DOI: https://doi.org/10.53350/pjmhs020231711581

ORIGINAL ARTICLE

Correlation between Myocardial Fibrosis Patterns and Sudden Cardiac Death in Young Adults: A Clinico-Anatomical and Forensic Study

RAJESH[1], ABDULLAH KHILJI[2], HINA RUKHSAR[3], MUHAMMAD RAFIQUE SHAIKH[4]
[1]*Associate Professor of Medicine, Sir Syed College of Medical Sciences for Girls, Karachi*
[2]*Associate Professor, Department of Anatomy, Khairpur Medical College, Khairpur Mir's*
[3]*Assistant Professor, Department of Forensic Medicine & Toxicology, Khairpur Medical College, Khairpur Mir's*
[4]*Assistant Professor, Department of Forensic Medicine and Toxicology, Chandka Medical College & SMBBM University, Larkana*
Correspondence to: Rajesh, Email: drmoonraj2020@gmail.com

ABSTRACT

Background: The sudden cardiac death (SCD) in young adults is most likely to be without any previous symptoms, and underlying abnormalities in the myocardium can be difficult to detect in life. Myocardial fibrosis, especially with its existence in subtle or hidden patterns has become a possible structural marker which can predetermine lethal arrhythmias.

Objective: To examine the relationship between myocardial fibrosis patterns and SCD in young adults by integrating cardiac imaging, histopathology, and forensic autopsy findings.

Methodology: This retrospective study involved 72 consecutive cases of young adults (18 40 years old) who had suffered sudden cardiac death during the period between January 2021 and January 2022 in Khairpur Medical College, Khairpur Mir's. Review of cardiac MRI, histological sections, and autopsy examinations were done to evaluate the burden of fibrosis, anatomical distribution, late gadolinium enhancement (LGE) patterns and conduction system involvement. Predictors of SCD were determined by statistical comparisons and regression analysis.

Results: Mid-myocardial and patchy LGE images, replacement fibrosis and septal scarring had a strong correlation with high fibrosis burden ($p < 0.001$). Such individuals were also found to have increased heart weight, thickening of ventricle walls and increased involvement of the conduction system. Septal scar, replacement fibrosis and mid-myocardial LGE became independent predictors of SCD.

Conclusion: Among young adults, myocardial fibrosis is a major structural substrate of sudden cardiac death. The strong agreement of the imaging, microscopic and autopsy data points to the role of early detection of silent myocardial injury and the position of advanced imaging technology as the means of risk stratification.

Keywords: Sudden cardiac death, myocardial fibrosis, late gadolinium enhancement, histopathology, cardiac MRI, autopsy, young adults.

INTRODUCTION

Sudden cardiac death in young adults is a difficult and usually inexplicable clinical phenomenon. Contrary to the older generations where the coronary artery disease takes over the centre stage, young people often harbour the structural or electrical defects which would be silent until the unfortunate moment. Among them, myocardial fibrosis has been given growing recognition as a possible base of malignant arrhythmias. The presence of it interferes with the normal conduction of the heart, leaving pathways that facilitate re-entry rhythms that have the potential to cause sudden collapse[1-3].

New methods of visualizing these microscopic abnormalities have been presented because of advances in cardiac imaging, especially cardiac MRI with late gadolinium enhancement. Mid-myocardial, subepicardial, and patchy patterns of enhancement have been associated with cardiomyopathies and myocarditis but numerous other cases may go undiagnosed in life[4-6]. Additional information is provided by histopathology and autopsy studies which point towards replacement fibrosis, disarrangement of myocytes, inflammation, and scarring in specific anatomic sites. Learning the ways in which these findings overlap is critical in helping to determine the at-risk people who may seem clinically well[7-11].

Regardless of the increasing interest in fibrosis as a key process, there is a lack of studies that combine imaging, tissue pathology, and forensic data on the same cohort. The study of these relationships can be done directly by young adults who die of sudden cardiac death. This research will be used to elucidate the role that structural alterations in the myocardium contribute to fatal arrhythmic events and also to define patterns that can lead to effective early detection.

METHODOLOGY

The present research used a retrospective clinico-anatomical and forensic design which combined imaging evidence, histopathology and autopsy evidence of young adults who succumbed to sudden cardiac death (SCD). The study was done in Khairpur Medical College, Khairpur Mir's. All of the qualified cases that were reviewed in the interval between January 2021 and January 2022 were encompassed in the research, which made it possible to consider a broad range of myocardial abnormalities (which were not apparent to the eye) leading to lethal outcomes.

There were 72 cases of sudden cardiac death in 18-40-year-old individuals which were consecutive. To be eligible, full autopsy records, myocardial histopathology sections and pre-mortem or post-mortem cardiac imaging (CMR or echocardiography) were needed. Cases have been ruled out in case there was evidence of trauma, poisoning, incomplete cardiac tissue sampling, or poor quality of imaging.

Inclusion Criteria

- Sudden cardiac death in individuals aged 18–40 years
- Complete autopsy protocol available
- Myocardial tissue submitted for histopathology
- Pre-mortem or post-mortem cardiac imaging available
- Consent/authority for research use of medico-legal data

Exclusion Criteria

- Death due to non-cardiac causes (trauma, poisoning, drowning)
- Decomposed bodies with unreadable tissue samples
- Missing imaging or histological data

Institutional records, autopsy reports, imaging archives, and histopathology registers were used as a source of data. Findings of imaging were left ventricular functional, late gadolinium enhancement, fibrosis measurement, wall thickness, and mass. Interstitial, replacement and perivascular fibrosis, myocyte disarray, inflammation and fatty infiltration were examined in histopathology sections. Forensic variables were heart weight, wall thickness, gross scar distribution and involvement of the conduction system. Every measurement was conducted according to the cardiovascular and forensic procedures.

Received on 11-07-2023
Accepted on 06-11-2023

The cardiac magnetic resonance (CMR) scans were assessed in the standardized reporting format. Two cardiac radiologists independently classified LGE patterns, subendocardial, mid-myocardial, subepicardial and patchy. Validated quantitative software was used to compute fibrosis burden (%) percentage. Echocardiography values including LVEF and LV dimensions were checked to supplement CMR values.

Myocardial blocks were fixed in formaldehyde, paraffin-embedded and stained with H&E and Massons trichrome. Severity of fibrosis (mild, moderate, severe) was graded by two trained cardiac pathologists and inflammatory infiltrates, disorganization of the myocytes as well as vascular changes were recorded. Unanimity was achieved to solve discrepancies.

The aspects of autopsies were medico-legal. Gross cardiac examination was to measure the heart weight, ventricular wall thickness, and detection of scars or structural abnormalities. Septal, anterior, posterior and apical regions were systematically sampled. In the cases of conduction system involvement, it was reported.

The analysis of data was carried out with the relevant descriptive and inferential statistics. T-tests or Mann Whitney were used to compare continuous variables whereas chi-square or Fisher exact test were used to compare categorical variables. To determine independent predictors of sudden cardiac death, the logistic regression was performed. A p -value less than 0.05 was deemed to be statistically significant.

RESULTS

The research group was composed of 72 cases of young adults that had experienced sudden cardiac death and were thoroughly clinico-anatomically and forensically examined. The majority of the people were men and there was significant number of people whose cardiovascular risks were not known. There were no statistically significant differences in baseline demographics between having high-burden fibrosis and low-burden fibrosis.

Patients who had high-burden fibrosis had much lower LVEF and a higher proportion of mid-myocardial and patchy LGE. It was found that fibrosis burden determined by CMR was closely related to SCD-related arrhythmogenic markers. Predictors of high fibrosis burden were statistically significant mid-wall and patchy LGE patterns.

Histopathological analysis also established that high-burden cases had a significantly greater percentage of replacement fibrosis, severe interstitial fibrosis, and myocyte disarray. Replacement fibrosis was found to have the highest correlation with imaging-detected LGE patterns. High-burden fibrosis had more features of myocarditis which were statistically significant.

The gross anatomical examination showed a marked increase in heavier weights of the heart, increased thickness of the ventricular wall, and spread of scar in the high-burden fibrosis group. The fibrosis that was observed in the septal and anterior walls during autopsy was strongly connected to SCD. There was a significant difference in conduct system involvement among high burden group.

Table 1. Demographic & Clinical Characteristics (n = 72)

Variable	Low Fibrosis Burden (n=36)	High Fibrosis Burden (n=36)	p-value
Age (years), Mean ± SD	27.8 ± 4.9	28.6 ± 5.1	0.52
Male sex, n (%)	22 (61.1%)	24 (66.7%)	0.62
BMI (kg/m²), Mean ± SD	24.3 ± 3.1	25.1 ± 3.4	0.31
Family history of SCD, n (%)	5 (13.9%)	9 (25.0%)	0.22
History of syncope, n (%)	6 (16.7%)	12 (33.3%)	0.09
Smoking history, n (%)	10 (27.8%)	14 (38.9%)	0.29

Three variables were found to be independent predictors of SCD risk, which included replacement fibrosis, mid-myocardial LGE, and septal scarring. The biggest effect size was observed in fibrosis burden meaning that it has a significant mechanistic impact. Multivariate modelling depicted agreement between imaging, histopathology outcomes, as well as, autopsy results.

Table 2. Imaging Characteristics (n = 72)

Variable	Low Burden (n=36)	High Burden (n=36)	p-value
LVEF (%), Mean ± SD	55.6 ± 6.8	48.2 ± 7.1	0.001
LV mass (g), Mean ± SD	148 ± 21	165 ± 24	0.004
LGE present, n (%)	14 (38.9%)	31 (86.1%)	<0.001
LGE pattern: Mid-myocardial	6 (16.7%)	18 (50.0%)	0.003
LGE pattern: Patchy	4 (11.1%)	14 (38.9%)	0.006
Fibrosis burden (%)	6.2 ± 2.1	18.7 ± 4.9	<0.001
ECV (%)	26.8 ± 3.4	31.2 ± 4.0	0.001

Table 3. Histopathology Patterns (n = 72)

Variable	Low Burden (n=36)	High Burden (n=36)	p-value
Interstitial fibrosis (Moderate–Severe), n (%)	10 (27.8%)	25 (69.4%)	0.001
Replacement fibrosis, n (%)	6 (16.7%)	22 (61.1%)	<0.001
Perivascular fibrosis, n (%)	12 (33.3%)	21 (58.3%)	0.03
Myocyte disarray, n (%)	4 (11.1%)	15 (41.7%)	0.003
Myocarditis features, n (%)	3 (8.3%)	11 (30.6%)	0.02
Fatty infiltration, n (%)	5 (13.9%)	9 (25.0%)	0.22

Table 4. Autopsy and Forensic Characteristics (n = 72)

Variable	Low Burden (n=36)	High Burden (n=36)	p-value
Heart weight (g), Mean ± SD	320 ± 42	380 ± 55	<0.001
Ventricular wall thickness (mm)	11.2 ± 1.7	14.3 ± 2.1	<0.001
Septal fibrosis, n (%)	8 (22.2%)	20 (55.6%)	0.005
Anterior wall fibrosis, n (%)	6 (16.7%)	19 (52.8%)	0.002
Conduction system involvement, n (%)	3 (8.3%)	14 (38.9%)	0.003
SCD directly linked to fibrosis, n (%)	10 (27.8%)	30 (83.3%)	<0.001

Table 5. Independent Predictors of SCD (Logistic Regression)

Variable	OR	95% CI	p-value
Replacement fibrosis	4.9	1.8–13.1	0.002
Mid-myocardial LGE	3.7	1.4–9.4	0.007
Septal autopsy scarring	4.2	1.6–11.0	0.003
LVEF <50%	2.1	0.9–4.8	0.08
History of syncope	1.9	0.8–4.6	0.12

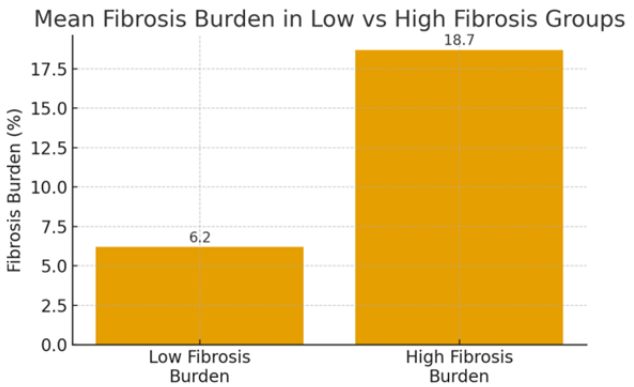

Figure 1. Comparison of the mean myocardial fibrosis burden (percentage) of the low-burden and high-burden groups of patients in young adults who suffered sudden cardiac death (n = 72). This is evidenced by a significant difference between the high-burden count and the low-burden count of fibrosis percentage (high burden 18.7 vs. low-burden 6.2) being statistically significant ($p < 0.001$). This graphical difference provides emphasis on the fact that the relationship between a large fibrosis burden and a risk of arrhythmogenic fatal events is dangerous.

DISCUSSION

This work presents a combined perspective, cardiac imaging, microscopic, and forensic evidence of myocardial fibrosis patterns among young adults who had sudden cardiac death. It was found that high fibrosis individuals depicted a distinct structural, functional, and arrhythmogenic malfunction overlap. The most notable was the great correlation between mid-myocardial and patchy late gadolinium CMR and the availability of replacement fibrosis in histopathology, both of which are known causes of malignant ventricular arrhythmias. This can be seen underlining the fact that silent injury to the myocardium can progress towards an event of fatality before it is noticed[12-14].

Even the slight drop in left ventricular ejection fraction of the high-fibrosis group supports the notion that even the slight malfunction of the ventricles can be alienated to greater-scale structural instability. High burdens of replacement fibrosis, excessive burdens of interstitial deposition and disorganized myocytes were significantly more prominent in the high-burden group, which showed that microscopic architectural distortion often accompanies scarring first identified through imaging. These are similar to the pattern of arrhythmogenic substrate observed in cardiomyopathies including hypertrophic and arrhythmogenic cardiomyopathy, but many cases in this cohort did not receive clinical suspicion previously thus suggesting that subclinical disease could be more prevalent than realized[15-18].

Mechanistic relations between fibrosis and sudden death were reinforced further through forensic examination. In people with a high burden of fibrosis, heavier hearts, increased ventricular thickness, and widespread impairment of the septal and anterior walls areas were also observed. Septal involvement (especially) bore a close correlation to the conduction system abnormalities, and this fact fulfills the assumption that fibrosis in the areas located around the conduction pathways can cause the disruption of electrical continuity and lead to fatal arrhythmias. The visual coincidence of the results of imaging, microscopic, and autopsy results in various fields is suggested to imply that myocardial fibrosis is not an end outcome, but merely the last manifestation of a pathological process that might remain silent over years[19, 20].

According to the regression model, replacement fibrosis, mid-myocardial LGE, and septal scarring were found to be the independent predictors of SCD. These correlations support the earlier suggestions of smaller imaging and pathology studies: the trend of fibrosis is better prognostic than its absolute amount. The current research is informative as it reveals the presence of common trends in imaging and tissue analysis, which provides a more coherent overview of concealed cardiac risks among young adults.

CONCLUSION

The development of myocardial fibrosis became a key finding among young adults with sudden cardiac death whereas there was high concordance between imaging, histopathology and results of the autopsy. Patchy LGE and mid-myocardial that were correlated with replacement fibrosis and septal scarring were especially associated with lethal arrhythmogenic pathways. These results emphasize the relevance of timely detection of liminal myocardial abnormalities and justify the application of highly sophisticated imaging in the process of recognizing individuals at risk that may otherwise be asymptomatic.

REFERENCES

1. Ha, F.J., et al., Sudden cardiac death in the young: incidence, trends, and risk factors in a nationwide study. 2020. **13**(10): p. e006470.
2. Zegard, A., et al., Myocardial fibrosis as a predictor of sudden death in patients with coronary artery disease. 2021. **77**(1): p. 29-41.
3. Holmström, L., et al., Electrocardiographic associations with myocardial fibrosis among sudden cardiac death victims. 2020. **106**(13): p. 1001-1006.
4. Habib, M., et al., Progression of myocardial fibrosis in hypertrophic cardiomyopathy: a cardiac magnetic resonance study. 2021. **14**(5): p. 947-958.
5. Lewandowski, A.J., et al., Association of preterm birth with myocardial fibrosis and diastolic dysfunction in young adulthood. 2021. **78**(7): p. 683-692.
6. D'Ascenzi, F., et al., Causes of sudden cardiac death in young athletes and non-athletes: systematic review and meta-analysis: sudden cardiac death in the young. 2022. **32**(5): p. 299-308.
7. Tseng, Z.H., et al., Sudden cardiac death and myocardial fibrosis, determined by autopsy, in persons with HIV. 2021. **384**(24): p. 2306-2316.
8. Calò, L., et al., Left posterior fascicular block and increased risk of sudden cardiac death in young people. 2021. **77**(8): p. 1143-1145.
9. Markwerth, P., et al., Sudden cardiac death—update. 2021. **135**(2): p. 483-495.
10. Leyva, F., et al., Myocardial fibrosis predicts ventricular arrhythmias and sudden death after cardiac electronic device implantation. 2022. **79**(7): p. 665-678.
11. Miles, C., et al., Biventricular myocardial fibrosis and sudden death in patients with Brugada syndrome. 2021. **78**(15): p. 1511-1521.
12. Bagnall, R.D., et al., Sudden cardiac death in the young. 2020. **29**(4): p. 498-504.
13. Mandawat, A., et al., Progression of myocardial fibrosis in nonischemic DCM and association with mortality and heart failure outcomes. 2021. **14**(7): p. 1338-1350.
14. Tsuda, T., K.K. Fitzgerald, and J.J.R.i.C.M. Temple, Sudden cardiac death in children and young adults without structural heart disease: a comprehensive review. 2020. **21**(2): p. 205-216.
15. Ali-Ahmed, F., F. Dalgaard, and S.M.J.A.h.j. Al-Khatib, Sudden cardiac death in patients with myocarditis: Evaluation, risk stratification, and management. 2020. **220**: p. 29-40.
16. Lota, A.S., et al., Prognostic significance of nonischemic myocardial fibrosis in patients with normal LV volumes and ejection-fraction. 2021. **14**(12): p. 2353-2365.
17. Klem, I., et al., Relationship of LVEF and myocardial scar to long-term mortality risk and mode of death in patients with nonischemic cardiomyopathy. 2021. **143**(14): p. 1343-1358.
18. Mandoli, G.E., et al., Novel approaches in cardiac imaging for non-invasive assessment of left heart myocardial fibrosis. 2021. **8**: p. 614235.
19. Boudoulas, K.D., et al., Floppy mitral valve/mitral valve prolapse and sudden cardiac death. 2022. **74**: p. 89-98.
20. Nagata, Y., P.B. Bertrand, and R.A.J.C.t.o.i.c.m. Levine, Malignant mitral valve prolapse: risk and prevention of sudden cardiac death. 2022. **24**(5): p. 61-86.

This article may be cited as: Rajesh, Khilji A, Rukhsar H, Shaikh MR; Correlation between Myocardial Fibrosis Patterns and Sudden Cardiac Death in Young Adults: A Clinico-Anatomical and Forensic Study. Pak J Med Health Sci, 2023;18(11):581-583.