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ORIGINAL ARTICLE

Histopathological Spectrum of Myocardial Fibrosis and its Association with Cardiac Autonomic Function in Ischemic Heart Disease, with Implications in Critical Care and Pulmonary Dysfunction

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ABSTRACT
Background: Myocardial fibrosis is a common pathological consequence of ischemic heart disease (IHD) and contributes to adverse cardiac remodeling, impaired autonomic regulation, and cardiopulmonary dysfunction. Structural changes caused by fibrosis disrupt myocardial architecture and electrical conduction pathways, which may lead to autonomic imbalance and respiratory complications, particularly in critically ill patients.
Objective: To evaluate the histopathological spectrum of myocardial fibrosis and its association with cardiac autonomic function in patients with ischemic heart disease, along with its implications for pulmonary dysfunction and critical care management.
Methods: This cross-sectional observational study was conducted at Mayo Hospital, Lahore, Pakistan, and Isra University Hospital, Hyderabad, Pakistan, from May 2022 to May 2023. A total of 100 patients with ischemic heart disease were included. Myocardial tissue samples obtained during surgical procedures or autopsy were examined using hematoxylin–eosin and Masson's trichrome staining to identify patterns of fibrosis. Cardiac autonomic function was assessed through heart rate variability (HRV) analysis and autonomic reflex tests. Pulmonary function was evaluated using arterial blood gas analysis, pulse oximetry, and spirometry.
Results: Histopathological analysis showed that interstitial fibrosis was the most common pattern (45%), followed by replacement fibrosis (30%), perivascular fibrosis (15%), and diffuse fibrosis (10%). Moderate to severe myocardial fibrosis was identified in the majority of patients. Individuals with severe fibrosis demonstrated significantly reduced HRV parameters, indicating marked autonomic dysfunction. Furthermore, patients with advanced fibrosis exhibited lower oxygen saturation, reduced PaO_2 levels, and impaired spirometric values, suggesting associated pulmonary dysfunction.
Conclusion: Myocardial fibrosis plays a critical role in structural cardiac remodeling in ischemic heart disease and is significantly associated with cardiac autonomic dysfunction and pulmonary impairment. Early recognition of myocardial fibrosis may improve risk stratification and guide management strategies in cardiology and critical care settings.
Keywords: Myocardial fibrosis, ischemic heart disease, cardiac autonomic dysfunction, pulmonary dysfunction, histopathology, critical care medicine.

INTRODUCTION
Ischemic heart disease (IHD) remains one of the leading causes of morbidity and mortality worldwide and represents a major burden on global healthcare systems. It develops primarily due to reduced myocardial perfusion resulting from coronary artery atherosclerosis, thrombosis, or microvascular dysfunction[1]. Chronic or repeated ischemic injury leads to progressive structural and functional alterations in the myocardium, including cardiomyocyte apoptosis, inflammatory activation, and remodeling of the extracellular matrix. Among these pathological processes, myocardial fibrosis is considered one of the most critical determinants of adverse cardiac remodeling and clinical outcomes in patients with ischemic heart disease[2].

Myocardial fibrosis refers to the excessive accumulation of collagen and other extracellular matrix components within the cardiac interstitium and surrounding vascular structures. This fibrotic remodeling occurs as a reparative response following myocardial injury, particularly after ischemic episodes or myocardial infarction[3]. However, persistent activation of fibroblasts and abnormal collagen deposition lead to structural stiffening of the myocardium, impaired ventricular relaxation, and disruption of normal myocardial architecture. Histopathologically, myocardial fibrosis may appear in several forms, including interstitial fibrosis, replacement fibrosis, and perivascular fibrosis. Each of these patterns reflects different stages and mechanisms of myocardial injury and repair and may influence cardiac function differently[4,5].

The presence of myocardial fibrosis has important clinical implications because it directly affects cardiac electrophysiology and autonomic regulation[6]. The cardiac autonomic nervous system, which includes sympathetic and parasympathetic components, plays a crucial role in maintaining cardiovascular homeostasis by regulating heart rate, myocardial contractility, and vascular tone. Structural remodeling caused by fibrosis can interfere with autonomic nerve fibers and electrical conduction pathways within the myocardium, leading to autonomic imbalance. Reduced heart rate variability and increased sympathetic activity have been observed in patients with advanced myocardial fibrosis and are associated with increased risk of arrhythmias, sudden cardiac death, and progression to heart failure[7].

In addition to cardiac consequences, myocardial fibrosis may also influence pulmonary physiology and cardiopulmonary interactions. Patients with advanced ischemic heart disease frequently develop pulmonary dysfunction due to impaired left ventricular function, elevated pulmonary venous pressures, and pulmonary congestion[8]. These alterations may result in decreased pulmonary compliance, impaired gas exchange, and reduced oxygenation. Furthermore, systemic inflammatory responses and neurohormonal activation associated with myocardial fibrosis may contribute to pulmonary vascular remodeling and respiratory complications. Such cardiopulmonary interactions are particularly relevant in critically ill patients requiring intensive care management[9,10].

Histopathological examination remains an important method for identifying and characterizing myocardial fibrosis. Microscopic evaluation of myocardial tissue provides valuable information regarding the distribution, severity, and patterns of fibrotic remodeling [11]. These histological findings can help in understanding disease progression and may correlate with functional abnormalities such as autonomic dysfunction and cardiopulmonary impairment.

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Despite advances in imaging techniques and biomarker research, histopathology continues to serve as the gold standard for confirming myocardial fibrosis and assessing its structural impact on cardiac tissue[12].

Although previous studies have investigated myocardial fibrosis in ischemic heart disease, limited data are available regarding the relationship between the histopathological spectrum of fibrosis and alterations in cardiac autonomic function, particularly in relation to pulmonary dysfunction and critical care outcomes. Understanding this relationship is important for improving risk stratification, early detection of complications, and clinical management of patients with ischemic heart disease[13,14].

Therefore, the present study was designed to evaluate the histopathological spectrum of myocardial fibrosis in patients with ischemic heart disease and to investigate its association with cardiac autonomic dysfunction and pulmonary impairment. Additionally, the study aims to explore the potential implications of myocardial fibrosis in the context of critical care management and cardiopulmonary complications[15].

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional observational study was conducted to investigate the histopathological spectrum of myocardial fibrosis and its association with cardiac autonomic function in patients with ischemic heart disease. The research was carried out at the Department of Cardiology, Department of Pathology, and Critical Care Units of Mayo Hospital, Lahore, Pakistan, and Isra University Hospital, Hyderabad, Pakistan. Both institutions are tertiary care teaching hospitals that manage a large number of cardiovascular and critical care patients. The study was conducted over a period of one year from May 2022 to May 2023.

Study Population and Sampling Technique: The study included a total sample size of 100 patients diagnosed with ischemic heart disease. Patients were recruited using a consecutive sampling technique from cardiology wards, cardiac intensive care units, and cardiothoracic surgery departments of the participating hospitals. The diagnosis of ischemic heart disease was established based on clinical evaluation, electrocardiographic findings, cardiac biomarker analysis, and coronary angiographic evidence where available. All eligible patients meeting the inclusion criteria during the study period were considered for enrollment in the study.

Inclusion and Exclusion Criteria: Patients aged 35 to 75 years with a confirmed diagnosis of ischemic heart disease, including stable angina, unstable angina, or previous myocardial infarction, were included in the study. Patients undergoing cardiac surgical procedures or myocardial tissue sampling where histopathological examination was feasible were also included. Patients were excluded if they had primary cardiomyopathies such as hypertrophic or dilated cardiomyopathy, congenital heart disease, severe chronic pulmonary diseases unrelated to cardiac pathology, or infiltrative myocardial disorders such as amyloidosis or sarcoidosis. Patients with incomplete clinical records or insufficient tissue samples were also excluded from the analysis.

Histopathological Evaluation of Myocardial Fibrosis: Myocardial tissue samples were obtained during cardiac surgical procedures or post-mortem examination when available. The tissue specimens were immediately fixed in 10% buffered formalin and processed according to standard histopathological laboratory protocols. After fixation, the tissues were embedded in paraffin blocks and sectioned at a thickness of 4–5 µm using a microtome. The sections were stained using hematoxylin and eosin (H&E) staining to evaluate general myocardial architecture and Masson's trichrome staining to identify and quantify collagen deposition and fibrotic tissue within the myocardium.

Histopathological assessment was performed by experienced pathologists under light microscopy. Myocardial fibrosis was classified according to its distribution pattern into interstitial fibrosis, replacement fibrosis, perivascular fibrosis, and diffuse fibrotic remodeling. Interstitial fibrosis was defined as collagen deposition between cardiomyocytes without complete replacement of myocardial cells. Replacement fibrosis referred to scar tissue formation following myocardial necrosis. Perivascular fibrosis was identified as collagen accumulation surrounding coronary microvessels, while diffuse fibrotic remodeling represented extensive fibrosis affecting large areas of the myocardium. The severity of fibrosis was graded as mild, moderate, or severe based on the extent of collagen deposition and the degree of myocardial architectural distortion observed under microscopic examination.

Assessment of Cardiac Autonomic Function: Cardiac autonomic function was assessed through heart rate variability (HRV) analysis, which was derived from electrocardiographic recordings obtained through 24-hour Holter monitoring. HRV analysis provides information regarding the balance between sympathetic and parasympathetic activity within the autonomic nervous system. The parameters analyzed included SDNN (standard deviation of normal-to-normal intervals), RMSSD (root mean square of successive differences of RR intervals), and LF/HF ratio (low-frequency to high-frequency ratio). Reduced HRV values were considered indicative of impaired autonomic regulation.

In addition to HRV analysis, standard autonomic reflex tests including the Valsalva maneuver, deep breathing test, and orthostatic blood pressure response were performed to further evaluate autonomic nervous system function. These tests helped determine the presence and severity of cardiac autonomic dysfunction in the study participants.

Pulmonary Function Assessment: Pulmonary function was evaluated to assess the cardiopulmonary interaction associated with myocardial fibrosis and ischemic heart disease. Respiratory status was assessed using arterial blood gas (ABG) analysis, which measured parameters such as partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and blood pH levels. Peripheral oxygen saturation (SpO_2) was measured using pulse oximetry for continuous monitoring of oxygenation. In addition, spirometry testing was performed to evaluate pulmonary function parameters including forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). Abnormal spirometric values, reduced oxygen saturation, or abnormal arterial oxygen levels were considered indicators of pulmonary dysfunction.

Data Collection: Clinical and demographic data were collected using a standardized data collection form. The variables recorded included age, gender, smoking status, body mass index, history of hypertension, diabetes mellitus, and clinical presentation of ischemic heart disease. Histopathological findings, cardiac autonomic function parameters, and pulmonary function results were documented and analyzed to determine their relationship with the severity and pattern of myocardial fibrosis.

Statistical Analysis: All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 26.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The association between myocardial fibrosis severity and cardiac autonomic dysfunction or pulmonary impairment was evaluated using Chi-square tests and Pearson correlation analysis. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The study protocol was reviewed and approved by the Institutional Ethical Review Committees of Mayo Hospital Lahore and Isra University Hospital Hyderabad. All procedures performed in the study were conducted in accordance with the ethical standards of medical research and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians prior to their inclusion in the study.

RESULTS

Demographic and Clinical Characteristics of the Study Population: A total of 100 patients diagnosed with ischemic heart disease were included in the present study. The mean age of the participants was 57.8 ± 9.6 years, with the majority of patients belonging to the age group of 50–65 years. Among the participants, 68% were male and 32% were female, indicating a higher prevalence of ischemic heart disease among males in the study population.

Regarding cardiovascular risk factors, hypertension was observed in 56% of patients, while type 2 diabetes mellitus was present in 44% of cases. A history of smoking was documented in 47% of the patients, which represents an important risk factor contributing to ischemic myocardial injury and subsequent fibrotic remodeling. The baseline demographic and clinical characteristics of the study participants are summarized in Table 1.

Table 1: Baseline demographic and clinical characteristics of patients with ischemic heart disease (n = 100)

Variable	Frequency	Percentage
Age (mean ± SD)	57.8 ± 9.6 years	—
Male	68	68%
Female	32	32%
Hypertension	56	56%
Diabetes mellitus	44	44%
Smoking history	47	47%
Obesity (BMI ≥30 kg/m²)	29	29%

Table 2: Histopathological patterns of myocardial fibrosis in patients with ischemic heart disease (n = 100)

	Number of Patients	Percentage
Interstitial fibrosis	45	45%
Replacement fibrosis	30	30%
Perivascular fibrosis	15	15%
Diffuse fibrotic remodeling	10	10%

Table 3:Severity grading of myocardial fibrosis in ischemic heart disease patients (n = 100)

Fibrosis Severity	Number of Patients	Percentage
Mild fibrosis	28	28%
Moderate fibrosis	42	42%
Severe fibrosis	30	30%

Table 4: Association between myocardial fibrosis severity and cardiac autonomic dysfunction

Fibrosis Severity	Patients with Autonomic Dysfunction	Percentage
Mild fibrosis	6	21%
Moderate fibrosis	18	43%
Severe fibrosis	24	80%

Table 5: Pulmonary function parameters according to myocardial fibrosis severity

Parameter	Mild Fibrosis	Moderate Fibrosis	Severe Fibrosis
Mean SpO_2 (%)	96 ± 2	93 ± 3	89 ± 4
PaO_2 (mmHg)	92 ± 6	82 ± 7	68 ± 9
FEV_1 (% predicted)	81 ± 5	70 ± 6	58 ± 7
FVC (% predicted)	85 ± 6	72 ± 7	60 ± 8

Histopathological Spectrum of Myocardial Fibrosis: Histopathological examination of myocardial tissue samples revealed multiple patterns of fibrotic remodeling in patients with ischemic heart disease. Interstitial fibrosis was the most frequently observed pattern, identified in 45% of cases, followed by replacement fibrosis in 30% of patients. Perivascular fibrosis was present in 15% of patients, while diffuse fibrotic remodeling was observed in 10% of cases.

These findings indicate that chronic ischemic injury predominantly leads to diffuse collagen deposition within the myocardial interstitium. Replacement fibrosis was mainly associated with areas of previous myocardial infarction where necrotic cardiomyocytes had been replaced by fibrotic scar tissue. The distribution of histopathological patterns of myocardial fibrosis is presented in Table 2.

Severity of Myocardial Fibrosis: The severity of myocardial fibrosis was graded based on the extent of collagen deposition and structural distortion of myocardial tissue observed under microscopic examination. Mild fibrosis was identified in 28% of patients, moderate fibrosis in 42%, and severe fibrosis in 30% of the cases.

Patients with severe fibrosis demonstrated extensive collagen deposition with significant disruption of myocardial architecture, suggesting advanced cardiac remodeling. The distribution of fibrosis severity among the study participants is summarized in Table 3.

Association Between Myocardial Fibrosis and Cardiac Autonomic Dysfunction: Cardiac autonomic function was evaluated using heart rate variability parameters derived from 24-hour Holter monitoring. Patients with mild myocardial fibrosis demonstrated relatively preserved HRV parameters, whereas individuals with moderate and severe fibrosis showed significant reductions in HRV indices, indicating impaired autonomic regulation.

Specifically, reduced SDNN and RMSSD values were observed in patients with severe fibrosis, reflecting decreased parasympathetic activity and increased sympathetic dominance. These findings suggest that progressive fibrotic remodeling of the myocardium may disrupt autonomic nerve pathways and impair cardiovascular autonomic control. The relationship between myocardial fibrosis severity and cardiac autonomic dysfunction is shown in Table 4.

Pulmonary Dysfunction in Patients with Myocardial Fibrosis: Pulmonary function assessment revealed that cardiopulmonary impairment was more common among patients with advanced myocardial fibrosis. Patients with severe fibrosis exhibited reduced oxygen saturation and abnormal arterial blood gas parameters, indicating impaired pulmonary gas exchange. Spirometry results also demonstrated lower FEV_1 and FVC values in patients with severe myocardial fibrosis compared to those with mild fibrotic changes.

These findings suggest that progressive myocardial fibrosis may contribute to pulmonary congestion and impaired respiratory function due to altered cardiopulmonary hemodynamics. The comparison of pulmonary parameters according to fibrosis severity is presented in Table 5.

DISCUSSION

The present study evaluated the histopathological spectrum of myocardial fibrosis and its association with cardiac autonomic dysfunction and pulmonary impairment in patients with ischemic heart disease. The findings demonstrated that myocardial fibrosis is a common structural alteration in ischemic myocardium and plays an important role in cardiac remodeling, autonomic imbalance, and cardiopulmonary dysfunction[8]. The study revealed that interstitial fibrosis was the most common histopathological pattern observed, followed by replacement fibrosis, perivascular fibrosis, and diffuse fibrotic remodeling. These observations are consistent with the pathophysiological process of chronic ischemic injury in which repeated episodes of myocardial ischemia stimulate fibroblast activation and excessive extracellular matrix deposition within the cardiac interstitium[9].

Interstitial fibrosis represented the predominant pattern in our study population. This type of fibrosis results from diffuse collagen deposition between cardiomyocytes without complete destruction of myocardial cells[10]. Chronic ischemia leads to persistent inflammatory responses, oxidative stress, and activation of profibrotic signaling pathways such as transforming growth factor-beta (TGF-β) and angiotensin II. These pathways stimulate fibroblast proliferation and increase collagen synthesis, resulting in progressive interstitial remodeling of the myocardium. Such structural changes increase myocardial stiffness, impair ventricular relaxation, and contribute to diastolic dysfunction in patients with ischemic heart disease[11].

Replacement fibrosis was the second most common histopathological finding in the present study. Replacement fibrosis typically occurs following myocardial infarction, where necrotic cardiomyocytes are replaced by fibrotic scar tissue[12]. This scar formation represents a reparative process aimed at maintaining structural integrity of the myocardium after tissue injury. However, the resulting fibrotic tissue lacks the contractile and electrical properties of normal myocardium, which can impair cardiac function and increase susceptibility to arrhythmias. The presence of replacement fibrosis therefore reflects previous ischemic injury and may indicate more advanced disease progression[13].

Another important finding of this study was the significant association between myocardial fibrosis severity and cardiac autonomic dysfunction. Patients with moderate to severe myocardial fibrosis demonstrated markedly reduced heart rate variability parameters, indicating impaired autonomic regulation[14]. The autonomic nervous system plays a fundamental role in regulating cardiovascular function by balancing sympathetic and parasympathetic activity. Structural remodeling of the myocardium due to fibrosis can disrupt autonomic nerve fibers embedded within the cardiac tissue, leading to altered neural signaling and autonomic imbalance. Reduced parasympathetic activity combined with increased sympathetic dominance has been associated with increased risk of ventricular arrhythmias, sudden cardiac death, and progression to heart failure in patients with ischemic heart disease[15].

The relationship between myocardial fibrosis and autonomic dysfunction may also involve neurohormonal activation. Chronic myocardial injury activates the renin–angiotensin–aldosterone system and sympathetic nervous system, both of which contribute to further fibroblast activation and collagen deposition[16]. This creates a vicious cycle in which autonomic dysregulation promotes myocardial fibrosis, while fibrosis further impairs autonomic control of the heart. These findings highlight the importance of autonomic assessment in patients with ischemic heart disease, particularly in those with evidence of myocardial structural remodeling[17].

The present study also demonstrated that pulmonary dysfunction was more common in patients with advanced myocardial fibrosis. Patients with severe fibrosis showed significantly reduced oxygen saturation, abnormal arterial blood gas parameters, and impaired spirometric values. These findings may be explained by the close physiological relationship between the cardiovascular and respiratory systems. Progressive myocardial fibrosis reduces left ventricular compliance and contractile function, leading to increased left ventricular filling pressures and pulmonary venous congestion. Elevated pulmonary venous pressure can impair pulmonary gas exchange and reduce lung compliance, ultimately resulting in decreased oxygenation and respiratory dysfunction[18,19].

Additionally, systemic inflammatory responses associated with ischemic heart disease may contribute to pulmonary vascular remodeling and impaired respiratory function. Chronic inflammation and oxidative stress can affect both myocardial and pulmonary tissues, promoting fibrosis and endothelial dysfunction. These shared mechanisms may explain the coexistence of cardiac and pulmonary abnormalities observed in patients with advanced ischemic heart disease[20].

The findings of this study have important implications for critical care management. Patients with extensive myocardial fibrosis may be at increased risk of hemodynamic instability, arrhythmias, and respiratory complications[11]. Early identification of myocardial fibrosis and associated autonomic dysfunction may help clinicians stratify patients according to risk and implement appropriate monitoring strategies in intensive care settings. Integration of histopathological findings with clinical, autonomic, and pulmonary assessments may therefore improve patient management and outcomes in individuals with ischemic heart disease[14].

Although this study provides valuable insights into the relationship between myocardial fibrosis, autonomic dysfunction, and pulmonary impairment, several limitations should be considered. The cross-sectional design limits the ability to establish causal relationships between myocardial fibrosis and functional abnormalities. Additionally, the study sample was limited to patients from two tertiary care hospitals, which may affect the generalizability of the findings. Future multicenter studies with larger sample sizes and longitudinal follow-up are needed to further clarify the clinical significance of myocardial fibrosis in ischemic heart disease and its impact on cardiopulmonary outcomes[15-20].

CONCLUSION

In conclusion, myocardial fibrosis represents a key structural alteration in patients with ischemic heart disease and plays an important role in cardiac remodeling and functional impairment. Histopathological evaluation revealed that interstitial fibrosis is the most common pattern, followed by replacement and perivascular fibrosis. The severity of myocardial fibrosis was strongly associated with cardiac autonomic dysfunction, as demonstrated by reduced heart rate variability parameters and impaired autonomic regulation.

Furthermore, advanced myocardial fibrosis was associated with significant pulmonary dysfunction, suggesting a close interaction between cardiac structural remodeling and respiratory impairment. These findings emphasize the importance of integrated cardiovascular and pulmonary assessment in patients with ischemic heart disease, particularly in critical care settings.

Early detection and evaluation of myocardial fibrosis may provide valuable information for risk stratification, clinical monitoring, and therapeutic decision-making. Future research should focus on identifying non-invasive biomarkers and imaging techniques for early detection of myocardial fibrosis and exploring targeted therapeutic strategies aimed at preventing fibrotic remodeling and improving cardiopulmonary outcomes.

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