ORIGINAL RESEARCH

Left Ventricular Thrombi in Takotsubo Syndrome: Incidence, Predictors, and Management: Results From the GEIST (German Italian Stress Cardiomyopathy) Registry

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***Background*—**Left ventricular (LV) thrombi during Takotsubo syndrome represent a potential complication and can be associated with cerebrovascular embolic events. The aim of this study was to evaluate the exact incidence, predictors, and management strategies of LV thrombi in patients with Takotsubo syndrome.

***Methods and Results*—**We enrolled 541 consecutive patients in a multicenter international registry. Clinical features and echocardiographic data at admission, during hospitalization, and after 3 months were evaluated. Survival rates for long-term follow-up (mean 984±908 days) were recorded. Twelve Takotsubo syndrome patients (2.2%) developed LV thrombi (all female presenting with apical ballooning pattern). All patients with LV thrombi were treated with oral anticoagulation therapy; however, 2 (17%) had a stroke before treatment initiation. These patients were characterized by a higher prevalence of ST-elevation (56% versus 16%; $P<0.001$) and higher troponin I levels (10.8±18.3 ng/mL versus 3.5±4.3 ng/mL; $P=0.001$) as compared with those without LV thrombi. At multivariate analysis including age, sex, LV ejection fraction, ST-elevation at admission, and apical ballooning pattern, troponin I level >10 ng/mL was the only predictor for LV thrombosis (hazard ratio 6.6, confidence interval, 1.01–40.0; $P=0.04$). After 3 months all LV thrombi disappeared. Oral anticoagulation therapy was interrupted in all patients except 1. At long-term follow-up, the survival rate was not different between patients with and without LV thrombi (84% versus 85%; $P=0.99$).

***Conclusions*—**LV thrombi have a relatively low incidence among patients with Takotsubo syndrome and were detected in female patients with apical ballooning pattern and increased troponin levels. Oral anticoagulation therapy for 3 months seems reasonable in these high-risk patients. **(*J Am Heart Assoc*. 2017;6:e006990. DOI: 10.1161/JAHA.117.006990.)**

Key Words: stress-induced cardiomyopathy • Takotsubo cardiomyopathy • thrombosis

Left ventricular (LV) thrombus formation is a well-known complication in the course of acute myocardial infarction and can be associated with thromboembolic events.[1] Major predisposing factors associated with LV thrombosis are blood stasis, endothelial injury, and hypercoagulability. During the acute phase of Takotsubo syndrome (TTS), LV thrombi can also occur with a rate of 1.3% to 5% because of the presence of distinct transient LV regional akinesia and increased catecholamine levels.[2,3] However, there is a lack of data regarding the natural history of LV thrombi in TTS and their optimal short-term and long-term pharmacological management. More systematic data are therefore needed to ascertain the exact incidence and clinical relevance including stroke because of LV thrombus formation in TTS. Moreover, it is unknown whether oral anticoagulation (OAC) reduces the risk of embolic strokes and whether it outweighs the risk of

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Clinical Perspective

What Is New?

- Left ventricular thrombi during the acute phase of Takotsubo syndrome occur in 2.2% of cases.
- Seventeen percent of patients affected by left ventricular thrombi can develop stroke.
- Presence of apical ballooning and elevated admission levels of troponin I (>10 ng/mL) are associated with an increased risk of left ventricular thrombosis.

What Are the Clinical Implications?

- Left ventricular thrombi can be successfully managed with 3 months of oral anticoagulation therapy with complete resolution.
- In case of presence of apical ballooning and increased troponin I admission levels (>10 ng/mL), prophylactic oral anticoagulation could be considered.
- Patients with midventricular or basal ballooning and normal troponin levels may not require prophylactic oral anticoagulation.
- Long-term survival rates of patients with left ventricular thrombosis are similar to those of patients without.

bleeding. The aim of this study was therefore to investigate, in a multicenter-international registry, the exact incidence, predictors, and clinical implications of LV thrombus formation in patients with TTS.

Methods

Study Population

The study group included 541 consecutive patients with TTS who were enrolled in a multicenter-international registry, GEIST (German and Italian Stress Cardiomyopathy registry) involving 6 institutions (Ospedali Riuniti, University Hospital, Foggia, Apulia, Italy; Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Apulia, Italy; Ospedale San Paolo, Bari, Apulia, Italy; San Giovanni di Dio Hospital, Cagliari, Sardinia, Italy; Medical Clinic II, University Heart Center Lübeck, University Hospital Schleswig-Holstein, Lübeck, Germany; and Department of Internal Medicine-Cardiology, University of Leipzig-Heart Center, Leipzig, Germany).

Inclusion Criteria

All patients with suspected TTS underwent coronary and LV angiography. The diagnosis of TTS was based on the revised Mayo Clinic criteria: (1) transient hypokinesis, akinesis, or dyskinesis of the LV mid segments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is 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) absence of pheochromocytoma and myocarditis.[4]

Clinical, Laboratory, and Echocardiographic Examination

All patients underwent clinical examination and baseline characteristics such as age, sex, medical history, and kind of triggering events/stressors were recorded. Circulating levels of troponin-I were obtained by venipuncture at admission (normal values <0.5 ng/mL). A 2-dimensional Doppler echocardiographic examination was performed on admission, serially according to clinical condition and in all patients at discharge for assessment of LV wall motion abnormalities and LV thrombi. The LV ejection fraction (LVEF) was calculated biplane using the Simpson method from the apical 4-chamber and 2-chamber view.[5] The pattern of LV dysfunction was classified as follows: apical ballooning type (akinesia/dyskinesia of the LV apex), midventricular ballooning type (akinesia/dyskinesia midventricular LV segments), and basal type (akinesia/dyskinesia of the LV basal segments).[6] In 1 institution, cardiac magnetic resonance (CMR) was also performed in patients without contraindications during hospitalization in order to confirm the diagnosis of TTS.[7]

LV thrombus was defined as an echo-dense mass, contiguous but distinct from the endocardium, located in an area of a-/hypokinesis that was seen in both systole and diastole in at least 2 echocardiographic views. A thrombus was classified as either mural (if it was flat and parallel to the endocardial surface) or protruding (if it was spherical and projected into the LV cavity). It was considered mobile if any portion moved independently of the underlying myocardium. The presence or absence of thrombus was determined by 2 independent observers. As stated above, in 1 institution CMR was performed for optimized thrombus detection.

Cerebrovascular Embolic Events and Management

Stroke was defined as ischemic or hemorrhagic stroke with an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction according to the updated stroke criteria for the 21st century.[8] All cerebrovascular events were independently confirmed by a neurologist and managed following the 2013 American Heart Association/American Stroke Association guidelines on acute ischemic stroke.[9]

Follow-Up and Definition of Outcome

Complete follow-up data were available in all patients with a mean follow-up time of 984±908 days. All patients with LV thrombi underwent clinical and echocardiographic evaluation 1 and 3 months after discharge. The primary clinical end point was overall survival. All patients gave written informed consent for participation in the GEIST registry; the study was approved by the institutional review committee.

Statistical Analysis

Continuous variables were expressed as mean±SD and compared with Student *t* test or Mann–Whitney *U* test as required. Categorical variables are presented as percentages and compared with χ^2 or Fisher test as required. The Kolmogorov–Smirnov test was used to identify variables with normal distribution.

Cox multivariable analysis was used to identify predictors for LV thrombus formation and for correcting bias of principal confounders. Hazard ratio as well as 95% confidence intervals were calculated. Kaplan–Meier survival plots were used to evaluate the prognostic significance of LV thrombi regarding event-free survival. Linear correlations were determined by measuring the Pearson correlation coefficient. A $P<0.05$ was considered statistically significant.

Results

Baseline Features

LV thrombus was found in 12 out of 541 patients (2.2%). When comparing these patients versus those without LV thrombi, no differences were found in terms of cardiovascular risk factors, stressors, and clinical presentation. Significant differences were observed only for the prevalence of ST-elevation at admission ECG (56% versus 16%; $P<0.001$) and troponin-I value at admission (10.8±18.3 ng/mL versus 3.5±4.3 ng/mL; $P=0.001$), which were both higher in patients with thrombi (Table 1).

Clinical and Echocardiographic Features Patients With LV Thrombi

Patients with LV thrombi were all female and their mean age was 72±10 years. On admission, LVEF was 36±7% and an apical ballooning pattern was found in all patients. LV apical thrombus was documented during hospitalization in a variable timing from the first to the fifth day of hospitalization (Table 2). The thrombus was mural in 5 (42%) and protruding in 7 (58%) patients (Figures 1 and 2).

Table 1. Population Characteristics and Comparison Between Subjects With LV Thrombi Versus Those Without

	Patients With LV Thrombus	Patients Without LV Thrombus	
	Mean±SD	Mean±SD	*P* Value
Number of patients	12	529	
Age, y	72±10	71±11	0.80
Male	0%	11%	0.21
Cardiovascular risk factors			
Hypertension	92%	75%	0.19
Dyslipidemia	58%	35%	0.09
Smoker	25%	18%	0.55
Diabetes mellitus	25%	23%	0.45
Clinical presentation			
No chest pain	17%	24%	0.84
Angina pectoris	75%	60%	0.21
Atypical chest pain	8%	16%	0.78
Dyspnea	8%	24%	0.21
Precipitating stressor			
Emotional stressors	50%	30%	0.12
Physical stressors	34%	39%	0.61
No stressors	16%	31%	0.86
Laboratory and echocardiogram findings			
Admission troponin I, ng/mL	10.8±18	3.5±4.3	0.01*
Admission EF%	41±11%	36±7%	0.12
Discharge EF%	49±5%	51±7%	0.35
Apical ballooning pattern	100%	81%	0.09
Midventricular ballooning pattern	0%	17%	0.11
Basal ballooning pattern	0%	2%	0.68
ECG findings			
ST elevation at admission	57%	16%	0.005*
Inverted T waves at admission	86%	91%	0.61
Prolonged QT interval at admission	57%	63%	0.74

Data represented as mean±SD. EF indicates ejection fraction; LV, left ventricular.
*Indicates differences statistically significant.

Predictors of LV Thrombus Formation

At univariate and multivariate analysis including age, sex, LVEF, ST-elevation at admission, and apical ballooning pattern, troponin I level >10 ng/mL was the only predictor for the occurrence of LV thrombosis (hazard ratio 6.3, 95% confidence intervals, 1.15–34.3; $P=0.03$; hazard ratio 6.6, 95% confidence intervals, 1.01–40.0; $P=0.04$) (Table 3). The

Table 2. Clinical and Echocardiographic Features and Follow-Up of Patients With LV Thrombi

Patient No.	Age, y	Sex	No. cardiovascular Risk Factors	LVEF % at Admission	LV Pattern	Feature Thrombus	Thrombus Detection Time	Duration Thrombus	Days of Hospitalization	Adverse Events During Hospitalization	LV EF% at 3-Mo FU	Follow-Up
1	76	F	2	38%	Apical ballooning	Mural	Second day	15 d	9	···	55%	Uneventful
2	81	F	1	42%	Apical ballooning	Protruding	Fifth d	40 d	16	Stroke	55%	Acute heart failure
3	64	F	1	30%	Apical ballooning	Protruding	First d	5 d	6	···	62%	Uneventful
4	74	F	3	45%	Apical ballooning	Protruding	Third d	5 d	9	···	58%	Uneventful
5	73	F	2	30%	Apical ballooning	Protruding+ spontaneous echo-contr.	Fourth d	10 d	17	···	66%	Uneventful
6	74	F	3	38%	Apical ballooning	Mural	Second d	7 d	9	···	60%	Uneventful
7	61	F	1	28%	Apical ballooning	Protruding+ spontaneous echo-contr.	Second d	12 d	8	···	55%	Uneventful
8	56	F	2	40%	Apical ballooning	Mural	Fourth d	16 d	11	Stroke	58%	Uneventful
9	61	F	2	35%	Apical ballooning	Protruding	Second d	NA	9	···	62%	Uneventful
10	76	F	3	43%	Apical ballooning	Protruding	Fourth d	NA	4	···	65%	Uneventful
11	82	F	2	21%	Apical ballooning	Mural	First d	NA	4	···	74%	Noncardiovascular death
12	91	F	2	40%	Apical ballooning	Mural	Second d	12 d	14	···	52%	Noncardiovascular death

FU indicates follow-up; LV, left ventricular; LVEF, left ventricular ejection fraction; NA, not available.

absence of both apical ballooning and troponin levels >10 ng/mL was associated with a negative predictive power of LV thrombosis of 100%.

The presence of both apical ballooning pattern at echocardiography and elevated admission levels of troponin I (>10 ng/mL) was associated with a LV thrombosis rate of 14%, the presence of either apical ballooning pattern at echocardiography and elevated admission levels of troponin I (>10 ng/mL) of 3%, and the absence of both conditions with a 0% rate of LV thrombosis (Figure 3) (*P* for trend <0.05).

Hospitalization and 3 Months' Follow-Up

Mean hospital stay was 10±4 days. During hospitalization, 2 of the 12 patients (17%) had an acute ischemic stroke (1 right temporoparietal stroke, 1 left corona radiata infarct). Patients with stroke were not on antiplatelet and/or OAC therapy at the time of the event. No other complications were recorded in these patients.

After LV thrombus detection all patients, except those presenting with stroke, received low-molecular-weight heparin (enoxaparin 1 mg/kg, maximum 100 mg) subcutaneously every 12 hours and vitamin K antagonists (among all patients taking warfarin). Enoxaparin was continued until a therapeutic International Normalized Ratio was reached (2.0–3.0). Patients presenting with stroke were not treated during the acute phase with OAC therapy. Restarting OAC was performed after neurological, clinical, and instrumental evaluation including a computed tomography brain scan performed 48 hours after the stroke event. Oral warfarin was prescribed for 3 months and the International Normalized Ratio was monitored every 2 to 4 weeks to maintain a therapeutic level.

After 3 months' follow-up, LV function recovered in all patients (mean LVEF 61±6%) and all LV thrombi had resolved. During follow-up, no patient experienced bleeding episodes except 1 patient who experienced cranial hemorrhage, probably related to OAC intake. This patient died because of acute respiratory failure.

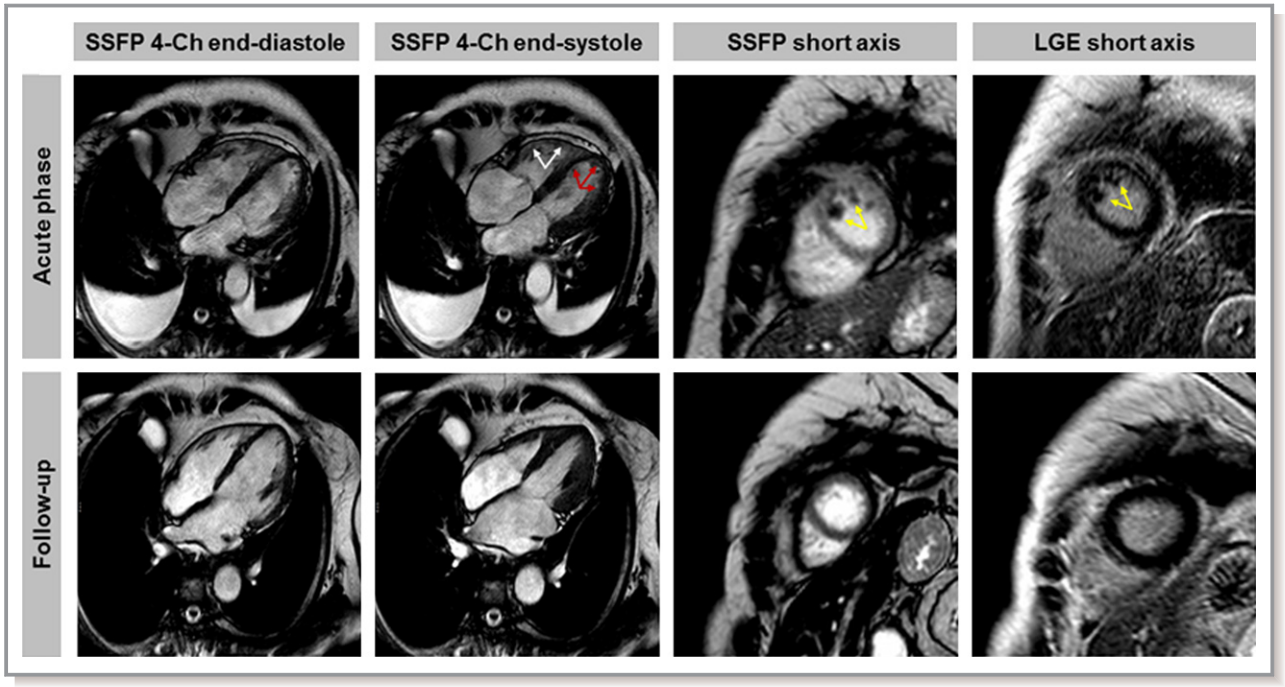

Figure 1. Acute phase: patient with typical apical ballooning (red arrows) and right ventricular involvement (white arrows) in steady-state free precession (SSFP) images in long-axis 4-chamber view. Bilateral pleural effusion. Evidence of thrombus in short-axis SSFP and LGE images (yellow arrows). Follow-up: Complete recovery of left and right ventricular function; no evidence of thrombus. 4-Ch indicates 4 chamber view; LGE, late gadolinium enhancement imaging.

After clinical and echocardiographic evaluation, OAC was stopped in all patients except for 1 who needed lifetime OAC because of the presence of paroxysmal atrial fibrillation and a CHADsVasc Score of 5 points.

Long-Term Follow-Up

After a mean follow-up of 984±908 days, no significant difference was found in terms of long-term survival between

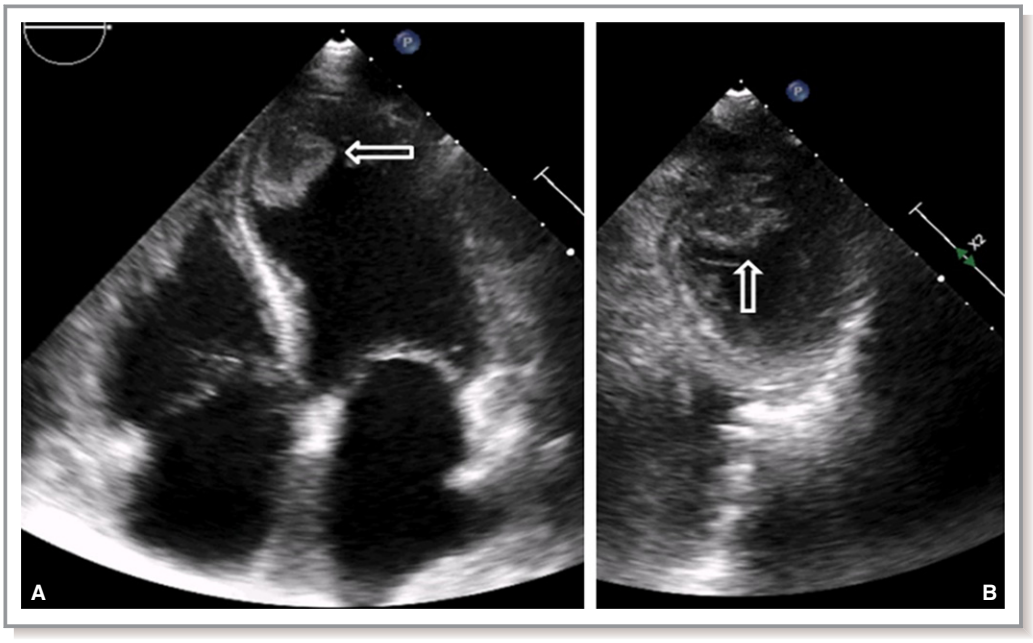

Figure 2. Left ventricular thrombus (protruding type, white arrow) evaluated with echocardiography: (A) 4-chamber view, (B) short-axis view.

Table 3. Univariate and Multivariate Cox Analysis of Predictors for LV Thrombosis During the Acute Phase of Takotsubo Syndrome

	Univariate Analysis			Multivariate Analysis		
Variable	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age	1.01	0.96–1.06	NS			
Male	0.04	0.001–128.1	NS			
Admission LVEF	0.96	0.91–1.02	NS			
ST elevation at admission ECG	1.85	0.50–6.87	NS			
Troponin I levels >10 ng/mL	6.3	1.15–34.3	0.03*	6.6	1.01 to 40.0	0.04*
Apical ballooning pattern	28.8	0.07–>100	NS			

CI indicates confidence interval; LV, left ventricular; LVEF, left ventricular ejection fraction; NS, not significant.
*Indicates differences statistically significant.

patients with LV thrombi and those without (84% versus 85%, respectively; *P*=0.99). Moreover, among patients with initial LV thrombi, no patient experienced neurological events during long-term follow-up.

Discussion

This is the largest study in TTS patients to date evaluating the natural history, predictors, clinical relevance, and therapeutic management of LV thrombi at short- and long-term follow-up. The main findings of this study can be summarized as follows:

1. The incidence of LV thrombi during the acute phase of TTS is 2.2% and if present this complication can be associated with cerebrovascular embolic events in 17% of patients;
2. The presence of both troponin I levels >10 ng/mL and apical ballooning pattern are associated with LV thrombus formation. Increased troponin I levels were identified as the only independent predictor of the occurrence of LV thrombosis;
3. LV thrombi can be successfully managed with 3 months of OAC therapy with complete resolution;
4. At long-term follow-up of 3 years, the survival rate of patients with LV thrombi was similar compared with patients without LV thrombi. After interruption of OAC therapy, no patient with initial LV thrombus experienced cerebrovascular thromboembolic event.

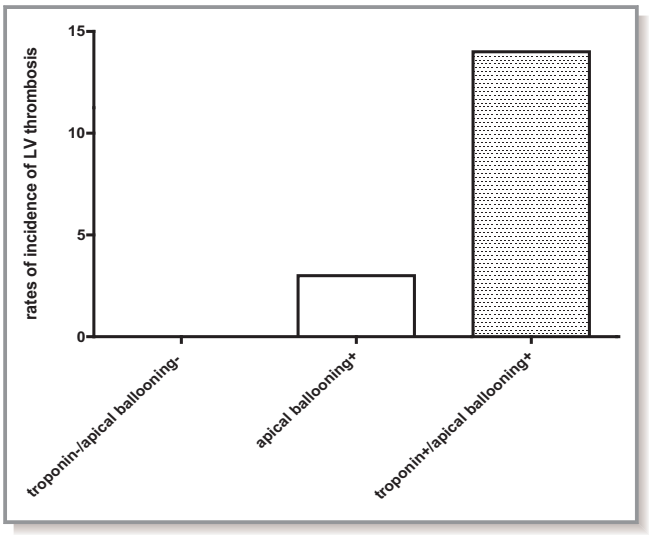

Figure 3. Incidence of left ventricular thrombosis according to presence of apical ballooning pattern at echocardiography and elevated admission levels of troponin I (>10 ng/mL) (*P* for trend <0.05). LV indicates left ventricular.

LV Thrombus Pathogenesis

A prerequisite for in vivo LV thrombus formation is the well-known Virchow's triad that consists of the combination of 3 factors: (1) blood stasis, (2) endothelial injury, and (3) hypercoagulability. In the context of TTS, all of these evoking factors are conceivable. Blood stasis is caused by the marked LV regional wall akinesia and ballooning of the LV. Interestingly, in the present study, apical ballooning was present in all patients with LV thrombus and therefore patients with apical ballooning seem to represent a high-risk cohort for thrombus formation. Moreover, endothelial injury is correlated with increased levels of catecholamines.[10] During the acute phase of TTS, a systemic inflammation[11] and severe endothelial dysfunction can be found.[12,13] Finally, a hypercoagulable state induced by a catecholamine surge may also be present.[14] It has been recently shown that patients with TTS show significantly greater values of whole blood viscosity, von Willebrand factor, and lower erythrocyte deformability.[15]

Incidence and Predictors of LV Thrombi in TTS

The reported incidence of LV thrombi during TTS varies widely. Templin et al, in a multicenter registry of 1750

patients, reported an incidence of 1.3%,[3] whereas Eitel et al, in a multicenter cohort of 256 patients who underwent CMR, found a rate of LV thrombi of 2%.[6] The difference may be related to the higher sensibility of CMR in thrombus detection.[16] Indeed, delayed-enhancement CMR using gadolinium contrast allows an optimized differentiation of thrombus from surrounding myocardium. LV thrombus is a nonvascular structure and thus is characterized by an absence of contrast uptake. CMR represents the criterion standard for thrombus detection and should be considered for optimized thrombus detection among high-risk TTS patients for thrombus formation.[17] As reported in a previous review by De Gregorio et al, LV thrombi can be mural and protruding, respectively, with a prevalence of 40% and 60% and can cause cerebrovascular thromboembolic events in 20% of patients.[18] According to previous literature, protruding and mobile thrombi have been associated with an increased risk of ischemic stroke. In the present registry, only 2 ischemic strokes were recorded and were related in 1 case to a protruding thrombus and in another one to a mural thrombus. Therefore, no clear conclusion can be drawn regarding thrombus texture and stroke risk.

We found that the presence of an apical ballooning pattern together with increased troponin I levels (>10 ng/mL) were present in all patients with LV thrombi. Increased troponin levels were identified as strong independent predictors of the occurrence of LV thrombus formation, while the absence of this echocardiographic pattern and low troponin I levels were associated with no LV thrombosis.

Apical ballooning represents a predisposing condition for blood stasis and thrombus formation because of a marked akinesia of apical and mid segments, combined with hypercontractility of the basal segments. On the other hand, the other echocardiographic patterns of TTS (midventricular ballooning and basal type) are characterized by preserved or even hyperkinetic apical segments that may avoid blood stasis of the apex. Moreover, increased levels of troponin could be associated with a more severe myocardial injury that could lead to a larger area of stunned myocardium predisposing to thrombus formation. It is well known that the amount of troponin increase is strongly associated with the severity of ischemia and may reflect ischemia/reperfusion injury as a trigger for LV thrombus development.[19]

Among patients with acute anterior myocardial infarction, even after primary percutaneous intervention, thrombus formation is mainly related to apical involvement, reduced LVEF,[20,21] and increased troponin levels,[22] while thrombus disappearance can be predicted by the absence of apical dyskinesis 6 weeks after infarction.[23] When comparing the acute phase of ST-elevation myocardial infarction and TTS, similar systolic and diastolic mechanisms have been described.[24] Therefore, it is not surprising that similar predictors of thrombus formation have been found in our comprehensive study.

In this registry, LV thrombi were found from the first until the fifth day of hospitalization; however, a late occurrence (after 14 days from admission) has also been described.[25] Therefore, especially in patients with apical balloon pattern and increased troponin levels, serial echocardiographic evaluation until complete LV systolic function recovery should be considered. Consequently, a longer hospitalization stay should be considered in the presence of risk factors for thrombus formation.

Management of LV Thrombi in TTS

Because of the absence of randomized studies and few multicenter registries, a recent European position paper recommends OAC therapy in patients with TTS and LV thrombosis for at least 3 months, whereas prophylactic OAC should be considered in high-risk TTS defined as patients with at least 1 major risk factor such as age (75 years), hemodynamic instability, reduced EF (<35%), LV outflow-tract obstruction, and mitral regurgitation (moderate or severe).[26] In ST-elevation myocardial infarction, repeated imaging of the LV after 3 months of therapy may allow the discontinuation of OAC, in the absence of LV thrombosis, particularly if recovery of apical wall motion is shown.[27] In this registry, OAC management was similar to the protocol proposed for ST-segment elevation myocardial infarction patients. After 3 months' follow-up and careful clinical and echocardiographic evaluation with documented complete recovery of LV function and thrombus disappearance, OAC was discontinued.

In this study, all patients were treated with vitamin K antagonist drugs with close monitoring of the International Normalized Ratio (between 2.0 and 3.0). No patient received novel OAC drugs and their role in this setting is not clear. Only a few case reports in infarction patients showed the feasibility of this therapeutic approach, and data of novel OAC use in TTS patients are completely lacking.[28,29] However, according to current guideline recommendations for stroke prevention,[30] novel OAC use in TTS with LV thrombus also seems reasonable.

According to our data, the limitation of OAC therapy for only 3 months is a safe and an effective approach. Indeed, no patient after OAC interruption experienced stroke. On the other hand, OAC therapy is characterized by an increased risk of intracranial and extracranial bleeding[31] that should be always considered. Moreover, patients with TTS are usually postmenopausal women with several comorbidities. In the present cohort, 1 patient who started OAC because of LV thrombus experienced an intracranial bleeding following an accidental brain injury. Therefore, the use of OAC therapy should be limited, when possible, for a short time in patients

with presence of LV thrombus or high-risk features. Prophylactic OAC therapy did not show clear benefit among patients with TTS[32] and was therefore not performed in this registry.

We propose a simplified approach regarding OAC therapy in patients with TTS (Figure 4) through echocardiographic evaluation combined with laboratory data (troponin levels). In case of an apical ballooning pattern and increased troponin I admission levels (>10 ng/mL), prophylactic OAC could be considered, also based on the possibility of late thrombus formation. When an apical ballooning pattern but no increased troponin admission levels are present, there is no clear indication for OAC. Moreover, patients with midventricular or basal ballooning and normal troponin levels do not require prophylactic OAC.

Prospective and randomized studies are required to clearly understand which patients have a high risk of thrombus formation and could benefit from OAC.

LV Thrombus and Stroke

Among patients who experience acute ischemic stroke because of LV thrombus embolization, the optimal timing of initiation of OAC therapy is uncertain. Current literature shows a higher risk of brain hemorrhage if OAC therapy is started in the first 48 hours after stroke.[33,34] Therefore, OAC therapy could be started between 48 hours and 15 days after ischemic stroke, taking into account the clinical severity, extent of neuroimaging lesions, the risk of cardioembolic recurrence, and risk factors for hemorrhagic transformation.

However, stroke is not only a consequence of thrombus embolization but could also be a physical trigger of TTS. Indeed, 1.2% of patients during stroke develop TTS, mainly in case of insular damage.[35] Extensive brainstem ischemia with autonomic disturbances is considered the leading mechanism.[36]

Clinical Implication at Long-Term Follow-Up

According to our data and the current literature, LV thrombosis in patients with TTS represents mainly the expression of severe LV dysfunction and apical dyskinesia, but carries no impact on long-term prognosis. Although TTS patients have an increased risk of mortality when compared with ST-segment elevation myocardial infarction patients,[37] survival rates of

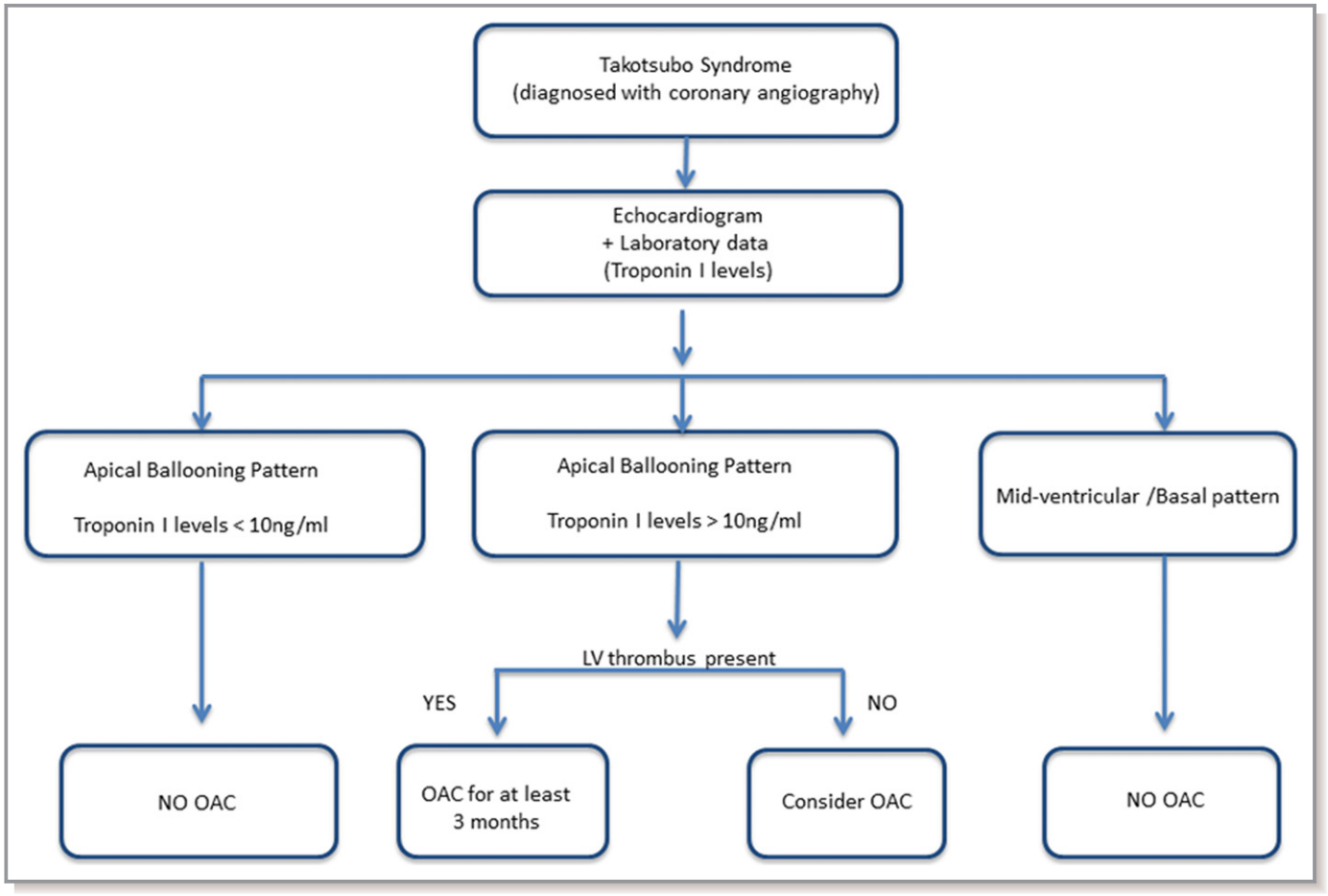

Figure 4. Therapeutic algorithm proposal for oral anticoagulation (OAC) management during the acute phase of Takotsubo syndrome. LV indicates left ventricular.

patients with LV thrombi were similar to those without LV thrombi after 3 years of follow-up. Therefore, a routine cardiological follow-up similar to those TTS patients without LV thrombi is reasonable. Besides anticoagulation management, a tailored therapeutic approach for patients with TTS is recommended. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers could have some benefit in term of improved survival at 1 year.[3] β-Blockers showed no effect on survival and recurrence rate,[3–38] whereas calcium antagonists could be used if coronary vasospasm has been proven during coronary angiogram or with acetylcholine test.[32]

Limitations

This was an observational study in which OAC therapy was applied to a small number of patients. Systematic data regarding bleeding were collected only among patients with LV thrombi. CMR represents the criterion standard method to evaluate the presence of LV thrombi; however, it was performed only in 1 out of 6 centers. Moreover, contrast echocardiography was not performed to optimize thrombus detection. Although serial echocardiograms were performed at admission, discharge and, for patients with LV thrombi, after 1 and 3 months, the timing of thrombus formation and dissolution cannot be exactly determined. Finally, we cannot provide a histopathologic validation of the presence or absence of LV thrombus.

Conclusions

Despite their relatively low incidence in patients with TTS, LV thrombi can be associated with cerebrovascular thromboembolic events. Increased troponin levels and apical ballooning pattern are strongly associated with the occurrence of LV thrombosis. Therapeutic management with 3 months of OAC is safe and feasible and should be considered in patients with apical ballooning and increased troponin levels. In all other TTS patients (midventricular and/or basal ballooning, troponin I <10 ng/mL) routine OAC should not be performed.

Disclosures

None.

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