Incidence and clinical significance of left ventricular thrombus in tako-tsubo cardiomyopathy assessed with echocardiography

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Summary

Background: Left ventricular (LV) thrombus is a known complication of tako-tsubo cardiomyopathy (TC). However, current literature almost exclusively consists of isolated case reports. The aim of this study was to determine the incidence and clinical significance of LV thrombus formation in TC.

Methods and Results: Over a 33-month period 52 patients with TC were assembled into a database at our institution. A retrospective database search was performed to identify patients with LV thrombus among these patients. LV thrombus, by echocardiography, was discovered in four patients [(8%); 95% confidence interval 3–19%]. Thrombus was present at the time of diagnosis in three patients. In one patient thrombus was absent initially and developed later. The LV apex was the site of thrombus formation in two patients, but the true apex was spared in the other two. All four patients had elevated serum levels of C-reactive protein (CRP). Two patients also had thrombocytosis. Treatment with low molecular weight heparin (LMWH) led to resolution of thrombus in all cases.

Conclusions: Our findings suggest that LV thrombus is a noteworthy complication in TC. It can occur both at initial presentation or at anytime later during the disease course. Elevated CRP levels and thrombocytosis may indicate a higher risk of thrombus formation.

Introduction

Intraventricular thrombus formation is a known complication of tako-tsubo cardiomyopathy (TC) but its true incidence is unknown. Current literature almost exclusively consists of isolated case reports. A notable exception is the study by Sharkey et al., who found left ventricular (LV) thrombus in one of their 22 patients. Therefore, it is timely to report the cohort of patients with TC focusing on the incidence and clinical impact of LV thrombus formation.

Methods

Patient population

Between November 2004 and July 2007, 52 patients (46 women; mean age 69 ± 12 years) with a clinical diagnosis of TC were assembled into a database at our institution. We performed a retrospective database analysis to identify patients with LV thrombus. Diagnosis of TC was based on the following criteria: (i) Acute onset of LV wall-motion...
abnormalities not confined to the vascular territory of a single major coronary artery; (ii) Rapid improvement of wall-motion abnormalities within a few days of initial diagnosis; and (iii) Exclusion of severe (>70% diameter stenosis) coronary artery disease or intraluminal haziness/thrombus by coronary angiography.

Inclusion of a patient in this series required at least one transthoracic echocardiogram within 48 h of diagnosis and another one upon follow-up demonstrating significant improvement of LV dysfunction.

Although not a prerequisite for inclusion, most patients had dynamic ST-segment elevation \( [n = 26 (50\%) ] \) or T-wave inversion \( [n = 17 (33\%) ] \) on ECG as well as mild elevation of troponin I \( [n = 42 (81\%) ] \) disproportionate to the extent of wall-motion abnormalities. Patients with subarachnoid hemorrhage or pheochromocytoma were excluded.

All patients had daily ECGs for three consecutive days. Additional ECGs were obtained as clinically indicated. Routine laboratory tests including cardiac enzymes were performed depending on the patients’ presentation and clinical course. Troponin I and C-reactive protein (CRP) were measured in all patients on the day of presentation and thereafter, if clinically indicated. The performance of this study was consistent with the standards of the local ethical committee at our institution.

Echocardiography

Cardiac ultrasound data were acquired in a standard fashion with a Vivid Five ultrasound scanner (GE, Vingmed, Norway) prior to December 2005 and with a Vivid Seven ultrasound scanner (GE, Vingmed, Norway) thereafter. Harmonic images were obtained using a 3.5 MHz probe. LV thrombus, by echocardiography, was defined as an echogenic mass with well-defined margins, adjacent to an asynergic myocardial segment, visible throughout the cardiac cycle. If deemed necessary, contrast agent (SonoVue® or Luminity®) was used to differentiate an abnormal mass from trabeculations and artifacts.

Results

We identified four patients \( (8\%); 95\% \) confidence interval (CI) 3–19\% \) with LV thrombus (Table 1).

Presence of LV thrombus could be demonstrated without the use of contrast agents in all cases. LV thrombus was suspected in three additional patients. However, in these patients applying a contrast agent could identify near field artifacts as the underlying cause and thrombi were excluded. All patients with LV thrombus had elevated serum levels of CRP. Twenty patients had normal CRP levels (mean 2.5 ± 2.4 mg/l) at the time of initial diagnosis. None of these patients developed LV thrombus. The sensitivity, specificity and positive and negative predictive values of elevated CRP for the prediction of LV thrombi were 100\% (95\% CI 40–100\%), 42\% (95\% CI 28–57\%), 13\% (95\% CI 4–30\%) and 100\% (95\% CI 80–100\%), respectively.

Case 1

A 69-year-old woman with hypertension and major depression presented to the emergency department (ED) of another hospital with a 2 weeks history of back pain. After a heavy argument with one of the nurses at the ED, her back pain became worse. At this point, an ECG was performed demonstrating ST-segment elevation in leads V1–V4. An echocardiogram showed extensive akinesis of the LV apex and midventricle and the presence of an apical thrombus. The patient was transferred for urgent coronary angiography, which excluded coronary
artery disease. A LV angiogram was not performed. An echocardiogram performed on the same day at our institution, demonstrated akinesis of the LV apex and midventricle with an ejection fraction (EF) of 39%, and two mobile thrombi in the LV apex measuring 5 × 6 mm and 8 × 10 mm. The patient was started on a full dose of low molecular weight heparin (LMWH). A repeat echocardiogram 2 weeks later demonstrated significant improvement of LV dysfunction and resolution of both thrombi. The EF was 61%, with no regional wall-motion abnormalities. The patient was switched to phenprocoumon for a total of 4 weeks. No thromboembolic events occurred in 6 weeks of follow-up.

Case 2
A 69-year old woman with no history of cardiovascular disease was 5-day post-operative from a Hartmann’s procedure for rectal cancer when she developed dyspnea and unexplained sinus tachycardia of up to 170 b.p.m. Her troponin I was 1.55 μg/l (normal <0.5), her creatinine kinase (CK) was 114 U/l (normal <145) and her D-dimer level was 2.92 mg/l (normal <0.5). A CT scan of the chest ruled out pulmonary embolism. There were bilateral pleural effusions present. An echocardiogram was performed on postoperative day 6 and showed extensive midventricular akinesis of both ventricles with a hypercontractile base and apex. LV EF was 30%. Coronary angiography excluded coronary artery disease. The patient was started on a full dose of LMWH. A repeat echocardiogram on the following day was unchanged. On postoperative day 13 another echocardiogram was performed. LV EF was 51% and the previous wall-motion abnormalities had improved. However, a mobile thrombus adjacent to the posteromedial papillary muscle was clearly visible (Figure 1A). Of note, the patient’s platelet count had gradually risen from 368,000 μl on

Figure 1. (A) Apical long-axis view in case 2 demonstrating a thrombus attached to the posterior wall (white arrow). (B) Close-up view of the left ventricular apex in case 3. There is an echogenic mural thrombus present (white arrows). (C) A large, lobulated, echogenic mass attached to the anteroseptal wall is visible in the apical long-axis view in case 4 (green arrows). (D) In these images of case 4, a 4-dimensional full-volume dataset was used to slice the left ventricle into nine equidistant short-axis views. Arrows indicate the presence of thrombus.
post-operative day 6 to 501 000 μl on post-operative day 11. No change in treatment was recommended and another echocardiogram 9 days later showed resolution of the thrombus. The patient’s platelet count had decreased to 361 000 μl. The patient was kept on LMWH for a total of 4 weeks. No thromboembolic events occurred in 4 months of follow-up.

Case 3

A 43-year-old woman with severe cerebral palsy developed sudden respiratory failure that was caused by aspiration of food. At the scene she was unconscious and severely cyanotic and required immediate intubation and mechanical ventilation by emergency personnel. She was admitted to the intensive care unit for further management. Upon admission, her ECG showed minor ST-segment elevation in leads I, aVL, V3–V6. Her ECG showed symmetric T-wave inversions in the precordial leads 3 days later. Urgent coronary angiography ruled out significant coronary artery disease. An echocardiogram was performed on day 4, which showed akinesis of the LV apex and hypokinesis of the midventricle. EF was 34%. There was a large immobile thrombus present in the LV apex with a false tendon cutting through it (Figure 1B). The patient was given full dose anticoagulation with LMWH for 2 weeks. The echocardiogram was repeated 11 days later and showed recovery of LV function and complete resolution of thrombus. No thromboembolic events occurred during the hospital course.

Case 4

A 69-year-old woman had an incidental diagnosis of incomplete thrombosis of the abdominal aorta during abdominal ultrasound for suspected gallstones at another hospital. An abdominal CT scan confirmed the diagnosis and revealed a right renal infarction. A transesophageal echocardiogram revealed a small patent foramen ovale. LV function was reportedly normal. Further work-up and treatment was refused by the patient and she was discharged home after cholecystectomy. Three weeks later, she had acute right common iliac artery occlusion requiring surgical embolectomy. She was 2-day postoperative when she started complaining of shortness of breath. On postoperative day 3 an echocardiogram was performed demonstrating akinesis of the LV apex and midventricle. EF was 45%. Coronary angiography through the radial approach ruled out coronary artery disease. A repeat echocardiogram 3 days later showed unchanged LV dysfunction. However, there was a large (28 × 22 mm), lobulated, echogenic thrombus attached to an akinetic segment of the anterior and anteroseptal wall. The thrombus spared the true LV apex (Figure 1C and D). At this time the patient’s creatinine had risen to 1.5 mg/dl, her lactate dehydrogenase (LDH) was 2697 U/l (normal <248) and the patient had mild discomfort in her left flank. A duplex scan of the left kidney showed renal infarction. Careful review of the echocardiogram performed 3 days earlier showed that a 4 × 4 mm mobile thrombus adjacent to the anterolateral papillary muscle had already been present but had been missed. The patient was given 100 mg of ASA and full dose anticoagulation with intravenous heparin that was switched to LMWH 2 days later. Her creatinine continued to rise and peaked at 5.5 mg/dl. After improvement of her kidney function the patient underwent magnetic resonance imaging of the aorta and abdominal vessels, which showed continued presence of incomplete aortic thrombosis and bilateral kidney infarction. A repeat echocardiogram on post-operative day 27 showed improvement of LV dysfunction and resolution of the LV thrombus. Of note, the patient’s platelet count ranged from 551 000 μl to 887 000 μl during the index hospitalization. Hematologic work-up was consistent with a diagnosis of the hypercellular stage of idiopathic myelofibrosis.

Discussion

To date the incidence and clinical significance of LV thrombus in TC has not been well established. Our literature search revealed only 14 reported cases (Table 2). All but one were single case reports. Thromboembolic events potentially attributable to LV thrombus occurred in three patients (one Stroke, one transient ischemic attack and one renal infarction). All patients were treated with some sort of anticoagulation. However, type and duration of anticoagulant treatment varied and details on dosing and the specific anticoagulants used for treatment were often not reported (Table 2). All patients had a follow-up study performed at some point after initiation of anticoagulation demonstrating complete resolution of the thrombus. No thromboembolic events occurred while patients were receiving anticoagulant therapy.

The present report describes a clinical experience over a 33-month period in 52 patients with TC. Of these, four had LV thrombi. This would give an incidence of thrombus formation of 8% with a wide 95% CI of 3–19%, indicating a significant degree of uncertainty about the true incidence of thrombi. However, there are many inherent difficulties in defining the true incidence of LV thrombus in TC. In particular, concomitant medication and...
co-morbidities may influence the formation of LV thrombus, while the number of echocardiograms performed per patient and their time point, acoustic windows, operator skill and use of contrast agents may all influence thrombus detection. For example, in a patient who presents with chest pain and is suspected of having an acute coronary syndrome, the chances of receiving anticoagulation upon first medical assessment are high, which can potentially decrease the rate of thrombus formation. On the other hand, if TC was diagnosed because of abnormalities occurring on a routine ECG in a mechanically ventilated patient in the intensive care unit, the time delay from onset of TC to initiation of anticoagulation would probably be significant or anticoagulant treatment might even be withheld, as there are no firm recommendations regarding treatment in these patients. This would potentially increase the rate of thrombus formation. Despite these limitations and at a rough estimate, the incidence of thrombus formation in TC seems to be slightly lower than in patients with acute anterior myocardial infarction or dilated cardiomyopathy. However, we cannot exclude that especially small thrombi may have been overlooked with echocardiography. Thus, the true incidence of thrombi may have been underestimated. In this regard, magnetic resonance imaging, which has higher sensitivity and accuracy in the detection of LV thrombi, may serve better than non-contrast enhanced echocardiography.

It seems, both from published cases and from the authors’ own experience, that the majority of LV thrombi are already present at the time of diagnosis. However, in one of our patients (case 3) and in several case reports, LV thrombus was initially absent and developed later in the course of disease. In one case, LV thrombus occurred even as late as several weeks after initial presentation.

Although the majority of thrombi occur in the LV apex, other sites may also be affected. In our experience (cases 3 and 4) the area adjacent to the papillary muscles seems prone to develop thrombus and should, therefore, carefully be examined during echocardiography.

Serum levels of CRP were elevated in all four cases with LV thrombosis, whereas none of the 20 patients with normal CRP levels developed LV thrombus, indicating a potential pathogenic role of inflammation in the process of thrombus formation. Similar findings have also been reported in patients with acute myocardial infarction who develop LV thrombosis. However, because of the limited number of cases with LV thrombus in our study, a chance effect cannot be excluded.

Of note, LV thrombus may develop despite full dose anticoagulation (case 2). In these cases, a search for hematologic abnormalities, such as thrombocytosis or heparin-induced thrombocytopenia, seems warranted. Further management decisions should be individualized. In the case of our patient, continued treatment with LMWH led to complete resolution of thrombus.

And finally, the overall risk of thromboembolic complications seems to be rather low. In fact, the only case of arterial embolism in our series could be that of a patient with a history of atrial fibrillation who developed stroke despite adequate anticoagulation. In this case, the thrombus appeared to have embolized to the brain, and the patient subsequently died of cardiac arrest. However, this outcome was likely due to the patient’s underlying comorbidities, including atrial fibrillation and previous stroke, rather than to the presence of LV thrombus itself.
not with certainty be attributed to the LV thrombus, as the patient might as well had embolized from her aortic clot which had previously been the source of embolism in this patient.

In summary, LV thrombus formation is a noteworthy complication of TC. It can occur both at initial presentation or at anytime later during the disease course. Patients with elevated serum CRP levels seem to be at higher risk of developing thrombi, as are those with thrombocytosis. A short course of full dose anticoagulation, by analogy to treatment strategies in acute myocardial infarction, could be considered in patients with TC. In patients at high risk of bleeding (e.g. postoperative patients) performing serial echocardiograms and delaying anticoagulation until presence of thrombus has actually been shown, could be an alternative, as the overall incidence of thromboembolic complications seems to be rather low. However, our data do not allow any firm recommendation regarding type and duration of anticoagulant therapy and clearly further research is required in this field.

Conflict of interest: None declared.

References


