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ORIGINAL ARTICLE

Initial troponin level may predict thrombus burden in patients with acute coronary syndrome. Optical coherence tomography study

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Abstract

Background: The major cause of acute coronary syndrome (ACS) is vessel thrombosis related to plaque rupture. Optical coherence tomography (OCT) is a feasible and effective technique to visualise a thrombus *in vivo*.

Aim: To present the relationship between cardiac enzymes leakage before coronary angioplasty and thrombus visualised by OCT.

Methods: A population of 48 consecutive patients (mean age 64.8 ± 9 years) with non ST elevation syndromes treated with primary coronary angioplasty was selected for the study. Angiographic and OCT quantitative assessment was performed for all patients, as well as qualitative thrombus assessment with a new index — the thrombus score (TS). Troponin I and creatine kinase and its MB fraction were measured for all patients at baseline and at least 6–8 hours after coronary angioplasty.

Results: The troponin level assessed before coronary angioplasty was 3.42 ± 7.31 ng/dL. The mean TS assessed before coronary angioplasty was 96 ± 56, and in 17 (35.4%) patients the score was greater than 100 points. Mean artery length occupied by thrombus was 7.8 ± 3.8 mm. There was a significant correlation between troponin level and thrombus score ($r = 0.44$, $p < 0.05$) in the whole studied population.

Conclusions: Initial troponin level may be associated with larger thrombus burden within a coronary artery. This finding may influence coronary flow and needs to taken into consideration during primary coronary intervention.

Key words: acute coronary syndrome, optical coherence tomography, troponin

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INTRODUCTION

The major cause of acute coronary syndrome (ACS) is vessel thrombosis related to plaque rupture [1] that can influence the clinical presentation of the patient, including unstable angina to ST elevation myocardial infarction or sudden death [2]. It has been demonstrated, albeit indirectly, that thrombus burden may affect the immediate results of coronary intervention and patient outcome [3]. Therefore, the direct assessment of thrombus burden may be of value, because this knowledge may influence the strategy of thrombus removal.

Recently used imaging modalities, i.e. angiography or intravascular ultrasound (IVUS), provide limited data on thrombus burden, and mainly indirect data [4]. The low resolution of IVUS, and the similar echogenicity of thrombus and soft plaques, make this modality useless in patients with ACS. Optical coherence tomography (OCT) is a novel intravascular modality producing high resolution images *in vivo* [5]. The main application of OCT is the assessment of stent and vessel healing after coronary angioplasty, mainly due to image resolution of 10–20 μm that is 10-fold larger than intravascular

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ultrasound. Early results show that OCT is a feasible and effective technique to visualise thrombus *in vivo* [6].

The aim of this study was to investigate the relationship between cardiac enzymes leakage before coronary angioplasty and thrombus visualised by OCT.

METHODS

Patient population

A group of 72 patients presenting ACS who were treated by coronary angioplasty with OCT guidance were screened and assessed by TIMI risk score (Antman scale) [7]. Eventually, a group of consecutive patients of intermediate and high risk was selected for the study population. It comprised 48 consecutive patients (mean age 64.8 ± 9 years) with ACS (non ST elevation syndromes) treated with coronary angioplasty. The rest of the screened patients (24 persons) had low risk according to Antman's scale, and were therefore excluded from final analysis. There was no pre-treatment with IIb/IIIa intravenous inhibitors, and most of the patients had coronary angiography within 6–9 hours after admission and cardiac markers tests. Only two (4.1%) patients had angiography delayed (15 and 18 hours, respectively). Other drugs, especially aspirin and clopidogrel, were given according to practice guidelines. The study protocol was approved by local ethics committees and all patients provided written informed consent.

Angiographic assessment

The coronary angiography was performed using either a transradial or transfemoral approach with 6 French guiding catheters. All patients received nitrates to obtain maximal coronary vasodilatation. The QCA analysis was performed offline at a certified Core Lab [4] with a computer-assisted system using an automated edge detection algorithm (MEDIS, Cardiovascular Angiography Analysis System II, Pie Medical Data, Maastricht, The Netherlands) by observers unaware of OCT. The studied segment was analysed using two orthogonal views. The analysis included minimal lumen diameter, reference diameter, and percentage of diameter stenosis as well as lesion length. The off-line angiographic analysis included TIMI flow, TIMI frame count and myocardial blush assessed before and after coronary angioplasty. The methodology of these measurements has been widely discussed elsewhere [8].

OCT assessment

Optical coherence tomography studies were performed using a non-occlusive technique that has been reported previously by our group [5]. Briefly, after wiring the artery with a regular angioplasty guidewire, ImageWire (LightLab Co) was advanced distally to the lesion and during continuous contrast media flush (Visipaque), the automatic pullback was performed. The commercially available console (M2 or M3 by LightLab Co) was used.

Off-line analysis was performed with dedicated software within region of interest. It was defined as artery site occupied by thrombus, so it means that first frame with thrombus appearance was a beginning of region of interest. Study calculations were performed every single frame from first frame with thrombus up to the last one without signs of the thrombus. The distance between two neighbouring frames was 0.128 mm.

A new index was developed for the purposes of this study — the thrombus score (TS). This was calculated for total thrombus burden in the studied artery. Each analysed frame was divided into four quadrants, with the presence of thrombotic material being scored as one point, up to a maximum of four for each frame. The sum of all analysed frames provided the thrombus score (Fig. 1).

The measurements of TS were repeated by the first observer six weeks after the first assessment to account for intraobserver variability. Every patient's thrombus score was also analysed by two independent observers to account for interobserver variability.

Cardiac marker tests

A blood sample was taken from each patient immediately after admission for basic lab and cardiac markers such as troponin I level as well as creatine kinase and its MB fraction. The measurements were repeated 6–8 hours after coronary angioplasty and again later according to the patient's clinical status. Lab tests were performed using commercially available immunoassay tests. Myocardial infarction was defined if the troponin level exceeded the 99th percentile of the upper reference limit of the local laboratory. For this study, 0.05 ng/dL was taken as the cut-off point for myocardial infarction. Patients with a troponin level that exceeded by 100 times the reference value were identified.

Statistical analysis

Statistical tests were performed with the STATISTICA Package, version 5.5 for Windows, (StatSoft Inc.). Continuous variables were presented as means ± 1 SD, whereas categorical variables were 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. Intraobserver and interobserver variabilities were determined with Pearson's correlation and equations previously reported [8]. P values < 0.05 were considered significant.

RESULTS

The study population consisted of 14 (29%) women and 34 men. Risk factors of coronary artery disease are presented in Table 1. The localisation of culprit lesions was equally distributed in the study group (LAD: 35.4%; Cx: 35.4%; RCA: 29.2%). Single vessel disease was present in 50% of patients. None of patients suffered from haemodynamic compromise.

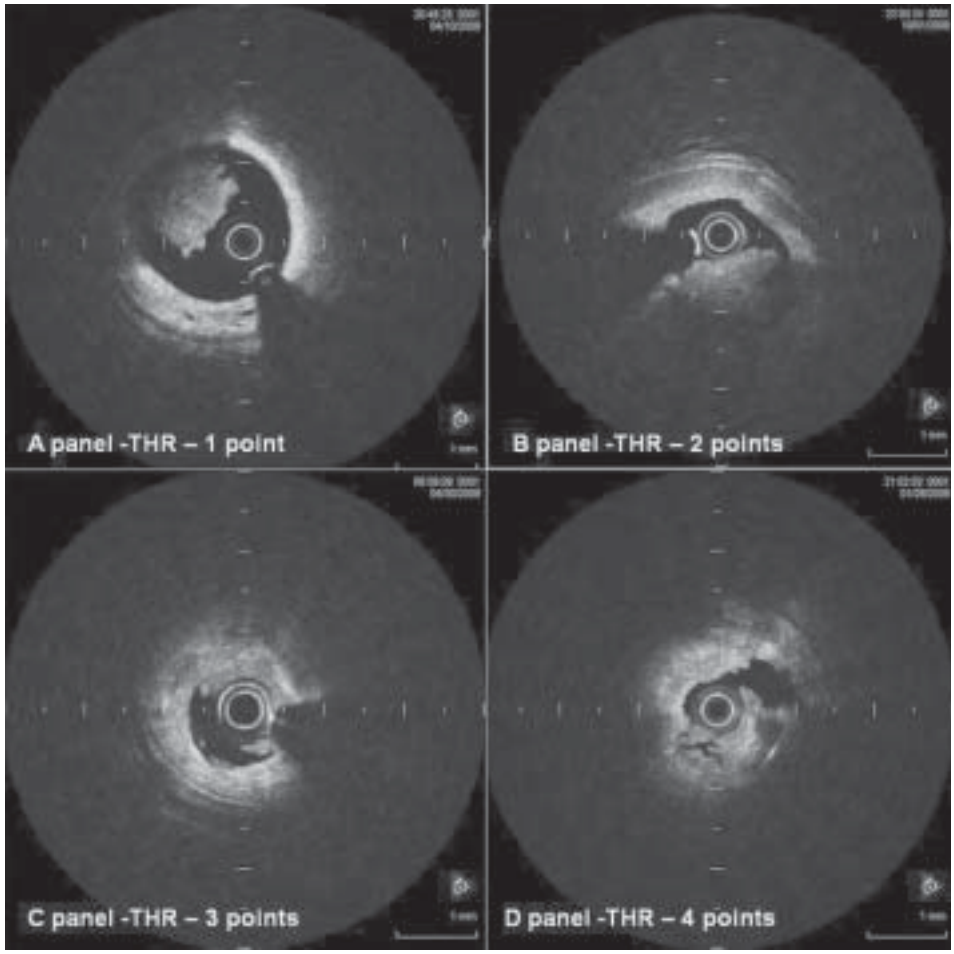

Figure 1. Case example of thrombus score calculation

Table 1. Baseline characteristics of the studied population

Hypertension	37 (77%)
Diabetes	8 (16%)
Smoking	22 (45%)
Hypercholesterolaemia	30 (62.5%)
Previous infarction	22 (45%)

The troponin level assessed before coronary angioplasty was 3.42 ± 7.31 ng/dL, but only in six (12.5%) cases did it exceed a value of 5 ng/dL. After the coronary angioplasty, troponin level was 5.87 ± 8.23 ng/dL.

The mean thrombus score assessed before coronary angioplasty was 96 ± 56, and in 17 (35.4%) patients the score was greater than 100 points. Mean artery length occupied by thrombus was 7.8 ± 3.8 mm. The thrombus score was assessed at least twice and the intraobserver variability was 3.3% and interobserver variability was 2.2%.

There was a significant correlation between troponin level and thrombus score ($r = 0.44$, $p < 0.05$) in the whole studied population. Figure 2 depicts the distribution of this relationship.

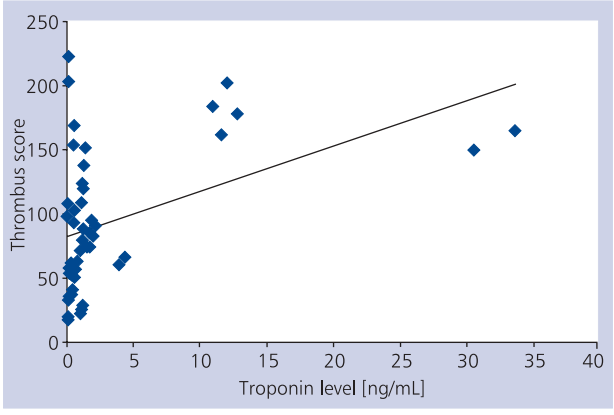

Figure 2. Relationship of thrombus score and troponin level

Angiographic analysis showed some significant results (Table 2). The studied population was divided according to TIMI flow before angioplasty. The subgroup of patients pre-

Table 2. Quantitative coronary angiography in the studied population

Reference diameter [mm]	Before PCI	2.64 ± 0.48
	After PCI	2.91 ± 0.39
Minimal lumen diameter [mm]	Before PCI	0.59 ± 0.33
	After PCI	2.97 ± 1.16
TIMI flow 3	Before PCI	12 (25%)
	After PCI	40 (83.3%)
TIMI flow 2	Before PCI	32 (66.6%)
	After PCI	8 (16.6%)
TIMI flow 0–1	Before PCI	4 (8.3%)
	After PCI	0 (0%)
TFC	Before PCI	27.2 ± 21
	After PCI	13.9 ± 8
Acute lumen gain [mm]		2.26 ± 1.16

PCI — percutaneous coronary intervention; TFC — TIMI frame count

senting with TIMI flow grade 2 or less did not have a significantly larger thrombus score than patients with a TIMI 3 flow (100 ± 160 *vs* 73 ± 22, respectively, p = NS). The difference in troponin level was insignificant for both subgroups (3.73 ± ± 11.5 *vs* 1.36 ± 1.3 ng/dL, respectively, p = NS). The same trend was observed with myocardial blush analysis. There was a non-significant larger thrombus score in the subgroup with impaired myocardial blush (grade 0–2) compared to the subgroup with baseline normal blush (100 ± 56 *vs* 66 ± 34, respectively, p = 0.07). There was no difference in thrombus score between subgroups after coronary angioplasty (93 ± 54 *vs* 93 ± 55, respectively impaired *vs* normal blush, p = NS). However, there was a very strong correlation between thrombus score and troponin level after coronary angioplasty in patients with limited myocardial blush (r = 0.94, p < 0.05)

The population was divided according to TIMI risk score into two subgroups: the first of intermediate risk (3–4 points), and the second of high risk (5–7 points). There was no difference in terms of thrombus score between these groups (94 ± 61 *vs* 90 ± 34, respectively, p = NS). A slightly larger concentration of troponin level (3.64 ± 6.06 *vs* 8.8 ± 18.5 ng/dL, respectively, p = NS) was observed in the subgroup with the high risk score. However, the correlation between troponin level and thrombus score was significant for the high risk subgroup (r = 0.74, p < 0.05).

DISCUSSION

For the last few decades, it has been believed that ACSs are caused by thrombus formation on an underlying plaque [2]. Angiographic studies have shown that ACSs are more likely to develop on non-critical, non-significant coronary plaques [2]. Several intracoronary imaging developments (e.g. IVUS derived virtual histology) have provided a new definition of thin-cap fibrous atheroma that are related to a high risk of ACS, although the resolution of this modality is very limited and it is difficult to differentiate fresh coronary thrombus from soft plaque. When replaced by OCT, the opportunity to visualise small thrombi *in vivo* as well as thin-cap fibrous atheroma increases significantly [9].

The main finding of this study is a positive correlation between troponin level and thrombus burden in patients with ACS. Previous evidence showed that OCT is feasible to detect thrombus with the same sensitivity as coronary angioscopy [10]. In a very elegant study, Kubo et al. [10] compared OCT, IVUS and coronary angioscopy in the detection of vulnerable plaques. Note that OCT imaging was done after manual thrombectomy with normal TIMI flow. This can lead to significant thrombus reduction, although it was present in all patients, while IVUS was able to identify thrombus only in one third of cases. In another study, Jang et al. [11] demonstrated that in patients with recent acute myocardial infarction treated by thrombolysis, thrombus was present in approximately 20% of cases. A comparison of these two trials and methodologies led us to the hypothesis that a combination of treatment modalities (pharmacological or mechanical) and time are needed to decrease thrombus burden.

Our study has shown that in patients with lower myocardial blush, there was a trend to larger thrombus score and subsequently to higher troponin level. In a recent study, Porto et al. [12] showed that troponin level predicts worse microvascular function measured by TIMI flow, myocardial blush and perfusion defect by magnetic resonance.

Another important question arising from this study is the management of patients with ACS. There is no doubt that for ST-elevation patients, immediate intervention is needed as soon as possible. The use of manual thrombectomy in patients receiving IIb/IIIa inhibitors is still an open issue [13], but early results are promising. One can believe that thrombus reduction is a key element of this topic. The same applies to non-ST elevation patients, especially with intermediate and high risk of adverse events [7]. Previous and current guidelines [14] advise the scheduling of these patients for early invasive strategy, especially if a troponin rise is observed. The results of our study have shown that the focus should be on patients with intermediate risk score by TIMI scale, and a medium increase of troponin. The previous evidence showed that patients with normal myocardial blush have a lower mortality risk [8], and our results confirmed that thrombus burden is smaller in this subgroup. It is reasonable to speculate that in some patients, a wide spectrum of actions (pharmacological and/or mechanical), can improve immediate and late patient outcomes. Of course, some future research should be performed to prove this hypothesis, but our recent experience (not published yet) shows that OCT measured thrombus can be reduced by intracoronary IIb/IIIa inhibitors administration.

Limitations of the study

The main limitation of our study was the number of included patients. One can hypothesise that were more patients to be included, some correlations could be significant. On the other hand, our study was performed using old OCT facilities. These ImageWires are thinner than the widely used new system: Dragonfly. It means that the possibility of Dotter effect or interrogation of the thrombus by the probe itself is less likely.

CONCLUSIONS

Initial troponin level may be associated with larger thrombus burden within a coronary artery. This finding may influence the coronary flow, and needs to be taken into consideration during primary coronary intervention.

Conflict of interest: *none declared*

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Przedzabiegowe stężenie troponiny wiąże się z objętością skrzepliny u pacjentów z ostrym zespołem wieńcowym. Badanie z wykorzystaniem optycznej tomografii koherentnej

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Streszczenie

Wstęp: Główną przyczyną ostrych zespołów wieńcowych (OZW) jest zakrzepica tętnicza powstająca z powodu pęknięcia blaszki miażdżycowej. Optyczna tomografia koherentna (OCT) jest techniką, która pozwala na zobrazowanie zakrzepu *in vivo*.

Cel: Celem badania była ocena zależności między stężeniem enzymów martwicy serca pobranych przed zabiegiem angioplastyki a wielkością zakrzepu uwidocznionego w OCT.

Metody: Na potrzeby poniższego badania wybrano grupę 48 kolejnych pacjentów z OZW (średnia wieku 64,8 ± 9 lat), którzy byli leczeni za pomocą angioplastyki wieńcowej. Ocenie poddano ilościowe i jakościowe parametry angiograficzne i uzyskane z badania OCT. Ponadto na potrzeby badania stworzono nowy wskaźnik objętości zakrzepu — TS (*thrombus score*). Stężenia troponiny I i CK-MB oznaczono u wszystkich pacjentów przed zabiegiem oraz co najmniej 6–8 godzin po angioplastyce.

Wyniki: Stężenie troponiny I przed angioplastyką wyniosło 3,42 ± 7,31 ng/dl, natomiast średni TS — 96 ± 56 punktów. U 17 (35,4%) pacjentów wyniósł on więcej niż 100 punktów. Średnia długość naczynia zajętego przez zakrzep wyniosła 7,8 ± 3,8 mm. Stwierdzono istnienie dodatniej korelacji między stężeniem troponiny a TS ($r = 0,44$; $p < 0,05$) w całej badanej populacji.

Wnioski: Stężenie troponiny przed zabiegiem może się wiązać z obecnością większej objętości zakrzepu w tętnicy wieńcowej u chorych z OZW. Wiedzę o tym należy uwzględnić podczas zabiegu angioplastyki wieńcowej.

Słowa kluczowe: ostry zespół wieńcowy, troponina, optyczna tomografia koherentna

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