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COMPARATIVE MORPHOLOGICAL CHANGES OF THE MYOCARDIUM IN CARDIAC ISCHEMIA

Tolqinov Islomjon,
Fergana Public Health Medical Institute, Department of Normal Anatomy.
Ergasheva Diligozal,
Fergana Public Health Medical Institute, Cardiology Department, 1st-year resident.
Email; islomjontolqinov09@gmail.com
ORCID; https://orcid.org/0009-0009-0609-1189

Abstract. Myocardial ischemia remains one of the leading causes of global morbidity and mortality, making the study of its structural consequences highly relevant for modern cardiology and pathology. When the coronary blood flow becomes insufficient, the myocardium undergoes a complex spectrum of morphological alterations that evolve over time depending on the severity and duration of ischemia. This study provides a comparative analysis of early and late morphological changes in ischemic myocardial tissue, integrating histological, ultrastructural, and pathophysiological perspectives to better understand the progression from reversible injury to irreversible cell death and chronic remodeling. In the early phase of ischemia, typically within the first six hours, myocardial cells demonstrate reversible alterations, including cellular swelling, loss of cross-striations, mitochondrial edema, and mild interstitial fluid accumulation. These changes reflect the initial breakdown of aerobic metabolism, depletion of ATP, and activation of anaerobic glycolysis. Ultrastructurally, the disturbance of mitochondrial cristae, formation of amorphous densities, and sarcolemmal membrane instability are noted. Although potentially reversible, failure to restore adequate perfusion propagates further damage. The intermediate stage of ischemia, occurring between 6 and 24 hours, is marked by the onset of irreversible injury. Histologically, coagulative necrosis becomes evident with cytoplasmic eosinophilia, nuclear pyknosis and karyolysis, contraction band necrosis, and disruption of myofibrils. Neutrophil infiltration intensifies during this stage, initiating inflammatory responses that contribute to secondary cellular injury. This period represents a critical transition zone where the balance between cellular survival and necrosis is determined. In late ischemia, typically after 24 hours, morphological changes shift toward tissue degradation and repair. Dead cardiomyocytes are replaced by macrophages and lymphocytic infiltrates responsible for removing necrotic debris. Fibroblast activation and collagen deposition emerge as prominent features, ultimately resulting in scar formation and myocardial fibrosis. This remodeling process, while essential for structural integrity, diminishes contractile function and contributes to long-term complications such as heart failure. Comparing these stages highlights the dynamic nature of myocardial injury, showing that the timing and severity of ischemia dictate the progression of morphological changes. Understanding these differences is crucial for improving diagnostic accuracy, optimizing therapeutic interventions, and predicting clinical outcomes. Therefore, this study underscores the importance of early detection, timely reperfusion, and targeted therapies that may limit irreversible damage and prevent pathological remodeling of the myocardium.

Keywords: English: myocardial ischemia, morphology, necrosis, fibrosis, cardiomyocytes

Annotatsiya Miokard ishemiyasi global miqyosda kasallanish va o‘limning yetakchi sabablaridan biri bo‘lib qolmoqda. Shu bois uning tuzilmaviy oqibatlarini o‘rganish zamonaviy kardiologiya va patologiya uchun nihoyatda dolzarb hisoblanadi. Koronar qon oqimi yetarli bo‘lmaganda, miokard ishemiya darajasi va davomiyligiga qarab vaqt o‘tishi bilan turli murakkab

morfologik o‘zgarishlarga duch keladi. Ushbu tadqiqot ishemiyaga uchragan miokard to‘qimasida yuzaga keladigan erta va kech morfologik o‘zgarishlarni qiyosiy tahlil qiladi hamda ularni chuqurroq anglash uchun gistologik, ultrastruktural va patofiziologik yondashuvlarni birlashtiradi. Bu esa qaytariluvchi jarohatlanishdan qaytarilmaydigan hujayra o‘limi va surunkali qayta tuzilish jarayoniga o‘tish mexanizmlarini yaxshiroq tushunish imkonini beradi. Ishemiyaning dastlabki bosqichida, odatda birinchi olti soat davomida, kardiomiyotsitlarda qaytariluvchi o‘zgarishlar kuzatiladi. Ularga hujayra shishishi, ko‘ndalang-qiya chiziqlar yo‘qolishi, mitoxondriyalarning shishishi va interstitsial suyuqlikning yengil to‘planishi kiradi. Bu o‘zgarishlar aerob metabolizmning buzilishi, ATFning keskin kamayishi va anaerob glikolizning faollashuvi bilan bog‘liq. Ultrastruktura darajasida mitoxondriya kristalarining buzilishi, amorf zichliklarning paydo bo‘lishi va sarkolemmaning beqarorligi kuzatiladi. Bu jarayonlar nazariy jihatdan qaytariluvchi bo‘lishi mumkin, ammo o‘z vaqtida qon ta’minoti tiklanmasa, shikastlanish chuqurlashadi. Ishemiyaning oraliq bosqichi, ya’ni 6–24 soat oralig‘ida, qaytarilmaydigan jarohatlanish belgilari paydo bo‘lishi bilan xarakterlanadi. Gistologik tekshiruvda sitoplazmaning eozinofilligi oshishi, yadro piknozi va kariolizi, kontraksiya tasmasi nekrozi hamda miofibrillarning buzilishi aniqlanadi. Shu bosqichda neytrofil infiltratsiyasi kuchayadi, bu esa yallig‘lanish jarayonlarini faollashtirib, ikkilamchi hujayra shikastlanishiga olib keladi. Mazkur davr hujayraning yashab qolishi yoki nekrozga uchrashi o‘rtasidagi muhim o‘tish bosqichi hisoblanadi. Ishemiyaning kech bosqichida, odatda 24 soatdan keyin, morfologik o‘zgarishlar to‘qimaning yemirilishi va tiklanishi tomon yo‘naladi. Nobud bo‘lgan kardiomiyotsitlar makrofaglar va limfotsitar infiltratlar bilan almashinadi, ular nekrotik massalarni tozalash uchun mas’uldir. Shu davrda fibroblastlar faollashadi va kollagen to‘qimasi ko‘payadi, bu esa chandiq hosil bo‘lishi va miokard fibrozining rivojlanishiga olib keladi. Ushbu qayta tuzilish jarayoni to‘qima barqarorligini ta’minlash uchun zarur bo‘lsa-da, yurakning qisqaruvchanlik xususiyatini pasaytiradi va uzoq muddatda yurak yetishmovchiligi kabi asoratlarni kuchaytiradi. Ushbu bosqichlarni qiyoslash ishemik jarohatlanishning dinamik xususiyatga ega ekanini ko‘rsatadi. Ishemiyaning davomiyligi va og‘irligi morfologik o‘zgarishlarning ketma-ketligini belgilab beradi. Bu farqlarni chuqur tushunish diagnostika aniqligini oshirish, davolash strategiyalarini optimallashtirish va klinik natijalarni oldindan baholashda muhim ahamiyatga ega. Shunday qilib, ushbu tadqiqot qaytarilmaydigan shikastlanishning oldini olish va miokardning patologik qayta tuzilishini cheklash uchun erta tashxis qo‘yish, vaqtida reperfuziya o‘tkazish va maqsadli terapevtik yondashuvlarning zarurligini ta’kidlaydi.

Kalit so'zlar: miokard ishemiyasi, morfologiya, nekroz, fibroz, kardiomiyotsitlar

Абстракт. Ишемия миокарда остаётся одной из ведущих причин глобальной заболеваемости и смертности, что делает изучение её структурных последствий чрезвычайно актуальным для современной кардиологии и патологии. При недостаточном коронарном кровотоке миокард подвергается сложному спектру морфологических изменений, которые развиваются со временем в зависимости от тяжести и продолжительности ишемии. Данное исследование представляет сравнительный анализ ранних и поздних морфологических изменений в ишемизированной миокардиальной ткани, объединяя гистологические, ультраструктурные и патофизиологические подходы для более глубокого понимания перехода от обратимого повреждения к необратимой гибели клеток и хроническому ремоделированию. На ранней фазе ишемии, обычно в течение первых шести часов, кардиомиоциты демонстрируют обратимые изменения, включая клеточный отёк, потерю поперечной исчерченности, митохондриальный отёк и умеренное скопление интерстициальной жидкости. Эти изменения отражают первичное нарушение аэробного метаболизма, истощение АТФ и активацию анаэробного гликолиза. На ультраструктурном уровне наблюдаются нарушения крист митохондрий, образование аморфных плотностей и нестабильность сарколеммальной мембраны. Хотя эти изменения потенциально обратимы, отсутствие своевременной реперфузии приводит к прогрессированию повреждения. Промежуточная стадия ишемии, наступающая между 6 и 24 часами, характеризуется появлением признаков необратимого повреждения. Гистологически выявляется

коагуляционный некроз с цитоплазматической эозинофилией, пикнозом и кариолизисом ядер, некрозом сократительных полос и нарушением структуры миофибрилл. В этот период усиливается нейтрофильная инфильтрация, инициирующая воспалительные реакции, которые способствуют вторичному клеточному повреждению. Эта стадия представляет собой критическую переходную фазу, в которой определяется баланс между клеточной выживаемостью и некрозом. На поздней стадии ишемии, обычно после 24 часов, морфологические изменения смещаются в сторону деградации и восстановления ткани. Погибшие кардиомиоциты замещаются макрофагами и лимфоцитарными инфильтратами, ответственными за удаление некротических масс. Активируются фибробласты, усиливается отложение коллагена, что приводит к формированию рубцовой ткани и развитию миокардиального фиброза. Этот процесс ремоделирования, хотя и необходим для структурной стабильности, приводит к снижению сократительной функции и способствует долгосрочным осложнениям, таким как сердечная недостаточность. Сравнение этих стадий подчёркивает динамичный характер ишемического повреждения миокарда, показывая, что время и степень ишемии определяют последовательность морфологических изменений. Понимание этих различий имеет важное значение для повышения точности диагностики, оптимизации лечебных вмешательств и прогнозирования клинических исходов. Таким образом, данное исследование подчёркивает важность раннего выявления, своевременной реперфузии и целевых терапевтических стратегий, направленных на ограничение необратимого повреждения и предотвращение патологического ремоделирования миокарда.

Ключевые слова: ишемия миокарда, морфология, некроз, фиброз, кардиомиоциты

INTRODUCTION:

Myocardial ischemia remains one of the leading causes of morbidity and mortality worldwide, representing a critical challenge for modern cardiology, pathology, and public health. It occurs when the coronary blood flow becomes insufficient to meet the metabolic demands of the myocardium, resulting in an imbalance between oxygen supply and myocardial oxygen consumption. This oxygen deficit initiates a cascade of biochemical, metabolic, and structural alterations that profoundly affect cardiac function. Understanding the morphology of ischemic myocardium is essential, as the progression of histological and ultrastructural changes determines the reversibility of injury, clinical presentation, and long-term prognosis. The significance of studying myocardial ischemia is further emphasized by its close association with ischemic heart disease, acute coronary syndromes, and sudden cardiac death. These conditions collectively account for millions of deaths annually, making the identification of underlying pathophysiological mechanisms crucial for improving preventive, diagnostic, and therapeutic strategies. While the clinical manifestations of ischemia, such as chest pain or electrocardiographic abnormalities, are well recognized, the microscopic and ultrastructural transformations within the myocardium remain the foundation for understanding disease evolution and tissue response to injury. Morphological changes in ischemic myocardium follow a time-dependent continuum, beginning with reversible cellular alterations and progressing toward irreversible injury and tissue remodeling. During the early phase, typically within the first hours of ischemia, cardiomyocytes undergo metabolic disturbances, loss of contractile function, and cellular swelling. If ischemia persists, these changes transition into coagulative necrosis, inflammatory cell infiltration, and ultimately, fibrotic scar formation. Comparing these early and late morphological stages provides valuable insights into the dynamic nature of myocardial damage. Moreover, in the era of advanced diagnostic techniques such as cardiac MRI, high-resolution echocardiography, and serum biomarkers, there is a growing interest in correlating imaging findings with actual histopathological changes. Such correlations help clinicians assess the extent of myocardial injury, predict functional recovery, and select appropriate therapeutic interventions, including reperfusion strategies, anti-ischemic therapy, and long-term cardiac rehabilitation. Despite significant progress in understanding ischemia at the molecular and cellular levels, gaps remain in differentiating subtle early changes from the onset of

irreversible damage. Therefore, comprehensive evaluation of myocardial morphology across different stages of ischemia is essential to refine diagnostic accuracy, strengthen prognostic assessment, and develop more effective treatment approaches. This study aims to compare the early and late morphological changes in myocardial tissue during ischemia, integrating histological and pathophysiological perspectives to enhance the understanding of ischemic injury progression and its clinical implications.

LITERATURE REVIEW

Numerous studies over the past decades have extensively investigated the sequence of morphological changes that occur during myocardial ischemia, providing a detailed understanding of the structural, cellular, and molecular events that accompany diminished coronary blood flow. Research in experimental pathology, cardiovascular histology, and clinical cardiology has consistently emphasized that the myocardium responds to ischemia in a time-dependent manner, progressing from reversible injury to irreversible necrosis and subsequent tissue remodeling. This chronological progression has been documented through light microscopy, electron microscopy, biochemical assays, and advanced imaging modalities, forming the basis of modern concepts of ischemic heart disease. Early literature, including classical histopathological studies, has characterized the initial phase of ischemia—typically within the first 30 minutes to 6 hours—as a period dominated by reversible cellular injury. Investigators such as Jennings, Reimer, and colleagues demonstrated that the earliest changes include cellular swelling, sarcoplasmic vacuolization, mitochondrial edema, and loss of glycogen stores. These findings were further corroborated by electron microscopy studies, which identified disruption of mitochondrial cristae, early formation of amorphous densities, and subtle sarcolemma instability. Although these changes do not immediately signal irreversible injury, the literature emphasizes that prolonged ischemia rapidly increases the risk of permanent cellular damage, establishing a “golden window” for successful reperfusion. Subsequent studies have focused on the transition from reversible to irreversible injury. Research by Kumar et al. and other contemporary pathologists described the hallmark of irreversible ischemic damage: coagulative necrosis. This typically becomes evident between 6 and 24 hours following the onset of ischemia. During this period, cardiomyocytes exhibit intense cytoplasmic eosinophilia, loss of nuclei through pyknosis and karyolysis, and fragmentation of myofibrils. The inflammatory response, driven primarily by neutrophils, becomes prominent as early as 12 hours, contributing to further breakdown of necrotic tissue. These findings highlight the importance of inflammation in the pathogenesis of myocardial infarction, a concept widely supported by modern cardiovascular immunology research. Literature addressing the late phases of ischemia—beyond 24 hours—shows that tissue destruction is followed by progressive inflammatory infiltration, macrophage activation, and fibroblast proliferation. Studies using animal models and human postmortem tissue samples demonstrate that macrophages play a crucial role in clearing necrotic debris, while fibroblasts initiate collagen synthesis that ultimately leads to scar formation. This fibrotic remodeling has been extensively examined in recent imaging studies using cardiac magnetic resonance (CMR), which can visualize late gadolinium enhancement corresponding to collagen-rich scar tissue. Such correlations between imaging and histopathology underscore the clinical importance of understanding myocardial morphology. Recent research has expanded the understanding of ischemic injury by integrating molecular and genetic analyses. Studies exploring oxidative stress, mitochondrial dysfunction, apoptosis, and inflammatory signaling pathways have deepened insight into how early biochemical events translate into the morphological changes observed microscopically. Moreover, contemporary literature highlights the role of reperfusion injury—damage that paradoxically occurs when blood flow is restored after a period of ischemia. Investigations into this phenomenon have shown that oxidative bursts, calcium overload, and microvascular dysfunction contribute to additional structural injury, complicating the interpretation of morphological findings. Comparative studies have also emphasized the clinical relevance of distinguishing early and late morphological changes. These findings have improved diagnostic precision in acute myocardial infarction, aided the development of biomarkers such as

troponins, and guided therapeutic approaches including thrombolysis, percutaneous coronary intervention, and anti-inflammatory treatments. Overall, the body of literature demonstrates that myocardial ischemia is a dynamic process involving a complex interplay of metabolic, inflammatory, and structural mechanisms, all of which contribute to the progression from reversible dysfunction to permanent myocardial damage.

RESEARCH METHODOLOGY

This study employed a comprehensive methodological approach to investigate the morphological changes in myocardial tissue during ischemia, integrating sample collection, histological processing, staining techniques, and morphometric analysis. The objective was to obtain a detailed and systematic evaluation of early, intermediate, and late ischemic alterations, ensuring reproducibility and accuracy of the observations.

Sample Collection

Myocardial tissue samples were obtained from clinically confirmed cases of ischemia, following ethical approval and standardized protocols for tissue handling. The samples were carefully dissected to include regions most representative of ischemic injury, ensuring that early, intermediate, and late-stage zones could be compared. To preserve structural integrity, the tissue was immediately fixed in 10% neutral buffered formalin, minimizing autolysis and postmortem artifacts.

Histological Processing and Staining

After fixation, the samples were processed using standard paraffin embedding techniques. Sections of 4–6 μm thickness were prepared for microscopic evaluation. To highlight cellular and extracellular structures, **hematoxylin and eosin (H&E)** staining was performed, providing clear visualization of nuclei, cytoplasm, and general tissue architecture. In addition, **Masson's trichrome staining** was employed to detect collagen deposition and assess the development of fibrosis during late ischemia. Periodic acid–Schiff (PAS) staining was also utilized to identify glycogen depletion in early ischemic cardiomyocytes.

Morphometric and Microscopic Analysis

Quantitative morphometric analysis was conducted using digital microscopy and image analysis software. Parameters such as **cell diameter, nuclear morphology, area of necrotic tissue, and collagen density** were measured and compared across the different stages of ischemia. High-resolution light microscopy was complemented by electron microscopy in selected samples, providing ultrastructural details of mitochondrial swelling, myofibril disruption, and sarcolemma integrity.

Data Analysis and Statistical Evaluation

Morphometric data were statistically analyzed to identify significant differences between early, intermediate, and late ischemic stages. Standard statistical tests, including ANOVA and post-hoc comparisons, were used to quantify morphological changes and validate observations. This rigorous approach ensured that the conclusions drawn were based on objective measurements rather than subjective interpretation.

Ethical Considerations

All procedures adhered to ethical guidelines for the use of human and animal tissue in research. Informed consent was obtained where applicable, and all experiments were conducted in accordance with institutional and international standards for biomedical research.

Through this structured methodology, the study achieved a reliable and detailed characterization of myocardial morphological alterations, providing a foundation for the comparative analysis presented in the subsequent sections.

ANALYSIS AND RESULTS

The comparative analysis of myocardial tissue samples across early, intermediate, and late stages of ischemia reveals a clear, time-dependent progression of structural changes. These transformations reflect underlying biochemical and physiological disturbances caused by inadequate coronary blood flow. The findings of this study, supported by histological,

ultrastructural, and morphological observations, demonstrate how myocardial injury evolves from reversible cellular dysfunction to irreversible damage, culminating in scar formation and chronic remodeling.

Early Stage of Ischemia (0–6 Hours)

In the early phase of ischemia, myocardial tissue exhibits predominantly reversible alterations. Microscopic examination shows **cellular swelling**, loss of normal **cross-striations**, and mild **interstitial edema**, indicating disturbances in ion pump function and membrane permeability. Mitochondrial swelling is consistently observed, reflecting the rapid depletion of ATP and impairment of oxidative phosphorylation. At this stage, nuclei remain intact, and the overall architecture of cardiomyocytes is preserved.

Ultrastructural analysis confirms **mitochondrial edema**, rarefaction of cristae, and early formation of amorphous densities. The sarcolemmal membrane becomes slightly irregular, although overt membrane rupture is not yet evident. These findings align with the concept that early ischemic damage is largely reversible if prompt reperfusion is achieved.
The metabolic shift toward anaerobic glycolysis and subsequent lactate accumulation correlate with the morphological features documented in this phase.

Intermediate Stage of Ischemia (6–24 Hours)

The intermediate stage marks the transition from reversible injury to **irreversible cellular damage**. Histological evaluation reveals the presence of **coagulative necrosis**, which is characterized by hypers eosinophilic cytoplasm, nuclear condensation (pyknosis), fragmentation (karyorrhexis), and eventual dissolution (karyolysis).
A hallmark finding in this period is the appearance of **contraction band necrosis**, reflecting calcium influx and hypercontracture of myofibrils. The structural integrity of the sarcolemma begins to deteriorate, leading to leakage of intracellular enzymes—correlating with elevated serum biomarkers such as cardiac troponins.
Inflammatory changes also become pronounced. **Neutrophil infiltration** increases significantly, with polymorphonuclear leukocytes accumulating around necrotic fibers. Their proteolytic activity contributes to further cellular degradation. This stage demonstrates a critical turning point: the distinction between surviving and non-viable myocardial cells becomes clear through both morphological and biochemical evidence.

Late Stage of Ischemia (>24 Hours)

In the late phase of ischemia, the myocardium undergoes substantial structural remodeling. Necrotic fibers are gradually removed and replaced by inflammatory and reparative cells. Histological analysis shows abundant **macrophages**, which play a crucial role in phagocytosing necrotic debris. This cleanup process is accompanied by infiltration of lymphocytes and activation of endothelial cells within the microvasculature.
One of the most significant findings in this stage is the proliferation of fibroblasts. These cells synthesize increasing amounts of **collagen**, leading to the development of **fibrosis** and eventual scar tissue formation. The collagen network progressively replaces dead cardiomyocytes, resulting in the loss of contractile elements and permanent reduction of myocardial elasticityandfunction.

In the final phase of remodeling, areas of fibrosis become well-demarcated and may appear as pale, firm regions on gross examination. Microscopically, dense collagen bundles dominate the affected region, indicating the completion of the healing process. While structurally stabilizing, this fibrotic transformation contributes to long-term complications such as ventricular remodeling, reduced ejection fraction, arrhythmias, and heart failure.

Comparative Findings

The comparative analysis highlights a consistent and predictable morphological progression:

1. **Early ischemia:** reversible injury dominated by cellular swelling and mitochondrial dysfunction
2. **Intermediate ischemia:** onset of irreversible necrosis and robust inflammatory response

3. **Late ischemia:** fibroblast activation, collagen deposition, and permanent scar formation

These findings confirm that the **duration of ischemia** is the most significant determinant of myocardial structural outcome. The transition from viability to necrosis occurs rapidly

CONCLUSION AND RECOMMENDATIONS

Myocardial ischemia follows a well-defined and predictable sequence of morphological changes, beginning with reversible cellular alterations, progressing to irreversible necrosis, and culminating in fibrotic remodeling and scar formation. This study's comparative analysis of early, intermediate, and late ischemic stages confirms that the **duration and severity of ischemia** are the primary determinants of structural damage, functional impairment, and long-term cardiac outcomes. Early-stage injury, characterized by cellular swelling and mitochondrial dysfunction, remains potentially reversible if prompt reperfusion and therapeutic interventions are implemented. Conversely, prolonged ischemia leads to coagulative necrosis, inflammatory infiltration, and eventual fibrotic replacement of necrotic tissue, which permanently compromises myocardial contractility.The findings highlight several key implications for clinical practice and future . First, early detection of ischemia using diagnostic modalities such as electrocardiography, serum biomarkers, and advanced imaging is crucial for limiting irreversible damage. Second, timely reperfusion therapies, including percutaneous coronary intervention and thrombolysis, are essential to restore oxygen supply before the transition to irreversible injury. Third, post-ischemic management should focus on minimizing adverse remodeling through pharmacological agents such as ACE inhibitors, beta-blockers, and anti-inflammatory therapies, which can modulate fibrosis and improve long-term cardiac function. From a research perspective, detailed understanding of the morphological evolution of ischemic myocardium provides valuable insight for the development of targeted therapies. For instance, interventions aimed at stabilizing mitochondrial function, reducing oxidative stress, or modulating inflammatory pathways could potentially extend the window of myocardial viability. Furthermore, integrating histopathological observations with clinical imaging and biomarker data can enhance the precision of risk stratification, guide individualized treatment, and improve prognostic assessment. In conclusion, the predictable pattern of myocardial morphological changes underscores the importance of rapid diagnosis, early intervention, and comprehensive post-ischemic care. By understanding the sequential structural alterations of the myocardium, clinicians and researchers can optimize therapeutic strategies, minimize irreversible damage, and improve patient outcomes in ischemic heart disease.

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