Takotsubo Cardiomyopathy Is Not Due to Plaque Rupture: An Intravascular Ultrasound Study

Address for correspondence:
Dariusch Haghi, MD
I. Medizinische Klinik
Universitätsklinikum Mannheim
68167 Mannheim, Germany
dariush.haghi@med.ma.uni-heidelberg.de

Dariusch Haghi, MD; Stefanie Roehm, Cand Med; Karsten Hamm, MD; Niels Harder, Cand Med; Tim Suselbeck, MD; Martin Borggrefe, MD; Theano Papavassiliu, MD
First Department of Medicine, University Medical Centre and Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany

ABSTRACT

Background: Plaque rupture with subsequent transient thrombotic coronary occlusion by a fast-dissolving clot is one of the proposed pathogenic mechanisms in Takotsubo cardiomyopathy (TC).

Hypothesis: The aim of this study was to seek evidence for the hypothesis of transient coronary thrombosis as the underlying mechanism of TC by means of intravascular ultrasound (IVUS).

Methods: In our database of 63 consecutive patients with TC we identified 10 patients (16%) who had undergone IVUS during their initial left heart catheterisation.

Results: A median length of 67 mm of the left anterior descending artery was analyzed (interquartile range [IQR]: 63.3–70.1 mm). Median lumen diameter, median vessel diameter, median plaque and media volume were 2.9 mm (IQR: 2.7–3.1 mm), 4.2 mm (IQR: 3.8–4.4 mm), and 90.9 mm^3 (IQR: 70.4–101.4 mm^3), respectively. Plaque rupture, positive remodeling, and presumed intracoronary thrombus were absent in all patients.

Conclusion: In conclusion, plaque rupture does not account for the regional wall motion abnormalities observed in TC. The previously reported observation of plaque rupture in TC seems to constitute an incidental finding. We suggest that the theory of aborted myocardial infarction as the underlying cause of TC should be abandoned once and for all.

Introduction

Despite increasing awareness of Takotsubo cardiomyopathy (TC) in the cardiology community and the growing number of publications on this issue, the discussion regarding its pathogenesis remains unsettled. One of the proposed mechanisms is transient thrombotic coronary occlusion by a fast-dissolving clot.[1] Evidence for this hypothesis is mainly based on a single study by Ibanez et al who performed intravascular ultrasound (IVUS) in 5 patients with the syndrome and found disrupted atherosclerotic plaques in all cases.

The aim of this study was to seek further evidence for the hypothesis of transient coronary thrombosis as the underlying mechanism of TC.

Methods

Between November 2004 and April 2008, 63 patients (56 women, 7 men) with a clinical diagnosis of TC were assembled into a database at our institution. We performed a retrospective database analysis to identify patients who had an IVUS study performed during their initial left heart catheterization. Diagnosis of TC was based on the following criteria: (1) acute onset of left ventricle (LV) wall motion abnormalities not confined to the vascular territory of a single major coronary artery; (2) rapid improvement of wall motion abnormalities, as seen by echocardiography, within a few days of initial diagnosis; and (3) exclusion of severe coronary artery disease (>70% diameter stenosis) or intraluminal thrombus/haziness as seen by coronary angiography.

Clinical examination, laboratory tests, 12-lead electrocardiograms (ECG), and chest x-rays were performed according to the standard protocol for the management of acute coronary syndromes at our institution and as clinically indicated. All patients underwent transthoracic echocardiography within 48 hours of admission and prior to discharge.

All angiograms were analyzed by a single experienced interventional cardiologist (Suselbeck) using standard technology who was blinded to the clinical and IVUS findings. Coronary lesions were considered complex if they had 1 or more of the following specific morphologies according to previously published criteria[2]: ulceration, intimal flap, lumen irregularities, thrombus, and aneurysm. Otherwise, they were considered simple lesions.

No criteria were prespecified to mandate performance of IVUS. Rather, IVUS was performed at the discretion of the operator during the initial left heart catheterization procedure. All IVUS images were acquired using a commercially available ultrasound system (Volcano Corporation, Rancho Cordova, CA). After intracoronary administration of nitroglycerin (200 μg), the imaging catheter

This work was done without financial support. The authors have nothing to declare.

Received: October 2, 2009
Accepted with revision: January 12, 2010

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20747

with a 20-MHz transducer was advanced into the distal left anterior descending artery (LAD) and withdrawn with an automated pull-back device at 0.5 mm/s. Off-line volumetric reconstruction of the entire imaged segment was performed using commercially available software (Volcano In-Vision Gold imaging system software, Volcano Corporation). Grey-scale measurements included external elastic membrane (EEM), plaque and media (P&M), and lumen cross-sectional areas (CSA). Plaque rupture was defined as a plaque containing a cavity that communicated with the lumen with an overlying residual fibrous flap fragment.[2] The remodeling index (RI) was calculated as the ratio of the EEM CSA at the site with the largest amount of atheroma to that of a proximal reference site (a normal-appearing frame within the 10 mm segment proximal to the lesion site). Positive remodeling was defined as RI $\geq$1.05.[3] A presumptive diagnosis for thrombus was made if there was an intracoronary mass present.[4]

Virtual histology (VH) IVUS was performed in the last 5 patients of the series. VH-IVUS uses advanced spectral analysis of radiofrequency ultrasound backscatter to characterize plaque as fibrous (dark green), fibro-fatty (light green), necrotic core (red), and dense calcium (white). VH-IVUS measurements included absolute and relative amounts of these 4 types of characteristics.

Review of these data was approved by our institutional review committee. Informed written consent was obtained in all patients.

Statistics

Continuous variables are presented as median and interquartile range (IQR) and categorical variables as percentages.

Results

We identified 10 patients (16%) who had an IVUS study during their initial left heart catheterization. Classical TC with apical ballooning was present in 9 patients. Only 1 patient had a mid-ventricular variant without apical involvement. All left heart catheterizations were performed within 24 hours of admission. The clinical features of patients are shown in Table 1.

Coronary Angiography

Complex lesions were not detected in any of the patients. Moderately severe coronary artery disease (diameter stenosis 50%–70%) was present in the mid-LAD in 2 patients and in the proximal LAD in 1 patient. In these 3 patients, percent diameter stenosis by quantitative coronary angiography (QCA) was 55%, 53%, and 51%, respectively. Mild coronary artery disease (diameter stenosis <50%) was present in the mid-LAD in 2 patients. Five patients had no obvious coronary artery disease on coronary angiography.

Table 1. Baseline Characteristics

n	10
Age (yrs)	78 (IQR: 75–85)
Female, n (%)	9 (90%)
Hypertension, n (%)	7 (70%)
Diabetes, n (%)	1 (10%)
Current smoker, n (%)	1 (10%)
Hypercholesterolemia, n (%)	1 (10%)
Presenting symptom, n (%)	
Angina	5 (50%)
Dyspnea	2 (20%)
Other	3 (30%)
Peak troponin I (μg/L; normal range, 0–0.4)	4.87 (IQR: 2.81–11.66)
ECG on admission, n (%):	
ST-elevation	5 (50%)
T wave inversion	3 (30%)
Other	2 (20%)
Type, n (%)	
Classical	9 (90%)
Variant	1 (10%)
Triggering factor, n (%)	
Physical stress	4 (40%)
Emotional stress	3 (30%)
Initial ejection fraction (%)	44 (IQR: 39–56)
Follow-up ejection fraction	62 (IQR: 60–66)

Abbreviations: IQR, interquartile range.

Examples of moderately diseased, mildly diseased, and non-diseased LADs are shown in Figure 1.

IVUS Analysis

A median length of 67 mm of the LAD was analyzed (IQR: 63.3–70.1 mm). Median lumen diameter, median vessel diameter, and median P&M volume were 2.9 mm (IQR: 2.7–3.1 mm), 4.2 mm (IQR: 3.8–4.4 mm), and 90.9 mm^3 (IQR: 70.4–101.4 mm^3), respectively. Plaque rupture or positive remodeling was absent in all patients. The predominant plaque component was fibrous tissue (19.5 mm^3 [IQR: 18.4–77.8 mm^3]), followed by necrotic core (16.7 mm^3 [IQR: 3.9–18.5 mm^3]), dense calcium (12 mm^3

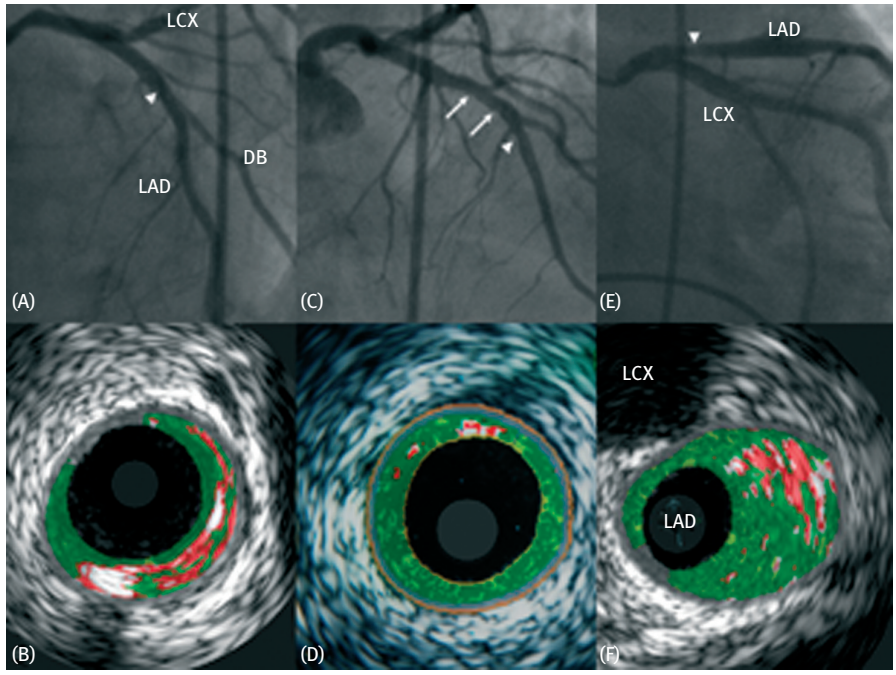

Figure 1. Examples of angiographically absent (A), mild (B), and moderate (C) coronary atherosclerosis of the LAD in 3 different patients. Representative VH-IVUS cross-sectional tissue maps of coronary fibroatheroma (B, D, and F) at different sites (arrowheads). Fibrous, fibro-fatty, necrotic core, and calcified regions are labeled dark green, light green, red, and white, respectively. Abbreviations: DB, diagonal branch; LAD, left anterior descending artery; LCX, left circumflex artery.

[IQR: 2.4–12 mm^3]), and fibro-fatty plaque (2.4 mm^3 [IQR: 2.3–10.6 mm^3]). The median percentage of fibrous, necrotic core, dense calcified, and fibro-fatty plaques were 66.3% [IQR: 54%–69.3%], 14.2% [IQR: 13.8%–16.4%], 10.2% [IQR: 8.5%–23.6%], and 8.4% [IQR: 6%–8.7%], respectively.

Discussion

Despite the growing number of publications on this enigmatic disease, the pathogenesis of TC remains obscure. There appears to be significant evidence in favor of the pathogenic role of catecholamines,[5–9] but the precise and detailed mechanisms of the disease are still unknown. Recently, the theory of coronary vasospasm, originally proposed by Sato et al,[10] has been revived.[11,12] Other alternative hypotheses include transient obstruction of the left ventricular outflow tract[13] and disturbed microcirculatory flow.[14,15]

Transient coronary occlusion by a rapidly dissolving thrombus is another proposed mechanism which is mainly based on data from a single IVUS study.[1] In their study of 5 patients with the syndrome, Ibanez et al found a single ruptured coronary plaque in the mid-LAD in all cases.[1] Coronary artery disease was reportedly absent in the remaining LAD.

Our results do not confirm the pathogenic role of plaque rupture in TC. None of the patients in our study had evidence of plaque rupture by IVUS. This observation was independent of whether there was moderate, mild, or no coronary artery disease present on coronary angiography. We also did not find plaques with positive remodeling, a feature that seems to be linked to unstable coronary plaques and acute coronary syndromes.[16] As can be expected in a predominantly elderly patient population, IVUS revealed some degree of coronary atherosclerosis in all our patients. In the few patients who underwent VH-IVUS examination, the percentage of fibrotic, necrotic core, and dense calcified plaques was similar to what has recently been reported in a large cohort of patients >68 years[17] with fibrous tissue being the predominant plaque component.

Another important piece to the puzzle of pathogenic mechanisms in TC comes from 2 recent studies, both reporting lower ejection fractions in patients with TC compared to controls with ST-elevation myocardial infarction.[18,19] Interestingly, in the study by Hoyt et al[18] the magnitude of systolic dysfunction was similar in patients with and without a "wrap around" LAD, further indicating that spontaneously aborted myocardial infarction is not the underlying mechanism in TC.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20747

Study Limitations

Whether or not patients underwent IVUS imaging was at the discretion of the cardiologist performing the initial coronary angiography. Thus, we cannot exclude some degree of selection bias. Only a small fraction of the TC patients at our institution underwent IVUS imaging. Therefore, the results of our study may not be applicable to all patients with TC. However, because we did not observe a single instance of plaque rupture, it seems very unlikely that a fast-resolving clot could be the underlying pathogenic mechanism. Compared to other imaging modalities, such as optical coherence tomography or coronary angioscopy, IVUS has low sensitivities for detecting fibrous cap disruption or intracoronary thrombus.[20] Therefore, it cannot be excluded that some instances of intracoronary thrombus were missed. Again, the total absence of ruptured plaques in our patients argues against a significant pathogenic role of thrombus.

Conclusions

Plaque rupture does not account for the regional wall motion abnormalities observed in TC. The previously reported observation of plaque rupture in TC constitutes an incidental finding.

References

1. Ibanez B, Navarro F, Cordoba M, et al. Tako-tsubo transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma? *Heart*. 2005;91: 102–104.
2. Maehara A, Mintz GS, Bui AB, et al. Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. *J Am Coll Cardiol*. 2002;40: 904–910.
3. Schoenhagen P, Ziada KM, Kapadia SR, et al. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation*. 2000;101:598–603.
4. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2001;37:1478–1492.
5. Abraham J, Mudd JO, Kapur NK, et al. Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. *J Am Coll Cardiol*. 2009;53:1320–1325.
6. Litvinov IV, Kotowycz MA, Wassmann S. Iatrogenic epinephrine-induced reverse Takotsubo cardiomyopathy: direct evidence supporting the role of catecholamines in the pathophysiology of the "broken heart syndrome." *Clin Res Cardiol*. 2009;98:457–462.
7. Tsoumakidou G, Buy X, Zickler P, et al. Life-threatening complication during percutaneous ablation of adrenal gland metastasis: Takotsubo syndrome. *Cardiovasc Intervent Radiol*. 2009; doi: 10.1007/s00270-009-9612-9. Available at: http://www.springerlink.com/content/xm2k348u61433720/.
8. Volz HC, Erbel C, Berentelg J, et al. Reversible left ventricular dysfunction resembling Takotsubo syndrome after self-injection of adrenaline. *Can J Cardiol*. 2009;25:e261–e262.
9. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539–548.
10. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure* [in Japanese]. 1st ed. Tokyo: Kagakuhyouronsha Publishing Co.; 1990; 56–64.
11. Angelini P. Transient left ventricular apical ballooning: a unifying pathophysiologic theory at the edge of prinzmetal angina. *Catheter Cardiovasc Interv*. 2008;71:342–352.
12. Haghi D, Suselbeck T, Wolpert C. Severe multivessel coronary vasospasm and left ventricular ballooning syndrome. *Circ Cardiovasc Interven*. 2009;2:268–269.
13. Villareal RP, Achari A, Wilansky S, et al. Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc*. 2001;76:79–83.
14. Bybee KA, Murphy J, Prasad A, et al. Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome. *J Nucl Cardiol*. 2006;13:244–250.
15. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. *Circ J*. 2005;69:934–939.
16. Raffel OC, Merchant FM, Tearney GJ, et al. In vivo association between positive coronary artery remodelling and coronary plaque characteristics assessed by intravascular optical coherence tomography. *Eur Heart J*. 2008;29:1721–1728.
17. Qian J, Maehara A, Mintz GS, et al. Impact of gender and age on in vivo virtual histology-intravascular ultrasound imaging plaque characterization (from the global Virtual Histology Intravascular Ultrasound [VH-IVUS] registry). *Am J Cardiol*. 2009;103:1210–1214.
18. Hoyt J, Lerman A, Lennon RJ, et al. Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (Takotsubo/stress induced cardiomyopathy). *Int J Cardiol*. 2009; doi: 10.1016/j.ijcard.2009.06.018. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0167-5273(09)00668-8.
19. Park SM, Prasad A, Rihal C, et al. Left ventricular systolic and diastolic function in patients with apical ballooning syndrome compared with patients with acute anterior ST-segment elevation myocardial infarction: a functional paradox. *Mayo Clin Proc*. 2009;84:514–521.
20. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol*. 2007;50:933–939.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20747