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Complications in the clinical course of tako-tsubo cardiomyopathy ☆

Birke Schneider [a,*], Anastasios Athanasiadis [b], Johannes Schwab [c], Wolfgang Pistner [d], Uta Gottwald [e], Ralph Schoeller [f], Wolfgang Toepel [g], Klaus-D. Winter [h], Christoph Stellbrink [i], Tobias Müller-Honold [j], Christian Wegner [k], Udo Sechtem [b]

[a] Medizinische Klinik II, Sana Kliniken Lübeck, Germany
[b] Abteilung für Kardiologie, Robert-Bosch-Krankenhaus, Stuttgart, Germany
[c] Medizinische Klinik 8, Klinikum Nürnberg Süd, Germany
[d] Medizinische Klinik 1, Klinikum Aschaffenburg, Germany
[e] Klinik für Kardiologie, Allgemeines Krankenhaus Celle, Germany
[f] Medizinische Klinik II, DRK-Kliniken Westend, Berlin, Germany
[g] Medizinische Klinik II, Klinikum Idar-Oberstein, Germany
[h] Klinik für Innere Medizin/Kardiologie, Hermann-Josef-Krankenhaus, Erkelenz, Germany
[i] Klinik für Kardiologie und Internistische Intensivmedizin, Klinikum Bielefeld Mitte, Germany
[j] Medizinische Klinik, Klinikum Augsburg, Germany
[k] Vienna Institute of Demography, Austrian Academy of Sciences, Vienna, Austria

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ABSTRACT

Objective: This study evaluated the frequency, severity and outcome of complications in the clinical course of tako-tsubo cardiomyopathy (TTC).
Background: TTC is regarded as a benign disease since left ventricular (LV) function returns to normal within a short time. However, severe complications have been reported in selected patients.
Methods: From 37 hospitals, 209 patients (189 female, age 69 ± 12 years) were prospectively included in a TTC registry.
Results: Complications developed in 108/209 patients (52%); 23 (11%) had >2 complications. Complications occurred median 1 day after symptom onset, and 77% were seen within 3 days. Arrhythmias were documented in 45/209 patients (22%) including atrial fibrillation in 32 (15%) and ventricular tachycardia in 17 (8%). Of 8 patients resuscitated (4%), 6 survived. Additional complications were right ventricular involvement (24%), pulmonary edema (13%), cardiogenic shock (7%), transient intraventricular pressure gradients (5%), LV thrombi (3%) and stroke (1%). During hospitalization, 5/209 patients (2.5%) died. Patients with complications were older (70 ± 13 vs 67 ± 10 years, p = 0.012), had a higher heart rate (91 ± 26 vs 83 ± 19/min, p = 0.025), more frequently Q\ waves on the admission ECG (36% vs 21%, p = 0.019) and a lower LV ejection fraction (47 ± 15 vs 54 ± 14%, p = 0.002). Multivariate regression analysis identified Q-waves on admission (OR 2.49, 95% CI 1.23–5.05, p = 0.021) and ejection fraction ≤30% (OR 4.03, 95% CI 1.04–15.67, p = 0.022) as independent predictors for complications.
Conclusions: TTC may be associated with severe complications in half of the patients. Since the majority of complications occur up to day 3, monitoring is advisable for this time period.

1. Introduction

Tako-tsubo cardiomyopathy (TTC) is regarded as a reversible and relatively benign disease [1,2]. However, some authors reported a high mortality of up to 12% [3–7] related mainly to the occurrence of malignant arrhythmias and cardiogenic shock [1,8]. Moreover, other complications such as pulmonary edema, intraventricular pressure gradients sometimes associated with acute mitral regurgitation [1,9,10], right ventricular involvement with pleural effusions [3,11], and intraventricular thrombi resulting in acute stroke [12,13] or arterial embolism [14] have been described. Due to the fact that most reports comprise relatively small patient numbers, the complication rate varies considerably.

In this study we report the frequency and the spectrum of complications in a large cohort of patients with TTC prospectively included in the registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Medizinische Klinik II, Sana Kliniken Lübeck, Kronsforder Allee 71–73, D-23562 Lübeck, Germany. Tel.: +49 4515851681; fax: +49 4515851699.
E-mail address: birke.schneider@sana.de (B. Schneider).

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2. Methods

2.1. Patients

Between February 2006 and August 2009, patients were prospectively enrolled in the TTC registry according to the following criteria: 1) acute chest symptoms (angina, dyspnea), syncope or other symptoms in combination with 2) ischemic ECG changes with ST-segment elevation ± T-wave inversion, 3) reversible left ventricular regional wall motion abnormality not corresponding to a single coronary artery territory, and 4) absence of significant coronary artery stenoses >50% by coronary angiography. Exclusion criteria were: intracranial hemorrhage, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy.

A structured case report form (CRF), admission notes, original ECG tracings, left ventricular (LV) and coronary angiograms, catheter protocols, and discharge letters were required for inclusion in the registry. The updated CRF used in the last 209 patients included in detail acute treatment and asked specifically for the following complications: arrhythmias (sustained or nonsustained ventricular tachycardia, new onset of atrial fibrillation), resuscitation, pulmonary edema, cardiogenic shock, intraventricular pressure gradient, right ventricular (RV) involvement, LV thrombus formation, and death. In addition, other observations during the clinical course could also be reported. A follow-up after 3 months was required with echocardiographic documentation of normalized LV function. The patients gave informed consent for including their anonymized data into the TTC registry. The study protocol was approved by the local ethics committees.

Clinical data, angiograms and ECGs of all cases and echocardiographic as well as cardiac magnetic resonance images (CMRI) of a subset of patients were reviewed by at least 2 observers experienced in diagnosing TTC. In questionable cases, 2 additional observers were involved, and the diagnosis of TTC was made by consensus. In addition to the clinical course, acute treatment was recorded. The baseline clinical characteristics of the patients were reported earlier [15].

2.2. Statistical analysis

Continuous variables are presented as mean ± SD or as median (interquartile range [IQR]), and data were assessed with Student's *t*-test for normally distributed variables or the Wilcoxon Rank Sum test for non-normally distributed variables. Categorical data are reported as number (percent) and were analyzed by Fisher's exact test. If a patient had more than 1 complication, the time from symptom onset to the latest complication was determined for calculating the days of a complicated clinical course. In order to determine in which time interval the majority of treatable complications occurred, the time from symptom onset to the latest complication (pulmonary edema, cardiogenic shock, arrhythmias, resuscitation, thrombus formation, death) was assessed. Clinical, electrocardiographic and angiographic variables that were statistically significant in the univariate analysis were included in a multivariate logistic regression model to determine the independent prognostic value for predicting complications in the clinical course of TTC. Statistical significance was defined as $p < 0.05$. Data analysis was performed using the statistical software package R Version 2.10.0 (R Development Core Team 2009).

3. Results

3.1. Patient characteristics

A total of 324 patients from 36 German hospitals and 1 hospital in Austria were included in the registry. Complete data on acute treatment and complications were available for the last 209 patients after updating the initial CRF for all more recently published complications in TTC. These 209 patients constitute the study population. Compared to the initial cohort of 115 patients there was no significant difference with regard to age, sex, symptoms, cardiac markers, heart rate, Q waves or mortality.

Mean age was 69 ± 12 years; 189 patients (90%) were female. A triggering event could be identified in 84%. Main symptom at presentation was angina in 69% (Table 1). Time from symptom onset to hospital admission was 8.3 ± 7.2 h, and 45% of the patients were admitted by an emergency team with physician. Initial clinical diagnosis was an acute coronary syndrome (ACS) in 86%. Concordant with the diagnosis of an ACS, 72% of patients were transferred to the intensive care unit and were treated according to the current guidelines.

LV angiography disclosed apical ballooning in 64% and mid-ventricular ballooning of the LV in 36%. No patient had a basal or a focal ballooning pattern. Ejection fraction was 51 ± 15%.

The ECG on admission showed ST-segment elevation (>1 mm in the limb leads, >2 mm in the precordial leads) in 88% of patients. Negative T-waves developed in 98% of patients on day 3 associated with lengthening of the QTc interval which was longest on day 2 (511 ± 59 ms).

Table 1
Clinical characteristics of 209 patients with tako-tsubo cardiomyopathy.

Patients	209
Female	189 (90%)
Male	20 (10%)
Age (years)	69 ± 12
Trigger present	175 (84%)
Emotional	74 (35%)
Physical	76 (36%)
Both	25 (12%)
None	34 (17%)
Symptoms	203 (97%)
Angina	145 (69%)
Dyspnea	36 (17%)
Syncope	6 (3%)
Shock/resuscitation	2 (1%)
Other	14 (7%)
None	6 (3%)
Acute management	
Intensive care unit	151 (72%)
Regular ward	58 (28%)
Initial diagnosis	
STEMI	111 (53%)
NSTEMI	69 (33%)
Other	24 (12%)
None	5 (2%)
ECG day 1	
Heart rate/min	87 ± 23
ST segment elevation	175 (88%)
T-wave inversion	142 (71%)
Q wave	57 (29%)
QTc interval (ms)	471 ± 54
Cardiac markers	
Troponin × ULN	Median 9.38 (3.4–20.0)
CK × ULN	Median 1.10 (0.67–1.78)
CK-MB × ULN	Median 1.36 (0.79–2.11)
Cardiac catheterization	
Symptom onset to angiography (days)	Median 1 (1–2)
LV ejection fraction (%)	51 ± 15
LV end-diastolic pressure (mm Hg)	23 ± 8
Apical ballooning	133 (64%)
Mid-ventricular ballooning	76 (36%)
Intraaortic balloon pumping	2 (1%)

CK = creatine kinase; LV = left ventricular; NSTEMI = non ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; ULN = upper limit of normal.

Peak cardiac markers are listed in Table 1. BNP was not available in all hospitals.

3.2. Overall complications

Complications were seen in 108/209 patients (52%), and 51 (24%) of the patients experienced more than one complication (Table 2). Complications occurred median 1 [IQR 1–3] day after symptom onset, and 77% were seen within 3 days. However, 23% of complications occurred later (up to day 56). Excluding RV involvement which likely begins immediately with the onset of symptoms, complications were encountered in 88 patients median 2 [IQR 1–5] days after symptom onset.

Acute treatment included a betablocker in 73% of the patients and an ACE inhibitor or angiotensin receptor blocker in 40% of the patients. There was a trend towards a lower complication rate in patients receiving a betablocker (40% vs 60%, $p = 0.055$) but not in patients receiving an ACE inhibitor (50% vs 48%, $p = 0.461$).

3.3. Arrhythmias

Ventricular tachycardia was documented in 17/209 patients (8%) and acute onset of atrial fibrillation in 32/209 patients (15%). Four patients (2%) had both types of arrhythmia. Thus, TTC associated arrhythmias were observed in 45/209 patients (22%). Eight of 209 patients (4%)