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ORIGINAL PAPER

Novel ECG-based scoring tool for prediction of takotsubo syndrome

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Abstract

Background Takotsubo syndrome (TS) usually involves ECG changes mimicking acute myocardial infarction (AMI). The differentiation of both disorders is crucial for selection of appropriate treatment. The aim of this study was to assess ECG parameters in patients with TS and AMI, and try to establish a scoring tool for TS prediction.

Methods The study consisted of two study parts: evaluation and validation cohorts. Overall, the study included 82 patients with TS and 141 subjects with AMI. In addition to the major demographic characteristics and comorbidities, the following ECG parameters were analyzed: heart rate, QRS duration, QTc, QRS amplitudes in frontal and precordial leads, frequencies for ST-segment elevation, combined sign of positive ST-segment elevation in -aVR and absent in V_1, negative T-wave in lead I and positive in III, inverted or biphasic T-waves in V_2–V_5, T-wave inversions in frontal and precordial leads. All significant variables were identified in univariate regression analysis and further included for multivariate logistic regression analysis predicting TS.

Results TS was frequently diagnosed in women and in elderly patients. Presence of ST-segment elevation, inverted/biphasic T-waves in V_2–V_5, QRS amplitudes in frontal and precordial leads were significantly different in evaluation group. By multivariate regression analysis sex, QRS amplitudes in frontal, inverted or biphasic T-waves in septal leads and QTc were identified as powerful variables to calculate TS probability. The diagnostic accuracy of the developed 6-points-TS-score was then evaluated in the validation group. Thus, no subject with a TS-score of ≥ 5 had AMI (specificity 99%, sensitivity > 92%).

Conclusion The developed ECG-based TS-score model may be a useful complimentary tool for TS prediction in acute clinical setting.

Keywords Takotsubo cardiomyopathy · Acute myocardial infarction · Electrocardiography

Introduction

Takotsubo syndrome (TS) is characterized by reversible left ventricular (LV) dysfunction frequently triggered by stress. TS generally affects postmenopausal women, whose symptoms and ECG changes mimic an acute myocardial infarction (AMI). Discrimination of TS from AMI is clinically relevant for selection of the appropriate treatment.

We aimed to assess the ECG parameters in patients with newly diagnosed TS and AMI and, possibly, to establish a scoring tool for TS prediction.

Methods

Patients with chest pain presented to Cardiology Department, University of Cologne, or Clinic of Internal Medicine I, Gütersloh Hospital, Germany between 2007 and 2014 (TS) or 2011–2014 (AMI) with first TS diagnosis according to Mayo Clinic Criteria [1] or anterior AMI with or without persistent ST elevation (STE) in anterior leads and evidence of culprit lesion in angiography were identified retrospectively in the institutional databases. Each patient obtained ECG within 4 h after symptom onset with the

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mean symptom-to-ECG-time of 3.5 h and underwent heart catheterization within 12 h of presentation. Patients with prior CAD, left bundle branch block, atrial fibrillation or ventricular pacing were excluded from the study. The most common TS-preceding triggers were physical or emotional stress (55%), whereas no stressful event was evident in 31% of TS patients.

The study consisted of two parts. Initially, ECG-based TS-score was developed based on the data of subjects treated at the University of Cologne (evaluation group; TS: $n=46$; AMI: $n=81$). The evaluated criteria were then validated in another independent cohort recruited in Gütersloh Hospital (validation group; TS: $n=36$; AMI: $n=60$) (Fig. 1).

Following ECG parameters were analyzed: heart rate, QRS duration, QTc, QRS amplitudes in frontal (fQRS) and precordial (pQRS) leads, presence or absence of STE in all leads and in lead -aVR (defined as ST-segment depression in lead aVR), negative T-wave in lead I and positive in III ($T_{III} > T_I$ pattern), inverted or biphasic T-waves in V_2–V_5 (Wellens pattern), T-wave inversions in frontal and precordial leads and combined sign of positive STE in -aVR and absent STE in V_1 (Table 1A, B).

ST-segment deviation was measured at the J point in at least 2 contiguous leads of ≥2 mm in men or ≥1.5 mm in women in leads V_2–V_3 and/or ≥1 mm in other contiguous chest leads or the limb leads, as recommended by the third universal definition of myocardial infarction [2]. T-wave inversion was defined as inversion ≥2 mm in amplitude in at least 2 leads. QRS voltage was measured from nadir to its peak in frontal (I, II, III, aVR, aVL, aVF) and precordial leads (V_1–V_6). QT-interval was defined from QRS beginning to the end of T-wave and corrected for heart rate by Bazett's formula.

Comparisons between groups were performed using one-way ANOVA (values are means ± SEM). In univariate regression analysis, significant variables were identified and further included for multivariate logistic regression analysis predicting TS. The overall diagnostic accuracy of scoring system was determined by calculating the area under the receiver operating characteristic curve with its 95% confidence intervals. All analyses were performed with SPSS Statistics 23.

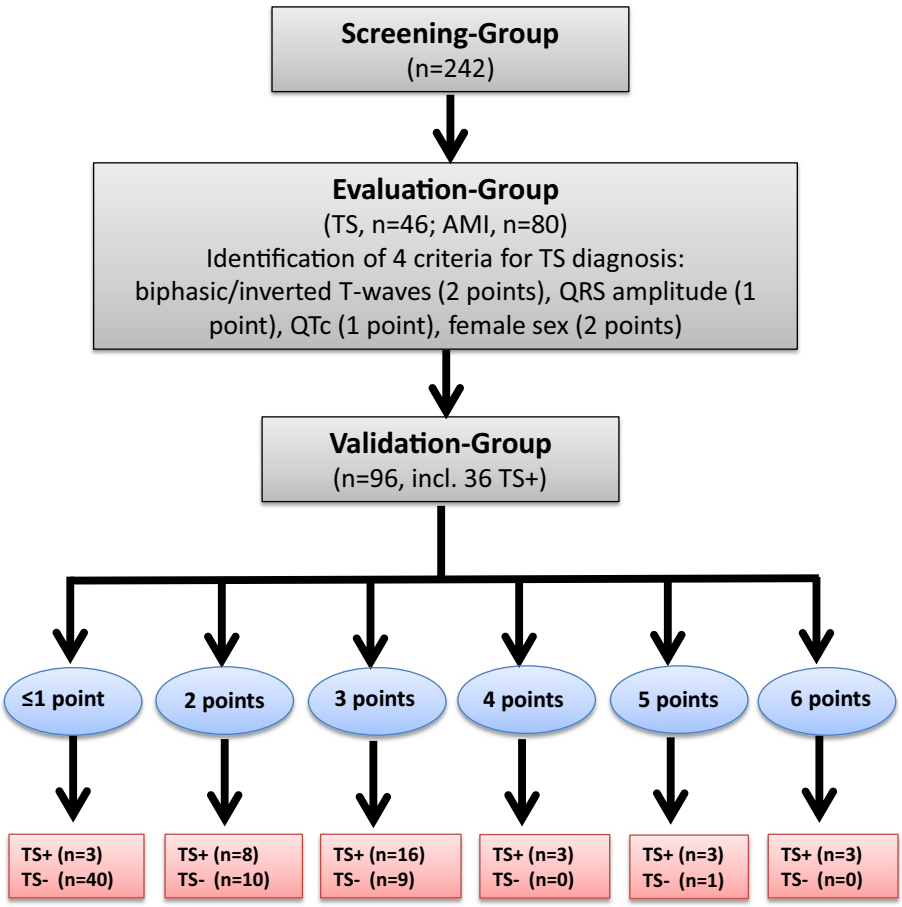

Fig. 1 Patients flow chart with risk estimation score derived from the multivariate dataset of sex (2 points), frequencies of inverted/biphasic T-waves in V_2–V_5 (2 points), prolonged QTc (1 point) and fQRS ≤0.5 mV (1 point)

Table 1 Clinical and ECG characteristics of study participants in the evaluation (A) and validation (B) group

A			
	TS ($n=46$)	AMI ($n=81$)	p value
Age (years)	68.1 ± 1.6	62.6 ± 1.3	0.01
Women	36 (78%)	18 (22%)	< 0.001
Diab. mellitus	6 (13%)	38 (47%)	< 0.001
Hypertension	21 (46%)	60 (74%)	< 0.001
Hyperlipidemia	11 (24%)	58 (72%)	< 0.001
Pericardial effusion	2 (4%)	5 (6%)	0.67
Troponin+	42 (91%)	78 (96%)	0.35
Hyperthyroidism	5 (11%)	11 (14%)	0.66
Hypothyroidism	3 (7%)	5 (6%)	0.89
LV-EF (mean)	48.2 ± 1.9	52.3 ± 1.7	0.06
Major clinical presentation			
Typical angina	38 (83%)	74 (91%)	0.16
Atypical angina	6 (13%)	3 (4%)	0.07
Dyspnoea	2 (4%)	4 (5%)	0.62
Heart rate (min^{-1})	81.4 ± 2.5	80.6 ± 2.1	0.8
QRS duration (ms)	89.2 ± 2.0	93.7 ± 2.2	0.17
fQRS (mV)	0.8 ± 0.05	1.0 ± 0.04	< 0.001
pQRS (mV)	1.4 ± 0.06	1.6 ± 0.06	0.02
QTc (ms)	463 ± 6.1	423 ± 5.0	< 0.001
STE	14 (30%)	55 (68%)	< 0.001
STE in -aVR	6 (13%)	15 (20%)	0.47
Inverted/biphasic T-waves	7 (15%)	2 (3%)	0.01
T-wave negative in I and positive in III	7 (16%)	9 (11%)	0.58
T-wave inversion	31 (67%)	58 (72%)	0.42
STE in -aVR + no STE in V_1	5 (11%)	11 (14%)	0.78
B			
	TS ($n=36$)	AMI ($n=60$)	p value
Age (years)	65.4 ± 2.3	63.8 ± 1.6	0.6
Women	31 (86%)	13 (22%)	< 0.001
Diab. mellitus	4 (11%)	22 (37%)	0.008
Hypertension	11 (31%)	41 (68%)	< 0.001
Hyperlipidemia	5 (14%)	38 (63%)	< 0.001
Pericardial effusion	1 (3%)	2 (3%)	0.88
Troponin+	35 (97%)	59 (98%)	0.71
Hyperthyroidism	2 (6%)	5 (8%)	0.71
Hypothyroidism	4 (11%)	9 (15%)	0.76
LV-EF (mean)	43.7 ± 2.7	50.7 ± 1.9	0.05
Major clinical presentation			
Typical angina	23 (64%)	49 (82%)	0.09
Atypical angina	7 (19%)	3 (5%)	0.04
Dyspnoea	6 (17%)	8 (13%)	0.77
Heart rate (min^{-1})	80.5 ± 2.8	79.5 ± 1.9	0.78
QRS duration (ms)	85.2 ± 3.7	91.2 ± 1.7	0.13
fQRS (mV)	0.8 ± 0.05	1.1 ± 0.05	< 0.001
pQRS (mV)	1.4 ± 0.07	1.7 ± 0.07	0.008
QTc (ms)	478 ± 8.4	433 ± 4.4	< 0.001
STE	9 (25%)	52 (87%)	< 0.001

Table 1 (continued)

B			
	TS ($n=36$)	AMI ($n=60$)	p value
STE in -aVR	3 (8%)	9 (15%)	0.53
Inverted/biphasic T-waves	8 (22%)	4 (7%)	0.03
T-wave negative in I and positive in III	5 (16%)	5 (8%)	0.49
T-wave inversion	27(75%)	44 (73%)	0.86
STE in -aVR + no STE in V_1	4 (11%)	9 (16%)	0.76

The categorical variables are expressed as observed numbers and percentage of observed/total numbers

Results and discussion

As expected, TS was frequently diagnosed in women with preference of elderly patients. Frequencies of STE (TS: 30.4%, AMI: $n=68\%$; $p<0.001$), QTc (TS: 463 ± 6.1 vs. 423 ± 5.0 ms in AMI; $p<0.001$), inverted/biphasic T-waves in V_2–V_5 (TS: $n=15\%$, AMI: $n=2.5\%$; $p=0.01$), fQRS (TC 0.8 ± 0.05, AMI 1.0 ± 0.04 mV; $p<0.001$) and pQRS (TS 1.4 ± 0.06, AMI 1.6 ± 0.06 mV; $p=0.02$) were significantly different in evaluation group (Table 1).

By multivariate regression analysis, sex, fQRS, inverted or biphasic T-waves in septal leads and QTc were identified as powerful variables to calculate TS probability (Table 2A). Incidence of female sex and biphasic/inverted T-waves was each associated with two risk points, while one point was assigned to fQRS ≤ 0.5 mV or prolonged QTc (females ≥ 460 ms; males ≥ 450 ms). Interestingly, presence of all risk factors had an estimated TS risk of 0.99.

The diagnostic accuracy of the developed 6-points-TS-score was then evaluated in the validation group ($n=96$, incl. 36 TS+ patients). The TS-score was zero or one in 43 subjects with 3 patients having TS. 8 TS and 10 AMI patients revealed a TS-score of 2. 25 subjects (16 TS, 9 AMI) revealed a TC-score of 3. The TS-score was 4 in 4 subjects, 3 of them with TS+. No subject with a TS-score of ≥ 5 ($n=6$) had AMI (specificity 99%, sensitivity > 92%) (Fig. 1; Table 2B).

Unfortunately, both AMI and TS exhibit similar clinical presentation, ECG and biomarkers, requiring eventually an invasive heart catheterization to rule out or confirm the either diagnosis [3–5]. In the current study, we present a simple ECG-based score, which may assist the rapid treatment decision in patients with chest pain and corresponding ECG changes especially in the emergency setting.

Indeed, several ECG criteria have been proposed to discriminate TS from ACS [6–9]. But data are still inconclusive or sometimes discrepant due to limited sample size and heterogeneity of study designs and study populations. Even racial and epidemiologic ECG differences, i.e., between

Table 2 (A) Multivariate predictors of TS and (B) diagnostic value of the 6-point-risk score for TS prediction

A			
Variable	OR	95% CI	p value
fQRS	4.683	0.990–22.143	0.051
Biphasic/inverted T-wave	10.980	1.395–86.448	0.023
QTc	3.546	1.220–10.305	0.020
Sex	18.748	6.432–54.646	<0.001

B				
Pts	Sensitivity	Specificity	PPV	NPV
1	0.083	0.783	0.188	0.588
2	0.306	0.8	0.524	0.615
3	0.75	0.85	0.75	0.85
4	0.833	0.983	0.968	0.908
5	0.917	0.992	0.985	0.952
6	0.986	0.992	0.986	0.992

OR odds ratio, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

Asians and Caucasians with TS, were suggested [1, 5, 101, 10].

Since time to presentation determines ECG changes, we included patients with ECG obtained within as early as 4 h after symptom onset. This is—to the best of our knowledge—the earliest ECG recording time reported yet in similar studies on TS. Therefore, some discrepancies in obtained results, such as a rare incidence of STE in lead -aVR and absent STE in V_1 compared to others [7, 8], may be due to ECG recordings in the very early time window, given the well-documented time-dependency of ECG changes in TS [10–12].

Furthermore, different ballooning patterns, such as mid-ventricular or atypical presentations, may also affect ECG changes [13, 14]. Only patients with apical ballooning were included in our study, whereas no such differentiation was undertaken in previously mentioned studies [7, 8].

Finally, our trial design enabled inclusion of patients with no persistent STE on admission ECG in both study arms to mimic a "real world" emergency setting, as AMI and TS may present with diverse ECG patterns on admission [15–17]. For TS, STE prevalence is even more variable with prevalence data ranging from 34 to 82% [17–19]. Therefore, the study design may additionally affect ECG findings reported in our current study.

In summary, the developed ECG-based TS-score model may be a useful complimentary diagnostic tool for TS prediction in acute clinical setting.

Limitations

Our study is limited by its retrospective design. Further studies are warranted to validate the TS-score in a prospective cohort of patients with chest pain.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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