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Virtual histology intravascular ultrasound evaluation of the left anterior descending coronary artery in patients with transient left ventricular ballooning syndrome

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Abstract

Background: Transient left ventricular ballooning syndrome (TLVBS) has been recently recognised as an acute disease mimicking myocardial infarction.

Aim: We used greyscale and virtual histology (VH) intravascular ultrasound (IVUS) to study the presence and characteristics of atherosclerotic plaque in the left anterior descending (LAD) artery in patients with TLVBS.

Methods: The study population consisted of 14 consecutive patients with a TLVBS diagnosis based on typical symptoms and balloon-like left ventricle abnormalities. The IVUS imaging and analysis included at least the mid and proximal segments of each LAD. Virtual histology (VH)-IVUS analysis colour-coded plaque as calcific, fibrotic, fibrofatty, and necrotic core; VH--IVUS-derived thin-cap fibroatheroma (TCFA) and high-risk plaques were identified.

Results: The total length of the IVUS-analysed LAD averaged 55 ± 14 mm. Greyscale analysis revealed a mean plaque burden of 28.9 ± 11%. There were 7 ruptured plaques; these were present in mid-segments of the LAD in 3 patients, and in the proximal segment in 4 patients. The VH-TCFAs were found in 8 patients, while the remaining 6 patients had a necrotic core > 25%. The average number of VH-TCFAs was 4.8 ± 2.9 per patient. Combining greyscale and VH-IVUS data, 8 patients had either a ruptured plaque or a VH-TCFA, while the other 6 patients had a necrotic core > 25%. The distance from the coronary ostium to the cross-sections with a VH-TFCA was 20 ± 2.8 mm.

Conclusions: Vulnerable plaques are observed in patients with TLVBS. Our findings support the hypothesis that TLVBS may be related to the natural course of atherosclerotic plaque development. Further study into the relations between vulnerable plaque surface, platelet activity and subsequent thrombus formation is needed in this population.

Key words: intravascular ultrasound, tako-tsubo, myocardial infarction

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INTRODUCTION

Transient left ventricular ballooning syndrome (TLVBS) has recently been recognised as a new, acute disease, mimicking myocardial infarction [1], but without a clearly defined pathogenesis. Postulated mechanisms include direct toxicity of catecholamines, multivessel coronary spasm, or the presence of ruptured plaques undetected by angiography as suggested by Ibanez et al. [2] and confirmed by intravascular ultrasound (IVUS) [3]. While IVUS provides tomographic images of the coronary arteries in vivo, greyscale IVUS provides limi-

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ted information about plaque composition. A new IVUS-derived, radio frequency-based technology called virtual histology (VH) provides incremental information about tissue characterisation of coronary plaques [4].

The aim of the current study was to use greyscale and VH-IVUS (Fig. 1) to assess left anterior descending (LAD) arteries in patients with TLVBS in an attempt to provide additional insights into the mechanisms of this phenomenon.

METHODS

The study population consisted of 14 consecutive patients with a diagnosis of TLVBS based on typical symptoms and previously published criteria [3] in whom coronary angiography was performed during the acute period (within 48 h of the onset of chest pain).

In the present series, a diagnosis of TLVBS was confirmed by the absence of significant visible atheroma (< 20% diameter stenosis) on angiography as well as no signs of plaque rupture or visible thrombus. Left ventriculography was predominantly characterised by hypokinesia or akinesia of the mid to distal portions of left ventricle (LV) with hypercontraction of basal segments.

After completing coronary angiography and left ventriculography, the LAD artery was wired. An IVUS catheter (Eagle Eye Gold, Volcano Corporation, Rancho Cordova, CA, USA) was advanced into the mid portion of the distal segment of the artery and pulled back at the speed of 1.0 mm/s until the guiding catheter was reached.

During off-line analysis, the proximal segment was marked from the artery's ostium to the origin of the first septal branch, and the mid segment was marked from this point to the second diagonal branch. Greyscale IVUS images were used to calculate lumen area (LA), total vessel area boarded by external elastic membrane (EEM), and plaque area (PA = = EEM – LA). The cross-section with the smallest LA and largest plaque burden were identified. The remodelling index was a ratio of EEM area at the site of maximal plaque burden to the mean EEM area of the proximal and distal reference sites; remodelling was classified as positive if the remodelling index exceeded 1.0. A ruptured plaque was identified as a structure with a cavity communicating with lumen and having an overlying fibrous cap fragment.

The IVUS console (Volcano Invision Gold V2.0 VH, Volcano Corporation) and specific software (pcVH 2.2, Volcano Corporation) were used to trace the lumen and EEM borders and to classify plaque based on mathematical autoregressive spectral analysis of IVUS backscattered data, as described previously [4]. Different plaque components (fibrous, fibrofatty, necrotic core, and dense calcium) were colour-coded as tissue maps. The area and percentage area of each plaque component were calculated automatically by the software. The VH-IVUS-derived thin-cap fibroatheroma (TCFA) was defined as 3 or more consecutive cross-sections with a plaque burden (PA divided by EEM) > 40% and necrotic core area > 20% of the sum of the 4 plaque components without evidence of a fibrous cap. Cross-sections with necrotic core

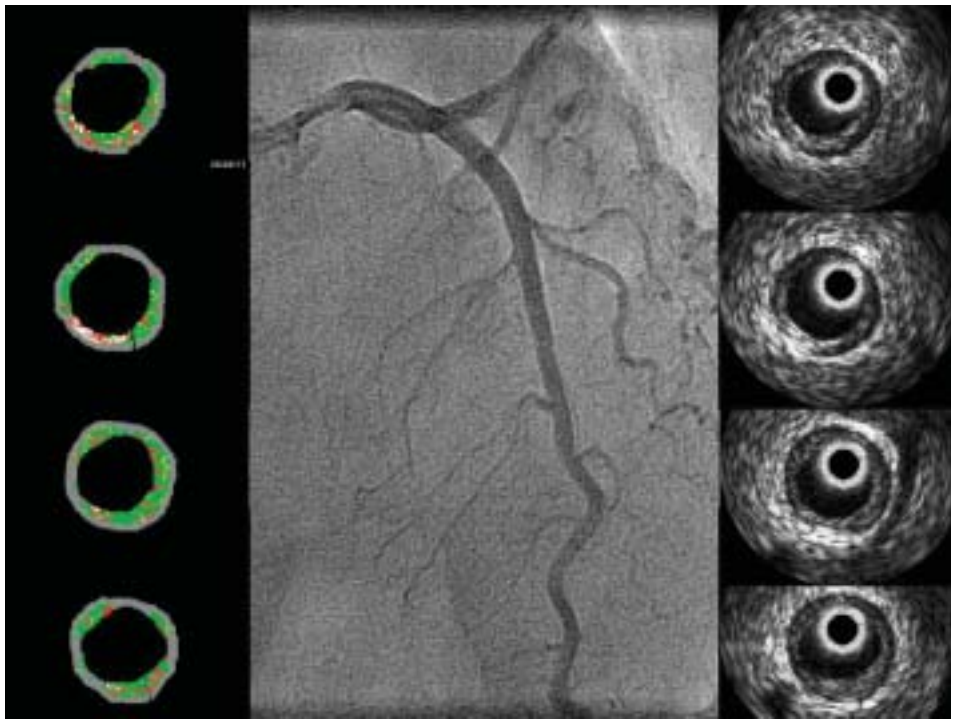

Figure 1. Left anterior descending artery and intravascular ultrasound images (greyscale and virtual histology) in a 77 year-old woman with transient left ventricular ballooning syndrome

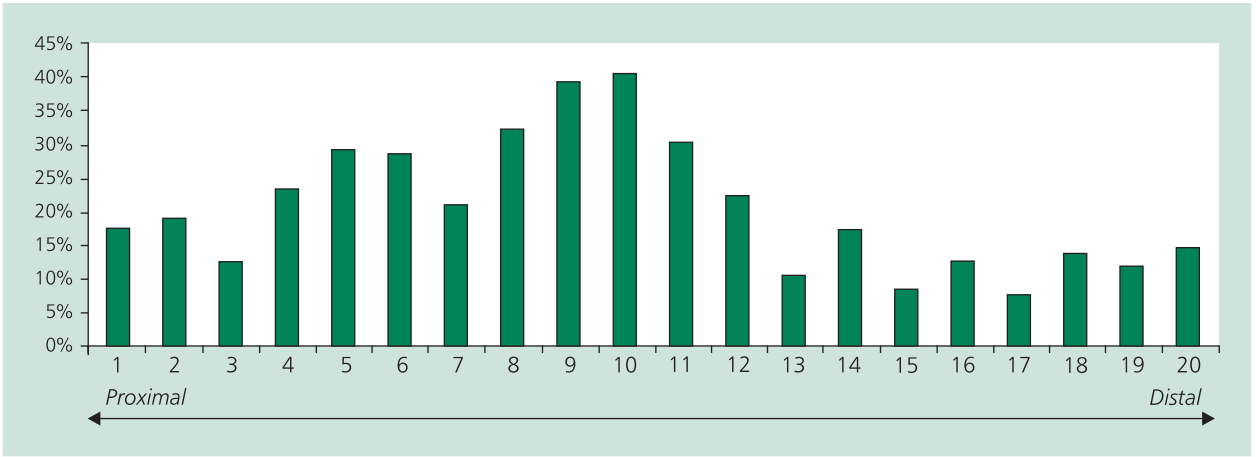

Figure 2. Longitudinal presentation of the necrotic core area (in percentage) in plaques recorded in the mid-portion of the left anterior descending (LAD). Note the difference between proximal and distal cross-sections. Bars 9–11 represent the cross-sections with the largest necrotic core plaques or thin-cap fibrous atheroma. The X-axis presents the 1 mm slices, starting at the beginning of the mid-segment of the LAD

area greater than 25% were classified as high-risk plaques (HRP) irrespective of their total plaque burden. The ratio of necrotic core to dense calcium (NC/DC) was calculated as described previously [5].

Statistical analysis

Statistical tests were performed with the Statistica package, version 5.5 for Windows (StatSoft Inc.). Continuous variables are presented as means ± 1 SD, whereas categorical variables are presented as percentages. Continuous variables were compared using the unpaired Student t test. Categorical variables were compared using the χ^2 test or Fisher's exact test. A p value < 0.05 was considered significant.

RESULTS

Patients' and angiographic characteristics

The patients' mean age was 75 ± 18 years, and all 14 patients were women. Seven patients had hypertension, 1 was diabetic, and 5 had a history of cigarette smoking. In this population TLVBS had been triggered by death of a close relative (6 patients), robbery (1 patient), a stressful medical procedure (4 patients), and workplace stress (1 patient). In the 2 remaining patients, the trigger was difficult to identify.

No patient had visible atheromata on coronary angiography or signs of plaque rupture or filling defects. The mean ejection fraction calculated by ventriculography was 42 ± 12%, and none of the patients had haemodynamic compromise.

Greyscale IVUS results

Overall, the total length of IVUS-analysed LAD averaged 55 ± 14 mm in the 14 study patients. All analysed arteries showed signs of atherosclerosis. The IVUS greyscale analysis revealed that the mean LA was 7.62 ± 2.59 mm^2, mean EEM area was 10.72 ± 3.57 mm^2, and mean plaque burden (mean PA divided by mean EEM area) was 28.9 ± 11%. The maximal plaque burden found within the 14 studied arteries averaged 39 ± 7%. The remodelling index was 1.13 ± 0.5, and positive remodelling was found in 10 (71%) patients. However, the results were considerably different for the proximal and middle segments of the LAD. The mean LA was 8.09 ± ± 2.59 mm^2 in the proximal segment and 5.26 ± 2.82 mm^2 in the mid-segment; the mean plaque burden was 31 ± 12% in the proximal segment and 42 ± 14% in the mid-segment ($p < 0.05$).

There were 7 (50%) ruptured plaques; these were present in mid-segments of the LAD in 4 patients and in the proximal segment in 3 patients. The distance from the LAD ostium to the ruptured plaques measured 18.8 ± 2.6 mm.

Virtual histology IVUS results

The VH-IVUS analysis showed that the major component of the LAD plaque was fibrous (52.7%). The percentages of fibrofatty plaque and necrotic core were similar (13.8% *vs* 27.2%, respectively, NS). The mid-segments of the LAD artery contained a significantly larger percentage of necrotic core than the proximal segments (28.2 ± 8.4% *vs* 19.2 ± 9.5%, NS). Figure 2 shows the linear distribution of the necrotic core percentage. There was a significant difference between proximal and distal portions ($p < 0.05$). The mean ratio of NC/DC was 4.4 ± 5.3; and there was a trend towards higher values at the mid portions than in the proximal portions of the LAD. The VH-TCFAs were found in 8 patients, while the remaining 6 patients had a necrotic core > 25%, although the plaque did not fit the definition of a TCFA. The average number of VH-TCFAs was 4.8 ± 2.9 per patient. Combining greyscale and VH-IVUS data, 8 patients had either a ruptured

Table 1. Individual patient data of intravascular ultrasound and virtual histology imaging

Patient	Min. LA [mm²]	Max. PB [%]	Dist. to plaque rupture [mm]	Fibro-fatty plaque [%]	Necrotic core [%]	Dist. to TCFA/HRP [mm]
1	5.67	41		15	27	21*
2	6.34	37	18	18	26	23
3	6.02	33		12	26	18
4	4.07	44	17	20	28	19*
5	6.26	23	16	10	30	19
6	5.12	56		14	24	24*
7	7.56	37	19	15	26	21
8	6.45	41	17	10	24	15*
9	6.98	43	23	12	29	20*
10	6.38	45		20	21	22*
11	5.85	39		10	26	18
12	6.78	43	22	11	22	19*
13	6.95	33		13	28	29
14	8.31	32		11	45	22*
Average	**6.3 ± 1.0**	**39.0 ± 7.7**	**18.8 ± 2.6**	**13.8 ± 3.5**	**27.2 ± 5.6**	**20.7 ± 3.3**

*Depicts patients with thin-cap fibroatheroma (TCFA); HRP — high-risk plaques; PB — plaque burden; LA — lumen area

plaque or a VH-TCFA, while the other 6 patients had a necrotic core > 25%. The distance from the coronary ostium to the cross-sections with a VH-TCFA was 20 ± 2.8 mm, whereas the distance to the cross-sections with a necrotic core > 25% was 21.3 ± 4.2 mm. The distribution of the distance of plaque rupture, TCFA, and HRP from the coronary ostium is presented in Table 1.

DISCUSSION

The hypothesis that prompted this study was our observation that in some cases, on coronary angiograms, very little plaque is seen in LAD artery in patients with TLVBS. In some cases, the degree of stenosis was 10–15% or even less. In a previous study, Ibanez et al. [2] linked apical ballooning to silent plaque rupture that was not seen on angiography. We sought to investigate this topic using a new tool: IVUS with VH assessment. Our study's findings confirmed that IVUS-identified unstable plaques i.e. ruptured plaques, VH-TCFAs, or plaques with a necrotic core > 25%, were present in all our patients with TLVBS with a relatively large percentage of necrotic core along the entire analysed length of the LAD. The importance of this finding is unknown, but one can speculate that the plaque vulnerability seen in this study may contribute to the pathophysiology of the syndrome, because they are more prone to rupture, thrombosis, or spasm. The literature provides evidence that mental stress (a major feature of TLVBS) is responsible for endothelial dysfunction and vasoconstriction [6] in humans. Moreover, there are data connecting endothelial dysfunction and plaque burden in the early stages of atherosclerosis [7]. Finally, women are more prone to plaque erosion, while men are at greater risk of plaque rupture and ST-segment elevation myocardial infarction [8].

Ruptured plaques were found in 7 of our TLVBS patients, strongly supporting the data and hypothesis presented by Ibanez et al. [2] linking apical ballooning to angiographically silent plaque rupture. It seems that plaque rupture could be one of the mechanisms of TLVBS (additionally to catecholamine release as discussed later). Another similarity to the Ibanez et al. [2] study findings was plaque burden detected by IVUS along LAD. However, our study also extends the observations of Ibanez et al. [2]. While only half of our patients had IVUS-detectable plaque ruptures, the remaining patients had VH-IVUS evidence of plaque vulnerability or instability. Furthermore, the location of the ruptured plaques and VH-TCFAs in the LAD in the current study was similar to previous angiographic, greyscale IVUS, and VH-IVUS reports showing that the proximal 30–40 mm of the LAD is the commonest site of ruptured, rupture-prone, or thrombosed plaques [9–12]. On the other hand, comparing our results with the historical control [11], one can speculate that the plaque burden and amount of vulnerable necrotic cores is smaller than in patients with regular acute coronary syndrome.

Based on this, we believe that our study results may also explain why symptoms of TLVBS are transient and self-limiting. The most reliable explanation is the fact that in these patients, the mechanisms of auto-fibrinolysis are quite active. The very elegant study by Newby et al. [13] demonstrated that activity of tissue plasminogen activator is inversely related to plaque burden detected by IVUS. This means that the smaller the plaque burden observed, the larger is the endo-

genous fibrinolysis present. Most of the patients (75%) had signs of positive remodelling without any atheroma at angiography; the mean LA was quite large and inconsistent with a significant stenosis. It may be speculated that a huge catecholamine release during mental stress in TLVBS patients may lead to vasoconstriction and/or plaque rupture with thrombus formation and subsequent auto-fibrinolysis. However, recent literature data do not confirm any correlation between variant angina and vulnerable plaque in patients with coronary artery disease [14].

Evidence so far indicates that the pathomechanisms of TLVBS are multifactorial [2, 3] and complete certainty regarding its causes is still some way off. Multivessel spasm, catecholamine leak and the consequences of ruptured plaques may play a role in this syndrome. One does not know what the first trigger is, and whether they relate to each other. One potential explanation could be a scenario in which huge catecholamine leak provides multivessel spasm and vulnerability of small untimely LAD plaques, causing thrombus formation, flow limitation and finally myocardial contractility disorder. The latter is possibly related to small plaque burden that produces a limited number of vessel wall's cytokines and thrombus burden. In other words, vessel wall activity is responsible for the patient's clinical presentation.

Based on our data, we believe that most cases of tako-tsubo syndrome represent a relatively benign form of acute coronary syndrome; it should be regarded as a form of myocardial infarction with very early self-reperfusion and a stunned myocardium that tends to improve, rather than as a cardiomyopathy [15]. In our case, detection of vulnerable plaque may change our thinking as to the drug management of TLVBS. Based on this study, we have started to treat our patients with double antiplatelet therapy, as well as heparin infusion.

Limitations of the study

The number of analysed patients is small. There is no direct comparison with patients with true acute coronary syndrome (STEMI, NSTEMI), although we have started collecting patients to compare them in a future prospective study.

CONCLUSIONS

Active atherosclerotic processes within the LAD are observed in patients with TLVBS. Our findings support the hypothesis that TLVBS may be related to the natural course of atherosclerotic plaque development. Further study into the relations between vulnerable plaque surface, platelet activity and subsequent thrombus formation is needed in this population.

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Ultrasonografia wewnątrzwieńcowa z opcją wirtualnej histologii w ocenie tętnicy zstępującej przedniej u pacjentów z przemijającymi zaburzeniami kurczliwości koniuszka lewej komory

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Streszczenie

Wstęp: Zespół przemijających zaburzeń kurczliwości koniuszka lewej komory (TLVBS) został niedawno opisany jako zespół objawów imitujących ostry zawał serca.

Cel: Celem niniejszej pracy była ocena blaszki miażdżycowej w tętnicy przedniej zstępującej za pomocą ultrasonografii wewnątrzwieńcowej.

Metody: Badaniem objęto 14 kolejnych pacjentów z TLVBS, zdiagnozowanych na podstawie typowych objawów klinicznych i obrazu wentrykulografii lewostronnej. U wszystkich chorych wykonano ultrasonografię wewnątrzwieńcową w zakresie proksymalnych i środkowych segmentów tętnicy przedniej zstępującej, ze szczególnym uwzględnieniem charakterystyki blaszki miażdżycowej (zwapniała, włóknista, włóknisto-tłuszczowa i martwicza). Analizie poddano także obecność blaszki z cienką czapeczką łącznotkankową (TCFA).

Wyniki: Średnia długość analizowanego segmentu tętnicy wyniosła 55 ± 14 mm, a objętość blaszki miażdżycowej 28,9 ± ± 11%. U 7 pacjentów stwierdzono cechy pękniętej blaszki miażdżycowej, z czego 3 były zlokalizowane w segmencie środkowym tętnicy, natomiast 4 w segmencie proksymalnym. Obecność TCFA stwierdzono u 8 osób, natomiast u pozostałych 6 były obecne blaszki miażdżycowe z martwiczym rdzeniem przekraczającym 25% objętości. Średnia liczba blaszek typu TCFA wyniosła 4,8 ± 2,9. U 8 pacjentów stwierdzono TCFA lub pęknięte blaszki miażdżycowe. Średnia odległość ujścia tętnicy do przekroju z TFCA wyniosła 20 ± 2,8 mm.

Wnioski: U pacjentów z TLVBS stwierdza się potencjalnie niestabilnie blaszki miażdżycowe. Uzyskane wyniki potwierdzają hipotezę, że TLVBS może się wiązać z naturalnym rozwojem miażdżycy. Należy przeprowadzić kolejne badania oceniające aktywność blaszki i płytek krwi z następczym tworzeniem zakrzepu.

Słowa kluczowe: ultrasonografia wewnątrzwieńcowa, zespół tako-tsubo, zawał serca

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