Morphogenetic Particularities of Acute Myocardial Infarction with and without Early Thrombolytic Therapy

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Despite continuous improvement of therapeutic tactics, current mortality from acute myocardial infarction (AMI) remains high (3, 4). The extent of AMI being of significant importance for the outcome depends on the time of blood flow restoration in the ischemic myocardium and the formation of the collateral flow. This imposes the necessity to achieve an early and consistent reperfusion in the occluded vessel, resulting in the decrease of the necrotic area expansion, the improvement of the blood flow in the peri-infarction area, the decrease of electrical instability of the myocardium and the improvement of the residual left ventricular (LV) function. The results of different clinical trials suggest that the use of thrombolytic therapy (TLT) after AMI allows for a significant decrease of the rate of morbidity and mortality (1, 2, 5, 6). The information concerning the TLT-related complications — the increased rate of external heart rupture, intracerebral hemorrhage, bleeding from the puncture site, allergic reaction to thrombolytic agent — is rather abundant (1, 2, 7, 8). It is worth noting that in any of the analyzed cases we did not reveal severe TLT-related complications, caused by the disturbances of rheological properties of the blood (hemostasis) and playing an important role in the thanatogenesis. Pathoanatomical particularities of AMI development and mechanisms of thanatogenesis in early reperfusion (RP) for AMI are virtually not discussed in the literature.

The purpose of our study consisted in the determination of the influence of early (within 6 hours after the onset of pain syndrome) TLT on the particularities of the course of AMI and the development of its lethal complications.

Material and methods. In order to achieve this purpose we have studied the results of 230 specimens of hearts of patients who died after AMI with early TLT (50 cases, TLT group) and without early TLT (180 cases — non-TLT group) during the period from 2003 through 2010 (145 males, mean age 63,7 years, 85 females, mean age 67,65 years). The groups did not significantly differ by sex and age, one third of patients from each group were under 60 years old (Tables 1, 2). The material of the study was collected in the joint prosectorium of the Sklifosovsky Research Institute of Emergency Medicine, and comprises the lethal cases from the Institute and from other high-skilled cardiological departments.

We determined macroscopic localization, surface area and depth of the myocardial infarction (in planar and transverse sections) and evaluated the presence of hemorrhagic component (hemorrhages) in the necrotic area. In each case the extent and the localization of the AMI was analyzed in relation to the extent and the degree of atherosclerotic coronary stenosis, the presence of thrombus in the lumen of the infart-related artery (IRA) and the type of coronary circulation.

Comparative analysis of lethal cases occurring after AMI with and without early TLT revealed the following features.

One of the important pathoanatomical macroscopic criteria of the TLT effectiveness is the absence of thrombus in the IRA. Our study has shown a clear tendency to the decrease of the rate of IRA thrombosis in the TLT group ($p<0,05$). Average index of the number of thrombi in the non-TLT group was 65% (117 of 180), while in the TLT group is was twofold lower — 34% (17 of 50).

The rate of IRA thrombosis was significantly decreased ($p<0,05$) with the increase of the number of the involved branches, as well as the involvement of the middle and distal segments of the coronary arteries (CA) into the atherosclerotic process in both groups (Fig. 1). In combined atherosclerotic stenosis of two or three coronary branches the rate of thrombosis of the IRA in the non-TLT group (68% of cases, 122 of 80) was 57% (69 of 122). In the TLT group the rate of AMI developed against the background of multivessel coronary disease was 64% (32 of 50), the occluding thrombus in the lumen of one CA was found only in 38% of cases (12 of 32).

The difference is mostly evident in the presence of AMI developed in the settings of isolated atherosclerosis of one CA. In the non-TLT group such AMI was revealed in 32% of cases (58 of 180). The rate of thrombosis of a single involved CA in this group was 83% (48 of 58). In the TLT group the single-vessel coronary disease was seen somewhat more frequently — in 36% of cases (18 of 50), and the rate of thrombosis of a single involved CA was significantly lower — 28% (5 of 18).

The second pathological macroscopic criterion of TLT impact is the presence of a hemorrhagic compo-

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Table 1.

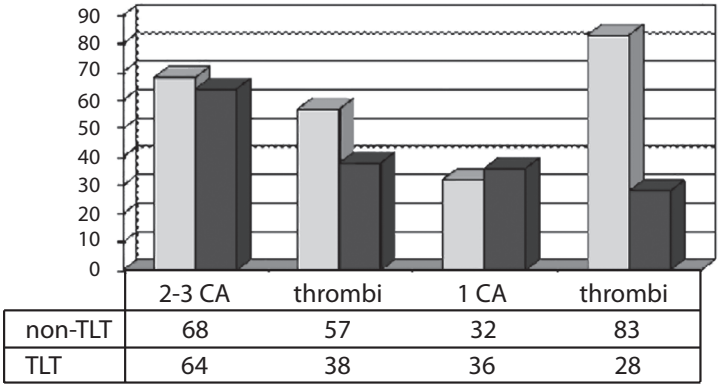
Distribution of cases by sex and age in TLT group

Sex	41 – 50		51 – 60		61 – 70		> 71		Total	
	Абс	%	Абс	%	Абс	%	Абс	%	Абс	%
Males	2	4%	8	16%	9	18%	9	18%	28	56%
Females	0	0	6	12%	7	14%	9	18%	22	44%
Total	2	4%	14	28%	16	32%	18	36%	50	100%

Table 2.

Distribution of cases by sex and age in non-TLT group

Sex	41 – 50		51 – 60		61 – 70		> 71		Total	
	Абс	%	Абс	%	Абс	%	Абс	%	Абс	%
Males	13	7,2%	35	19,4%	38	21,1%	31	17,3%	117	65%
Females	0	0	18	10%	25	13,8%	20	11,2%	63	35%
Total	13	7,2%	53	29,4%	63	35%	51	28,4%	180	100%



	2-3 CA	thrombi	1 CA	thrombi
non-TLT	68	57	32	83
TLT	64	38	36	28

Fig. 1. The rate of stenotic atherosclerosis in thrombosis in the coronary branches

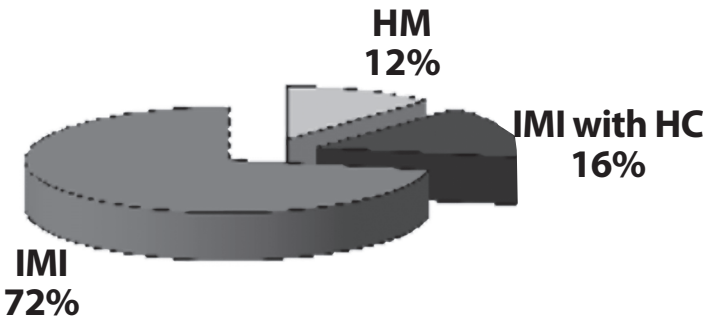


Fig. 2. The rate of various forms of myocardial infarction in the TLT group.

nent (HC) in the myocardial infarction area (within the central sites of a formed necrotic focus).

The intensity of HC in the myocardial necrotic focus was different.

The cases with diffusely dark-red coloration of the necrotic zone appearing within the first hours after the onset of the disease (min. 2 hours) were considered as hemorrhagic myocardial infarction (HMI) — such cases made 12% (6 of 50). Commonly HMI was located transmurally, somewhat less frequently — subendocardially and subepicardially (Fig. 3). As a rule, the HMI had clear borders, a faint pale-yellow peri-infarction area of varying width was seen at the periphery of the focus; this zone had rather distinct boundaries with the preserved myocardium.

In 16% of the other cases (8 of 50) the infarction was represented by a faint pale-yellow focus with distinct borders and multiple merging dark-red hemorrhages — an ischemic myocardial infarction with hemorrhagic component (IMI with HC). Most commonly the hemmorhages were revealed in the peripheral segments of the focus, somewhat less frequently — in its central area (Fig. 4).

Ischemic myocardial infarction (IMI) was found in 72% of cases (36 of 50) in the TLT group (Fig. 5).

Unlike the TLT group, ischemic infarction (without hemorrhagic component) was found in all 180 cases in the non-TLT group. Within the first hours the IMI either could not be revealed macroscopically, or its area seemed somewhat paler than the surrounding myocardium. Only by the end of the first day the infarction's borders became relatively distinct, and its color changed to faint pale-yellow. No hemorrhages were seen neither in the center, nor at the periphery of the focus.

We analyzed the association of hemorrhagic component in the myocardial infarction area with the absence on intracoronary thrombus in the IRA.

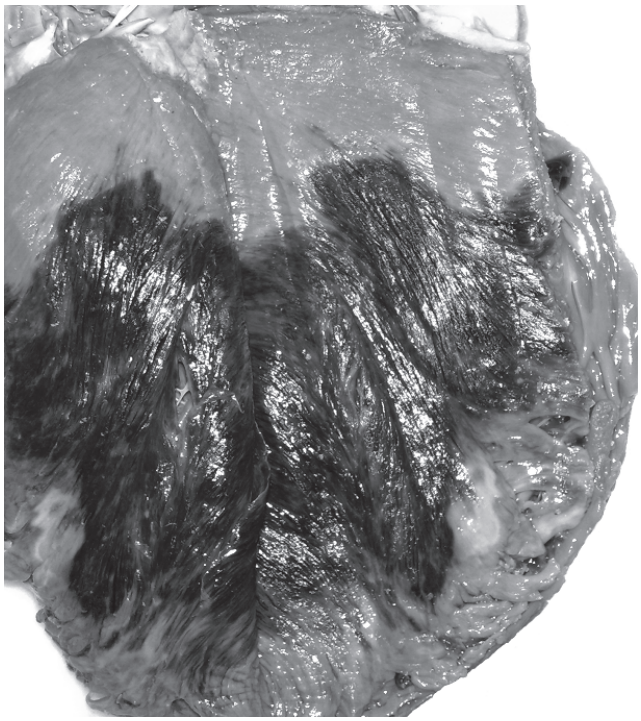


Fig 3. Hemorrhagic myocardial infarction

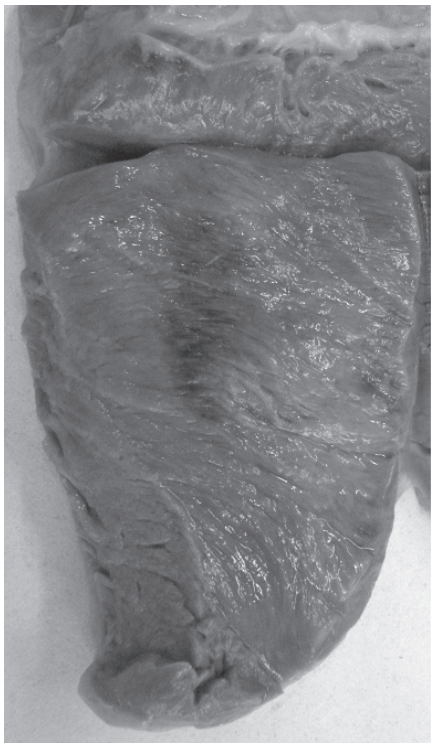


Fig 4. Ischemic myocardial infarction with hemorrhagic component

In the TLT group of our series the presence of a HC in the area of AMI was not always associated with the absence of thrombus in the IRA. In 12 cases of AMI with the signs of accomplished RP after TLT (i.e., with HC of various intensity in the infarction area) the intracoronary thrombus was absent. Unlike this observation, in 2 cases of HMI a thrombus was present in the lumen of the left coronary artery.

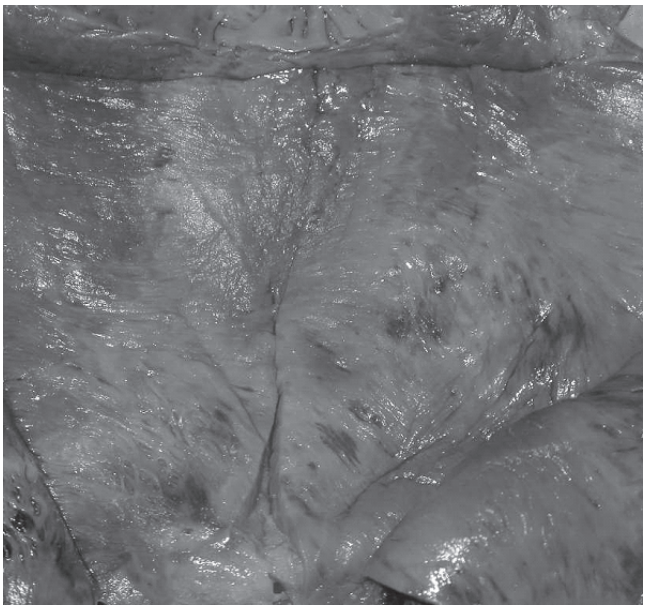


Fig. 5. Ischemic myocardial infarction

Comparative analysis of AMI-related lethal cases in both groups says for the tendency to decreasing area of contractile myocardial lesion after TLT ($p<0,05$).

Non-extensive (< 30% of the working surface of the LV) AMI was seen only in 22% of cases (40 of 180) in the non-TLT group (Fig 6), and in 34% of cases (17 of 50) in the TLT group.

In the non-TLT group, non-extensive AMI was more commonly associated with atherosclerotic stenosis of one CA — 67% of cases (27 of 40) with a lumen-occluding thrombus in 78% (21 of 27). Rarely severe atherosclerosis of all coronary branches was revealed in 33% of cases (13 of 40), the frequency of IRA thrombosis was 59%.

In the TLT group, non-extensive AMI was more commonly associated with severe atherosclerosis of all coronary branches — 59% (10 of 17), with a lumen-occluding thrombus in one half of cases (5 of 10). Atherosclerotic stenosis of one CA in this group was revealed in 41% of cases (7 of 17), and the rate of thrombosis was only 29% (2 of 7). The LAD or the RCA were the most common sites of isolated lesions.

Fatal complications of a non-extensive AMI in the groups of study were different (Fig.7 A, B).

In the non-TLT group the death was most commonly caused by external heart rupture (EHR, 55%, 22 of 40), by decompensation of an important concomitant disease, or resulted from thromboembolic complications (25%, 10 of 40).

Unlike these findings, in the TLT group a non-extensive AMI most commonly — in 53% of cases — led to complex heart rhythm and conduction disturbances (9 cases out of 17), and only in 41% (7 of 17) the death was caused by EHR or the decompensation of an important concomitant disease.

A certain tendency towards the increase of life duration was noted in the TLT group.

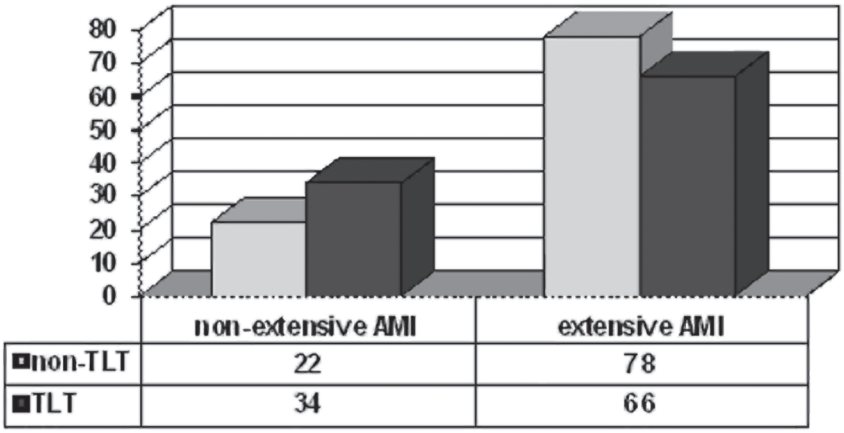


Fig. 6. The rate of extensive and non-extensive myocardial infarction in the groups of study

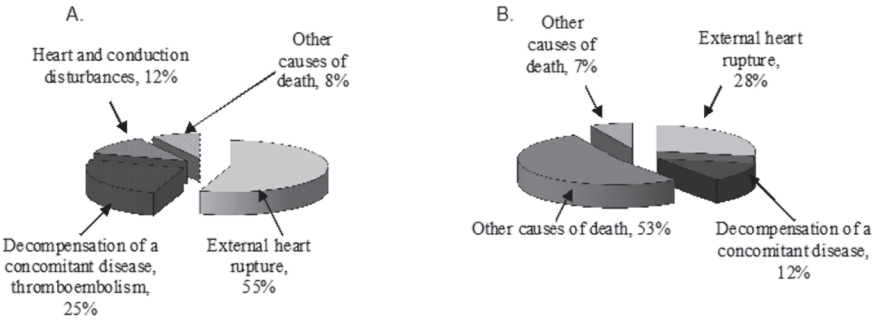


Fig. 7 Fatal complications of non-extensive AMI in the non-TLT (A) and the TLT (B) groups

TLT gave clinically positive results in 30% of cases with non-extensive AMI (5). In 3 cases the section revealed a hemorrhagic component of different intensity in the area of AMI without coronary thrombosis. The death occurred at day 2-9 from the onset of the disease and the administration of TLT, and was due to complex rhythm and conduction disturbances or EHR.

However in 70% of cases on non-extensive AMI, the TLT did not result in the improvement of the patients' condition and positive changes of the ECG (12). An occluding thrombus in the coronary artery was found in 7 of these cases, and HMI — in 3. The patients died within the first hours after the onset of the disease from EHR and complex rhythm and conduction disturbances.

An extensive AMI was found in the majority of the analyzed cases (Fig. 6). Its surface area varied from 40 to 80% of the working surface of the LV, in cases of re-infarction the cumulative surface of myocardial damage was 85-90%. Rather frequently the AMI involved the papillary muscles, less often — the right ventricular myocardium. This was seen in 78% of cases in the non-TLT group (140 of 180), and in 66% (33 of 50) in the TLT group.

The extensiveness of the AMI commonly was determined by severe atherosclerotic stenosis of all coronary branches: 78% of cases in the non-TLT group (109 of 140) and 67% of cases in the TLT group (22 из 33). Fibrotic and calcified atherosclerotic plaques narrowing the arterial lumen by 75-90%, were found in all segments of the involved CA, in the second-order branches. A lumen-obturating thrombus was found in 59% of cases in the non-TLT group (64 of 109), and more rarely– in 32% of cases — in the TLT group (7 of 22).

Sometimes an extensive AMI developed in atherosclerotic stenosis of one CA: 22% of cases in the non-TLT group (31 of 140) and 33% of cases in the TLT group (11 of 33). Alike the non-extensive AMI, isolated lesions were found most commonly in the LAD or the RCA. A single atherosclerotic plaque, narrowing the lumen by 75-90%, usually was located in the proximal segment of the involved CA. Up to 50% stenosis was found in the distal segments as well as in other branches of the CA. It is worth noting that an occluding thrombus was revealed in the vast majority of cases in the non-TLT group — 87% (27 of 31), and only in 27% of cases in the TLT group (3 of 11).

The character of lethal complications was similar in the groups with extensive AMI (Fig. 8 A, B). One half of patnets in both groups died from true cardiogenic shock (TCS) and acute left ventricular failure (ALVF), and in the one third of cases — from complex rhythm and conduction disturbances.

As well as in non-extensive AMI, a certain tendency towards the increased life time was noted. TLT was clinically effective in 18% of cases (6) of extensive AMI, the patients' condition improved, pain syndrome did not recur, positive ECG changes were noted. In two of these cases the section revealed a hemorrhagic component of different intensity in the infarction area, which is suggestive of the presence of reperfusion syndrome. In 5 of these cases no intracoronary thrombi were revealed. The patients died at day 3-12 after TLT, with the signs of rhythm and conduction disturbances and ALVF caused by the extensive lesion of the contractile myocardium. Along with AMI many patients had other, not less severe diseases — cancer, decompensated diabetes mellitus, chronic pyelonephritis with renal failure — that have played an important role in thanatogenesis.

In 82% of other post-TLT lethal cases due to extensive AMI (27) the patients' condition did not improve and there were no positive ECG changes. The patients died from ALVF, TCS, complex rhythm and

conduction disturbances at day 1-2 (22 cases) and at day 3-5 (5 cases) after the onset of the disease. However one cannot completely exclude the fact of accomplished reperfusion, as in 11 of these cases the section has revealed either the HMI or the hemorrhagic component of different intensity within the necrotic focus; in 9 cases there were no intracoronary thrombi. In another 11 cases the AMI was ischemic, with an occlusive thrombus present in 4 of these cases.

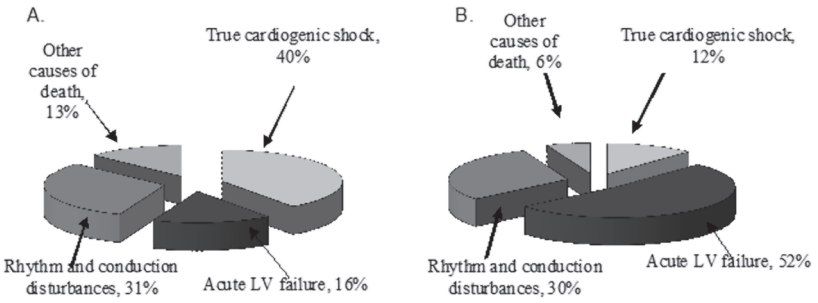


Fig. 8. Lethal complications of extensive AMI in the non-TLT (A) and TLT (B) groups

Therefore, comparative analysis of the deaths form AMI with and without early TLT reveals the following particularities. Firstly, they concern the frequency of IRA thrombosis with a clear tendency towards the decrease of the number of thrombi in the TLT group ($p<0,05$). Thus, the average rate of thrombosis in the non-TLT group was 65%, while in the TLT group — only 34%. This difference is mostly evident in the cases of AMI developed in the settings of isolated atherosclerosis of one CA. The rate of thrombosis in the non-TLT group was 83%, while the TLT group demonstrated an abrupt decrease of this value — 28%.

Another important distinguishing feature of the accomplished reperfusion (RP) is the presence of hemorrhagic component in the infarction area. Its intensity can be different. A bright earmark of reperfusion after TLT is diffuse hemorrhagic imbibition of the necrotic focus, it becomes dark-red and acquires the character of a hemorrhagic MI. We did not find HMI in the non-TLT group. In the TLT group HMI was found in 12% of cases. In 16% of cases the hemorrhages in the central parts of necrosis were focal and of different intensity. However in 72% of cases there were no focal hemorrhages within the IMI.

The presence of hemorrhagic component is not always associated with the absence of a thrombus in the IRA. Thus, in 3 cases the HMI developed in the presence of a thrombus in the left main coronary artery, which, probably, is suggestive of a temporal antegrade reperfusion and (or) is a result of collateral blood flow. Evidently, the opinion on blood flow restoration in the area of IMI after TLT should be based on the analysis of clinical parameters, such as positive dynamics of the course of AMI and regular deterioration of patients' condition as a result of reperfusion syndrome.

An extensive AMI was revealed after TLT in 66% of cases (with all CA involved — 67%, with a single-vessel disease — 33%), which is consistent with the data in the non TLT group (with all CA involved — 78%, with a single-vessel disease — 22%). The mechanisms of thenatogenesis were not significantly different. In both groups the extensive AMI was most commonly complicated by the true cardiogenic shock and acute left ventricular failure, and in one third of cases by complex rhythm and conduction disturbances.

Some data are suggestive of a tendency towards the increase of cases of AMI with a small surface area (up to 30% of the working surface of the LV). Thus, in the TLT group there were 34% of small AMI, and in the non-TLT — 22%; this could occur in the presence of three-vessel disease as well as in isolated atherosclerotic lesion of one CA. In such cases the mechanisms of thanatogenesis are significantly different. Thus, in the non-TLT group the most common cause of death was external heart rupture (55%) followed by decompensation of a concomitant disease (25%), while in the TLT group the most important cause of death was severe rhythm and conduction disturbances (53%, 9 out of 17 non-extensive AMI), and external heart rupture occurred only in 28% of cases (5 of 17).

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