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The Frequency of Type 2 Myocardial Infarction in the Structure of Hospital Mortality According to 7-Years Data of a State University Clinic

Aim — To evaluate the proportion of type 2 myocardial infarction (MI) in the structure of mortality at a multidisciplinary hospital; to describe major causes for MI development, and characteristics of patients with a verified diagnosis of type 2 MI by data of postmortem examination.

Material and methods — 1574 protocols of the autopsies performed at the Central Pathology Department of the I.I. Mechnikov North-West State Medical University from 01.01.10 through 31.12.16 were studied retrospectively by the continuous sampling method. A group with verified diagnosis of type 2 MI was isolated from the total sample of autopsies. Major causes for and the proportion of type 2 MI among the causes of death were studied. Also, major demographic parameters, hospitalization profile, and condition of coronary arteries (CA) were compared in patients with fatal type 2 MI and those who died from atherothrombotic type 1 MI.

Results — Analysis of 1574 fatal cases among patients of the multidisciplinary hospital showed that in 360 cases (22.87%), the cause of death was MI, including 137 cases of fatal type 2 MI. Proportions of men and women among the patients with postmortem verification of type 2 MI were comparable. Analysis of the age structure showed the highest incidence of type 2 MI in elderly (48.2%) and senile (34.3%) age. Mean age of patients with type 2 MI was 71.7 years (68.2 years for men and 75.3 years for women), which was comparable with the age range of patients with fatal type 1 MI. In both groups, men with fatal MI were significantly younger than women. Analysis of causes for type 2 MI demonstrated that the most frequent ones were tachysystolic arrhythmias (59.12%) and severe hypoxia of different origin (35.04%). Analysis of the type of CA lesions showed that significant lesions were significantly more frequently absent in type 2 MI (32.85%) while in type 1 MI, the proportion of patients with unchanged CA was 1.84%. In the group of patients with fatal type 1 MI, 67.29% had multivascular lesions, and one in two patients had an occlusive lesion. In the group with type 2 MI, multivascular lesions were half as frequent (31.38%), and only 4.38% of patients had a complete occlusion of a coronary vessel. Comparison of death rate in different departments of the multidisciplinary hospital showed that only 29.2% of patients with type 2 MI originally were managed at a specialized cardiological department; 45.3% of patients were admitted to an internal medicine department for different conditions often not related with ischemic heart disease. Furthermore, 25.5% of patients with subsequently developed type 2 MI originally even received scheduled or emergency medical care for a leading surgical condition.

Conclusion — Cardiovascular diseases predominate among causes of mortality in a multidisciplinary hospital. This study showed that almost one in four patients dies from MI, and type 2 MI accounts for more than one third of fatal MIs. Among major causes for type 2 MI, tachysystolic arrhythmias (59.12%) and pronounced hypoxia associated with anemia and severe respiratory failure (35.04%) should be noted. Gender and age characteristics of patients with type 2 MI were comparable with those of patients with fatal type 1 MI. Furthermore, surgical patients accounted for 25.5% of fatal cases of type 2 MI.

Keywords — Type 2 myocardial infarction; cardiovascular mortality; fatal myocardial infarction

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Despite the rapid growth of contemporary medical science, including the development of new high-tech methods of diagnosis and treatment in cardiology, cardiovascular mortality, particularly that due to myocardial infarction (MI), is still relatively high [1]. The heterogeneity of MI, which is expressed in differences in pathogenesis and clinical manifestations determined by the direct cause of heart muscle necrosis

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[2], gave rise to the clinical classification of MI, which was first offered in 2007 [3], and includes currently five types of MI [4].

Type 2 MI, according to this classification, develops due to supply-demand mismatch when reduced coronary perfusion and inadequate oxygen delivery to the myocardium do not correspond to its increased energy demand. This type of MI occurs in a number of pathological conditions (Table 1) not related to coronary heart disease (CHD) and instability/rupture of atherosclerotic plaque [5, 6].

Type 2 MI has been of increasing interest to researchers and cardiologists around the world in recent years as it is the least studied type of MI. The lack of the critical evidence base for the development of new clinical guidelines for the management of patients with this type of MI, as well as the difficulties of its timely diagnosis as compared with the other forms of MI, has resulted in increased attention to this diagnosis [6]. The current literature on type 2 MI shows a relatively high variability of results: according to various studies, type 2 MI accounts for 1.6% – 36.6% of all cases of MI [7–10]. Prognostic data for type 2 MI are also contradictory. According to some studies, the prognosis in patients with type 2 MI is comparable to that in patients with type 1 MI [11, 12], yet it is two to three times worse in other studies [13–15]. The absence of typical clinical symptoms of myocardial ischemia in many cases and a variety of nonspecific clinical manifestations related to the primary pathological condition, against which MI type 2 develops, are the likely cause of such wide variability of data. Massive bleeding, severe respiratory failure (RF), shock, severe anemia, tachy- and bradysystole, hyper – and hypotension, and among others are the common pathological conditions [16] that can lead to secondary ischemic damage to the myocardium and the development of type 2 MI, and directly affect the prognosis. It is evident from this range of symptoms, depending on the primary pathology, that patients diagnosed with type 2 MI may be admitted to almost any hospital department. Therefore, in our view, it is not entirely correct to adequately and fully assess the prevalence and mortality from type 2 MI only in patients of cardiological and therapeutic departments. Instead, we considered it necessary to estimate the prevalence of type 2 MI in the mortality structure of all departments of the multispecialty hospital (629 beds), followed by the assessment of the hospitalization profile of patients with this type of MI, the leading causes of its development, and the share of type 2 MI among the causes of mortality.

Table 1. The leading causes of myocardial lesions and type 2 myocardial infarction

I. Myocardial lesions due to supply-demand mismatch*
Decreased coronary perfusion
Coronary spasm, microvascular dysfunction
Coronary embolism
Spontaneous coronary dissection
Bradysystolic rhythm disorders
Shock/hypotension
Severe hypoxemia and severe RF
Hemic hypoxia in severe anemia
Increasing energy demand of the myocardium
Tachysystolic disorders
Severe hypertension, hypertensive crisis
II. Other causes of myocardial lesion**
Cardiac
Severe CHF
Myocarditis
Cardiomyopathy (any type)
Takotsubo syndrome
Coronary revascularization
Procedures on the heart (except revascularization)
Catheter ablation
Defibrillator discharge
Concussion/injury
Other noncardiac conditions
Sepsis, infections
Chronic kidney disease with severe CRF
Stroke, subarachnoid hemorrhage
PE, severe pulmonary hypertension
Infiltrative diseases such as amyloidosis, sarcoidosis
Chemotherapy
Shock and terminal conditions
High physical activity

*, can cause both myocardial lesion and type 2 MI; **, not type 2 MI. MI, myocardial infarction; CA, coronary artery; RF, respiratory failure; CHF, chronic heart failure; CRF, chronic renal failure; PE, pulmonary embolism.

Material and methods

The longitudinal, retrospective descriptive, and analytical study was conducted under the principles of the Declaration of Helsinki. Local ethics committee approval was not required for the study, since our goal

was to retrospectively investigate medical records and autopsy reports of patients who died in the multispecialty hospital. Postmortem examinations were carried out in compliance with the valid regulatory documents and laws. The method of continuous sampling was used to study 1,574 reports of autopsies performed in the Central Pathology Department of the I. I. Mechnikov North-Western State Medical University from January 1, 2010, to December 31, 2016. Diagnosis was verified by the pathologist who performed the autopsy, based on a combination of macroscopic patterns and histological findings of myocardial necrosis. If the duration of MI was less than 24 hours, additional histological examination methods were used to detect the prenecrotic stage of ischemia, including macroscopic staining with tetrazolium salts or potassium tellurite, followed by the histological examination of tissue sections using Lie's hematoxylin-based fuchsin-picric acid or Regaud's hematoxylin staining. Electron microscopy was not used as a common diagnostic technique. Old cardiomyocyte necrotic lesions with signs of organization of cells and formation of dense connective tissue, accompanied by fibroblast hyperplasia and accumulation of thick collagen fibers around damaged and hypertrophic myocardial cells were considered as post-infarction cardiosclerosis. Macroscopic and histological findings of signs of acute necrosis in the post-infarction scar area were considered as recurrent acute MI.

Assessment of coronary arteries (CA) was performed in the context of the necrosis and taking into account the myocardial blood supply. Verified MI was classified as type 1 in case of detecting signs of coronary thrombosis, the compromised integrity of the unstable atherosclerotic plaque, the presence of erosions, ulcers, and intraplaque hemorrhages, and in the absence of a direct relationship between the coronary lesions and recent percutaneous coronary intervention and coronary artery bypass grafting. Existing IM was classified as type 2 in the absence of signs of thrombotic changes in the CA associated with the compromised integrity of the unstable atherosclerotic plaque.

Clinical data (postmortem summary and medical record) were assessed in addition to the morphology section of the autopsy report made by the pathologist. Special attention was paid to the symptoms of MI, electrocardiography findings, levels of cardiac markers, and coronary angiography findings in the medical records. It should be noted that evidence of intravital verification of MI among the analyzed cases was not always available.

Electrocardiography monitoring and determination of the levels of cardiac enzymes often were not conducted in the majority of severe co-morbid (mainly surgical) patients who did not have typical clinical manifestations. If MI was suspected intra vitam, the diagnosis was carried out according to the recommendations of a cardiologist. The following biochemical parameters of myocardial necrosis were evaluated urgently and reevaluated in 6, 12, and 24 hours: troponin T and I, creatine phosphokinase, and its myocardial band. Moreover, the levels of the less specific enzymes aspartate aminotransferase and alanine aminotransferase were estimated on days 2–3 in some cases. Clinical data and laboratory and other examination findings in the medical records not only verified the diagnosis of MI intra vitam, but also helped to establish the type of fatal MI in controversial cases. Somatic state, the principal diagnosis, and thanatogenesis from the clinical part of the postmortem summary were carefully analyzed by a group of experts, if the intravital diagnosis of MI had not been performed and if a secondary mechanism of myocardial ischemia was suspected, which was most frequently observed in the postoperative period and in terminal co-morbid patients. In these cases, autopsy-verified MI was classified as type 2 if the medical records confirmed the presence of conditions contributing to the development of a clinically significant myocardial supply-demand mismatch.

The statistical analysis of data was performed using Statistica 10.0. The statistical hypothesis on the normal distribution of parameters was tested using the Shapiro-Wilk and Liliefors tests, and taking into account descriptive statistical characteristics. The properties of normal distribution were applied to the study sample since it fitted the Lyapunov equation. For this reason, parametric methods of statistical analysis were used for further evaluation of the data: the mean was used as a measure of the central tendency, and the standard deviation was used as a measure of variability. The significance of differences was determined using the Student's t-test, and the relationship between the parameters was assessed using the Spearman's rank correlation coefficient. The difference was considered statistically significant at $p<0.05$.

Results

The analysis of the causes of death of patients treated at the multispecialty hospital during the study period (January 1, 2010 – December 31, 2016) showed that cardiovascular diseases were the leading causes of death, accounting for more than 50% of all

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Table 2. The leading causes of mortality at I. I. Mechnikov North-Western State Medical University, January 1, 2010–December 31, 2016

Leading causes of mortality	Percentage of the total number of deaths
Circulatory disorders	51.78
Cancers	22.86
Other diseases (obstetrics, gynecology, urology, injuries, poisonings)	8.71
Kidney and urinary diseases, CRF	4.65
Infectious diseases (severe respiratory infections, influenza, tuberculosis, HIV/AIDS)	4.51
Chronic digestive diseases	3.87
Respiratory disorders	3.62

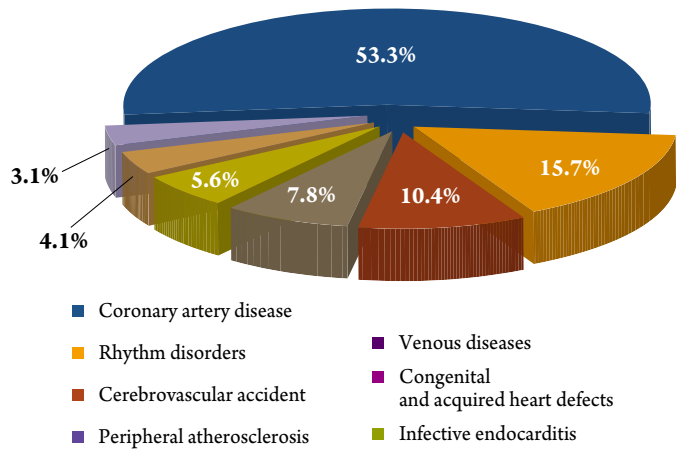
CRF, chronic renal failure; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

Table 3. Structure of underlying and immediate causes of cardiovascular mortality

Parameter	Percentage in the structure of fatal cardio-vascular complications
Underlying causes of death	
CAD including: • MI • Chronic forms of CAD	53.3 44.2 9.1
Rhythm disorders	15.7
Cerebrovascular accident	10.4
Peripheral atherosclerosis	7.8
Congenital and acquired heart defects	5.6
Venous diseases	4.1
Infective endocarditis	3.1
Immediate causes of death	
Acute heart failure	46.5
Chronic heart failure	25.4
Pulmonary embolism	15.5
Brain swelling	9.2
Other causes (intoxication, multiple-organ dysfunction syndrome, shock)	3.4

MI, myocardial infarction; CAD, coronary artery disease.

Figure 1. Structure of the leading causes of mortality at I. I. Mechnikov North-Western State Medical University, January 1, 2010–December 31, 2016



fatal cases (Table 2). Cancer was the second-leading cause of death and led to one-fifth of all deaths. The structure of mortality is described in Table 2.

CAD was the leading underlying cause of death among cardiovascular diseases, accounting for 53.3%, including MI 44.2% and chronic forms of CAD 9.1%. Lethal cardiac arrhythmias were the second-most common underlying cause, accounting for 15.7% of deaths; cerebrovascular accidents were the third-most common cause, accounting for 10.4%. These were followed by peripheral atherosclerosis, venous diseases causing thromboembolic complications, valvular heart disease, and infective endocarditis (Figure 1). The most common immediate causes of death were acute heart failure (45.6%), progressive heart failure (25.4%), and pulmonary embolism (15.6%). The structure of the underlying and immediate causes of mortality from cardiovascular disorders is presented in Table 3.

MI was verified in 360 cases of 1,574 autopsies performed during the 7-year study period. The changes in the percentage of MI cases in the structure of all causes of death during the study period remained relatively stable: the mean percentage of MI is 22.87% of all deaths.

Reliable autopsy signs of coronary atherothrombosis typical of type 1 MI were detected in 60.28% (n=217) of all patients diagnosed with MI, as demonstrated by the analysis of the structure of lethal outcomes of MI. In 137 (38.05%) cases of postmortem verification of acute myocardial necrosis, there were no signs of coronary thrombosis, erosions, ulcers, hemorrhages, and compromised integrity of unstable atherosclerotic plaque, suggesting a secondary mechanism of the

Table 4. Comparative characteristics of coronary arteries in patients with type 1 MI and type 2 MI

Parameter	MI type 1		MI type 2		p
	abs.	%	abs.	%	
No significant stenosis	4	1.84	45	32.85	0.001
Hemodynamically significant stenosis of one CA	17	7.83	17	12.41	0.193
Hemodynamically significant stenosis of two CAs	50	23.04	32	23.36	0.272
Multivessel coronary disease	146	67.29	43	31.38	0.005
Total	217	100	137	100.00	-
Including occlusive lesion	109	50.23	6	4.38	0.001

MI, myocardial infarction; CA, coronary artery.

development of MI. The remaining 6 (1.67%) cases were MI associated with the percutaneous coronary intervention and coronary artery bypass grafting (types 4 and 5 of MI).

Analysis of the CA damage showed that no hemodynamically significant lesion (stenosis less than 50%) was detected in 45 (32.85%) of 137 patients with type 2 MI. At the same time, only 4 (1.84%) of the 217 patients who died from type 1 MI had no hemodynamically significant lesions (p<0.001). Two-thirds of patients with fatal type 1 MI had multivessel disease, and every second patient had an occlusive lesion with complete obstruction of at least one CA. Among 137 patients with type 2 MI, 43 (31.38%) had multivessel disease, and only 4.38% of patients with type 2 MI had complete occlusion of a coronary vessel (p<0.001). More detailed information about the nature of coronary lesions is given in Table 4.

There were no statistically significant differences in sex among patients with a postmortem diagnosis of type 1 MI and type 2 MI. There were slightly more male patients in both groups: 54.84% in the type 1 MI group and 51.09% in the type 2 MI group. The mean age of patients in both study groups was comparable (70.9 and 71.7 years in the groups of type 1 MI and type 2 MI, respectively). However, male patients with both type 1 and type 2 MI were significantly younger than female patients: the mean age of men was 67.6 years in the type 1 MI group and 68.2 years in the type 2 MI group versus 76.7 and 75.3 years for women, respectively (p=0.017). The age group analysis based on the World Health Organization (WHO) classification showed that 82.5% of those who died from type 2 MI were elderly (60–74 years; 48.2%) and senile (75–89 years; 34.3%) patients.

The leading cause of type 2 MI was tachysystolic rhythm disorders – 59.12% of cases, the majority of which were by atrial fibrillation (AF) and atrial flutter (AFL). It was not possible to reliably estimate the percentage of newly detected and preexisting paroxysmal, persistent, or chronic arrhythmias, since often (especially in surgical patients) there was no information about the form of arrhythmia in the diagnosis wordings, medical records, and autopsy protocols. However, it should be noted that supraventricular tachyarrhythmias were the primary factor in the described cases leading to the development of demand-supply mismatch and type 2 MI, despite the lack of anamnestic data on the duration of heart rhythm disorders. Moreover, 3.65% of cases of type 2 MI detected during the autopsy, which developed in tachyarrhythmias, were associated with newly diagnosed thyroid diseases with severe thyrotoxicosis. In these cases, histological examination often revealed severe myocardial dystrophy.

Severe hemic and hypotonic hypoxia were the second leading causes of type 2 MI (n=48) and accounted for 35.04% of all lethal outcomes of type 2 MI. Immediate causes of hypoxia, which led to fatal type 2 MI, are described in Table 5.

According to available data, sepsis was an essential factor in the development of type 2 MI. It causes not only direct infectious and toxic effects on cardiomyocytes but also secondary mediated damage to the myocardium of ischemic origin [8]. Detailed analysis of the pathoanatomical report and the clinical part of the medical records demonstrated the leading role of a severe infectious process as the main cause of type 2 MI in three (2.2%) cases. Sepsis was not evaluated by the site of entry, etiology, and form due to the small absolute number of such cases.

According to analysis of all 137 cases of fatal type 2 MI by hospitalization profile, 45.3% of patients were admitted to therapeutic departments with various diseases that do not imply acute forms of CAD. Only 29.2% of patients were initially admitted to the emergency and intensive cardiology department. The remaining 25.5% of patients with subsequently

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Table 5. Causes of hypoxic conditions leading to type 2 MI

Parameter	abs.	%
Hypoxic causes of hypoxia		
Pneumonia	12	25.00
Chronic obstructive pulmonary disease	8	16.67
RF in the pulmonary circuit congestion	7	14.58
Secondary RF due to atelectasis, pneumo- and hemothorax	3	6.25
Causes of hemic hypoxia		
Chronic anemia	7	14.58
Bleeding	5	10.42
Intraoperative massive hemorrhage	4	8.33
Blood disorders (hemoblastosis, bone marrow aplasia)	2	4.17

MI, myocardial infarction; RF, respiratory failure.

verified type 2 MI received planned or emergency medical care for the leading surgical pathology, most often including open abdominal and thoracic surgery, vascular surgery.

Discussion

The study demonstrated that cardiovascular diseases and cancer are the leading causes of death. Our findings fully correspond to the structure of causes of mortality both in the Russian Federation [1] and in developed countries [17]. According to the study results, MI ranks first among fatal cardiovascular complications, with a mortality rate of 22.87%, which is also comparable to the structure of causes of mortality in the Russian Federation [1, 18].

The analysis of fatal MI cases showed, according to autopsy data, that type 1 MI was present in 60.28% of cases, and type 2 MI in 38.05%. The prevalence of type 2 MI appeared to be significantly higher than the literature claims. For example, according to most published clinical studies [7, 8, 10, 19, 20], the maximum percentage of currently known type 2 MI cases does not exceed 30%. However, it should be noted that these studies were focused on the prevalence of MI type 2 and were usually conducted in patients with cardiovascular disorders who had been hospitalized urgently.

This study is limited by a retrospective design and may be less accurate and reliable than prospective randomized trials. Thus, a small number of patients with fatal type 1 atherothrombotic MI could undoubtedly be included in the type 2 MI group, since antithrombotic therapy could contribute to the lysis of coronary blood clots at the time of autopsy. At the same time, the presence of coronary thrombosis described in the autopsy report also does not exclude the possibility of overdiagnosis of type 1 MI, since coronary thrombosis is also possible in embolic MI, which is type 2 MI, often developing in patients with chronic forms of AF. Moreover, histological examination of the fibrous cap to detect compromised integrity was not carried out in the absence of visual changes in the existing unstable atherosclerotic coronary plaque. The study assessed the clinical notes in the medical records and postmortem summaries as well as autopsy data to determine the intravital verification of the type of MI and to identify pathological conditions causing a supply-demand mismatch and secondary ischemic damage to the myocardium, to avoid possible distortion of the results for the above reasons.

The findings on the age groups of patients with type 2 MI and its causes are fully comparable with the available data of prospective studies. Most authors note that type 2 MI is most common in those of elderly and senile age, and tachysystolic forms of AF and AFL, different types of anemia, and RF are among most common causes of its development [7, 8, 16, 19]. The expected statistically significant differences in sex and mean age of patients between the groups with fatal type 1 MI and type 2 MI was not found. The possible explanation is the characteristics of the study sample and the specifics of the study, since it was based on the examination of fatal cases registered in a multidisciplinary hospital, while studies demonstrating the predominance of type 2 MI among older women were performed among the clinical group of patients with cardiovascular disorders who were urgently hospitalized [7, 8, 10, 19, 20].

Hemodynamically significant stenosis and multivessel coronary disease in type 2 MI are observed much less frequently than in type 1 MI [19, 21, 22] according to the results of other large studies, which correspond with the results of our analysis of the causes of coronary lesions.

It should be noted that only 29.2% of patients with fatal MI type 2 were initially admitted to the department of emergency cardiology. That means that the clinical manifestations of type 2 MI are variable and often nonspecific. Type 2 MI is known to develop often in the postoperative period in co-morbid surgical patients [13]. The percentage of patients with an underlying surgical disease and verified postmortem type 2 MI was 25.5%. This pattern is consistent with

other observations that the majority of patients with verified type 2 MI are treated in departments other than cardiology [13, 21].

Conclusions

Cardiovascular diseases were the leading cause of death in this study. Among the underlying causes of mortality, coronary heart disease was first (accounting for 53.3%), followed by fatal cardiac arrhythmias (15.7%) and cerebrovascular accident (10.4%). The most common immediate causes of death were acute heart failure (45.6%), progressive heart failure (25.4%), and pulmonary embolism (15.6%). It should be noted that myocardial infarction caused the death of almost every fourth patient in the hospital, and more than 30% of fatal cases are type 2 myocardial infarction.

It is necessary to mention a leading role of tachysystolic rhythm disorders (59.12%) and severe hemic hypoxia associated with anemia and severe respiratory failure (35.04%) as the leading causes of type 2 myocardial infarction. The sex and age characteristics of patients who died from type 2 myocardial infarction are comparable to those of patients with fatal type 1 myocardial infarction. Surgical patients account for 25.5% of all cases of fatal type 2 myocardial infarction.

Thus, it should be emphasized that the high prevalence of fatal type 2 myocardial infarction in patients of the multidisciplinary hospital proves the diversity and nonspecificity of clinical manifestations of this type of myocardial infarction and challenges the intravital diagnosis. Systematization of the causes of type 2 myocardial infarction and further study of the pathogenesis in direct dependence on the leading cause of the myocardial supply-demand mismatch can contribute to better diagnosis and treatment of different variants of this type of myocardial infarction.

No conflict of interest is reported.

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