It is characterized by a unique configuration of the ventricles: typically, mid-segment and apex become hypokinetic, while the basal portion demonstrates compensatory hyperkinesis, leading to balloon-like motion of the left ventricle. The incidence is higher in women (80–100%) than men, especially in postmenopausal women. Even though clinical presentation can be similar to acute coronary syndrome, angiographic studies usually do not show flow-limiting lesions and only a small number of patients demonstrate coronary spasm with acetylcholine challenge test.

TCM is hypothesized to be catecholamine mediated because studies have shown that most TCM patients present with elevated plasma catecholamine levels and the observation of reversible ventricular dysfunction in patients with pheochromocytoma. TCM may possibly be caused by diffuse catecholamine-induced vascular
Figure 2: Electocardiogram (ECG) from four patients while wearing a wearable cardioverter-defibrillator (WCD). (a) ECG shows VT that was treated with shock. (b) ECG shows VF that was treated with shock. (c) ECG shows artifact which was treated inappropriately with a shock. (d) ECG shows marked bradycardia–asystole and the patient died. (e) ECG shows marked bradycardia and was found to have complete heart block. (The asterisks show WCD shocks).
In our study, two patients had significant bradyarrhythmias, and asystole documented by the WCD, prompting cardiac intervention. This may suggest that TCM is associated with a significant risk of cardiovascular events or death. Seventy-one patients (70%) in our study reported WCD use; 66 patients improved within 90 days, and five patients had improved EF after 90 days. Although TCM may recover, it may recur at a later date. Recurrence rates of 10% have been reported in the case series with the longest follow-up. In our study, four patients (3.9%) had a previous history of TCM.

An increasing number of case series have reported VA in TCM patients. One systematic review indicated that the incidence of life-threatening VF was 1.8%. Repolarization abnormalities predisposing to VA are often observed in TCM patients, including diffuse T-wave inversion and QT prolongation. This pattern of electrocardiographic changes may also be seen in patients with hyperadrenergic states. This concept is supported by the fact that catecholamines are known to cause triggered activity and early after-depolarizations, which in turn may predispose to torsade de pointes (TdP). There is a high prevalence of QT prolongation in TCM, but rates differ among different case series from 50–100%. Heart block and asystole have also been reported in TCM.

In our study, two patients had significant bradyarrhythmias. Given the fact that early β-blockade therapy is the mainstay of treatment for TCM, it should be used cautiously due to the potential risk of pause-dependent VAs and life-threatening bradyarrhythmia. Since the WCD is effective only when worn, compliance is critical to assessing effectiveness. We found that compliance was comparable to a previous report of WCD use by Chung et al. In our study, patients who wore the WCD less than 1 month wore it fewer hours per day than patients who wore the WCD for more than 1 month (p=0.031). Seventy-eight percent of our patients had at least 20 hours per day of WCD use, which is classified as “good” compliance.

**Limitations**

Voluntary registry databases leave many important gaps in clinical data. Diagnosis of TCM was not based on a uniform set of criteria nor did all patients undergo uniform medical treatment or WCD prescription based on predetermined criteria. Documentation of EF at various stages after diagnosis and serial biomarker values may have helped our understanding of the disease process and was not available in all cases. We were unable to evaluate the possible predictors for outcomes, progression, or improvement in left ventricular function. We did not have uniform follow-up data after the end of WCD use and mortality data were obtained via the SSDI, so we do not know medication compliance or other outcome measures after discontinuation of WCD use. The absence of well-defined diagnostic criteria, uniform medical therapy, and a predefined basis for WCD prescription and discontinuation are important factors that may limit generalizability.

**Conclusions**

TCM may be associated with a significant risk of death due to tachy- or bradyarrhythmias and the risk of SCD may persist even if the EF improves to ≥35%. WCD compliance was >90% and detected VAs reliably without detection failures and a low risk of inappropriate shocks. These preliminary observations warrant prospectively designed studies to clarify the risk of SCD and the utility of WCD in this unique cardiomyopathy.

**References**


