Prevalence & Natural History of Tricuspid Regurgitation in Ischemic Mitral Regurgitation Patients

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Abstract

Background

Functional tricuspid regurgitation (FTR) is most often secondary to left-sided heart pathology involving the mitral valve. We studied the incidence, clinical impact, risk factors, and natural history of patients who developed FTR due to an ischemic cause of mitral regurgitation (IMR). We conducted a retrospective cohort study based on data collected from January 2012 to December 2014. Patients diagnosed with IMR were eligible for the study. The mean follow-up was five years.

RESULTS

The study group consisted of 134 patients with IMR divided into two groups based on FTR development (FTR vs non-FTR group). Forty patients were diagnosed with FTR (30.1%). FTR patients were older (63.0 ± 10.4 vs 57.1 ± 11.0 , respectively, $p < 0.05$) with a high incidence of previous coronary artery disease ($p < .006$). Severe IMR, high pulmonary arterial pressure (PAP), and failed revascularization were significant predictors of FTR development ($p < .001$, $p < .005$, $p < .003$, respectively). Low systolic left ventricle function was a predictor for FTR progression.

CONCLUSION

Clinical observations showed that FTR development due to IMR is common. Elderly patients with ischemic heart disease are at particularly high risk. FTR incidence and severity are directly proportional to the severity of IMR. FTR tends to deteriorate in about one-fifth of IMR patients and is mainly affected by the left ventricular systolic function.

Introduction

Acute myocardial infarction directly affects myocardium viability and functionality and leads to structural remodeling and conduction changes seen immediately after an injury. The remodeling process results in valvular dysfunction and eventually hemodynamic changes. Ischemic mitral regurgitation (IMR) is a complication observed following the remodeling of the injured left ventricle.^{1–3}

IMR is defined as mitral regurgitation following structural remodeling due to ischemic myocardial injury that is not directly related to valvular or sub-valvular pathologies such as mitral valve prolapse, endocarditis, autoimmune disease, medication, or direct radiation effect. The mechanism of IMR seems to be limited to leaflet motion, mainly due to shortening and limited relaxation of the ischemic papillary muscles. IMR is often classified as type IIIb of the Carpentier classification introduced in 1983, involving a restricted leaflet motion, most commonly the posterior leaflet.⁴ There can also be a widening of the annulus diameter of the failing LV and secondary leaflet malcoaptation. Ischemic mitral regurgitation may develop after myocardial infarction in 11–59% of patients.^{5–7}

Functional tricuspid regurgitation (FTR) is the consequence of various structural and functional changes involving the tricuspid annulus and the right ventricle. It is mostly secondary to left-sided mitral pathology in the setting of mitral regurgitation, mitral stenosis, and aortic stenosis.^{8–10} patients with FTR and IMR have a three-fold higher risk of developing heart failure and double the risk of mortality.^{11–16} The prevalence of tricuspid regurgitation in relation to mitral valve disease was described in recent studies addressing general left-sided pathology.^{17–20} The prevalence and natural history of FTR in the setting of mitral regurgitation following myocardial infarction was less known.

Methods

PLANNING OF THE STUDY

We conducted an observational cohort study using the computerized database of Emek Medical Center, a university-based secondary care center. Information regarding patient characteristics, demographic, and angiographic details were collected and analyzed using the Clalit health service database. Patients enrolled in the study were admitted to our heart institute for acute myocardial infarction from January 2012 to December 2014. Patients with primary mitral and tricuspid pathology and secondary pulmonary-related tricuspid regurgitation were excluded. The study population consisted of patients who developed mitral regurgitation following myocardial infarction. Patients were eligible for the study provided they met the inclusion criteria (Table 1s-supplementary) and had at least one transthoracic echocardiogram (TTE) at the time of hospitalization and at least one TTE during follow-up with no new MIs. The mean follow-up time was five years.

ECHOCARDIOGRAPHIC ANALYSIS

All echocardiograms were performed at the time of hospitalization using General Electric VIVID-75 s, VIVID 95, Philips CVx, and a portable bedside VIVID-1. The echocardiographic reports were prospectively reviewed independently by senior cardiologists using the Carestream Vue imaging system. In case of disagreement, an additional certified cardiologist was consulted. Echocardiographic images were assessed based on mitral and tricuspid insufficiency using an integrated approach taking into consideration valvular morphology, width of the proximal jet, color Doppler flow, jet area relative to the atrium, and hepatic and pulmonary flow patterns. LV ejection fraction (LVEF) was visually assessed (eyeball) in multiple acoustic windows and calculated using the biplane Simpson method according to the American Society of Echocardiography guidelines 2017. Systolic pulmonary artery pressures were calculated as the sum of the peak tricuspid regurgitation systolic gradient and the estimated vena cava central pressure (taking into consideration size and respiratory variation).

SAMPLE SIZE

The planned sample size is based on multiple variables such as IMR and FTR prevalence and a group difference of at least about 15% to demonstrate a statistical difference of 80% and alpha of 5% in a two-sided test. We had to include a minimum sample size of 164 patients. Preliminary analysis reveals that

one out of five patients will be eligible for the study. Following these analyzes, we extended the duration of recruitment for two years.

ETHICS

The study was approved by Emek Medical Center Ethics Committee following the Helsinki Convention No 0105 – 17 EMC. Informed consent was waived due to the use of anonymous patient data and the retrospective nature of the study.

STATISTICAL ANALYSIS

A chi-square test was performed to analyze the association between the study groups and categorical variables. For continuous variables, we used the t-test (alternatively the Wilcoxon two-sample test). Categorical variables were presented using frequencies and percentages. Continuous variables were presented using mean $\pm$ standard deviation. All confidence intervals are at the 95% level. TR progression was analyzed using the Mantel-Cox multivariant analysis and R-squared analysis. Multivariable models and logistic regression analysis were used to estimate the predictors of FTR. Differences considered statistically significant were at the 2-sided p level of 0.05. The statistical analyses were performed using SAS 9.4 software. A p-value < 0.05 was considered significant.

Results Of The Study

During the study period, 960 patients were admitted to the intensive cardiac unit due to acute MI. Of these, 275 patients were excluded from the study: 260 patients due to non-ischemic originating mitral regurgitation or previous known mitral regurgitation, five patients due to primary mitral disease (two due to rheumatic heart disease, two due to mitral valve prolapse and one due to chest radiation), and nine patients due to secondary non-IMR-related tricuspid pathology.

Of the 685 eligible patients, 175 (25.6%) developed ischemic mitral regurgitation. Thirty-five patients were excluded due to a lack of adequate follow-up TTE exams and poor imaging quality. Thus, 134 patients were in the final study cohort (Fig. 1).

Forty patients (29%, 95% CI: 22.75–38.07%) developed functional tricuspid regurgitation (FTR) during follow-up. Demographic characteristics of the two groups revealed that patients who developed FTR were older (63.0 ± 10.4 and 57.1 ± 11.0 , respectively, $p < 0.05$) with a high incidence of vascular disease either coronary ($p < 0.006$) or peripheral ($p < 0.009$). Failed coronary revascularization was a strong positive predictor of FTR development ($p < .003$). No gender difference was found between the groups. Smoking, hyperlipidemia, diabetes, and chronic kidney failure were not predictive of FTR development (Table 1).

Table 1
Baseline Characteristics

Characteristic	FTR (n = 40)	No-FTR (n = 94)	p-Value
Age	63.0 ± 10.4 (62.5; 45–85)	57.1 ± 11.0 (57; 34–89)	.005
Male	30 (75.0)	76 (80.9)	.45
Female	10 (25.0)	18 (19.1)	
Smoking	16 (40.0)	59 (62.8)	.02
Chronic Kidney Failure	3 (7.5)	3 (3.2)	.36
Diabetes (types 1 and 2)	14 (35.0)	38 (40.4)	.56
Previous Coronary Catheterization	20 (50.0)	23 (24.5)	.004.
Previous Bypass Surgery	4 (10.0)	3 (3.2)	.20.
Peripheral vascular disease	5 (12.5)	1 (1.1)	.009
Atrial fibrillation	4 (10.0)	3 (3.2)	.20
STEMI	39 (97.5)	84 (90.4)	.17.
KILLIP Score			
1	0 (0.0)	0 (0.0)	.16.
2	32 (80.0)	83 (88.3)	
3	1 (2.5)	0 (0.0)	
4	4 (10.0)	3 (3.2)	
New Q on ECG	8 (20.0)	11(11.8)	.22.
Infarct Area			.39
Anterior	20 (51.3)	42 (44.7)	
Inferior	15 (38.5)	37 (39.4)	
Lateral	1 (2.6)	4 (4.3)	
Posterior	1 (2.6)	0 (0.0)	
Other	2 (5.1)	11 (11.7)	
Ψ Defined as failed to perform balloon dilatation or stent implantation			
PCI, percutaneous coronary intervention			

Characteristic	FTR (n = 40)	No-FTR (n = 94)	p-Value
Failed PCI [‡]	5 (12.5)	4 (4.3)	.03
Complications after PCI	6 (15.0)	6 (6.5)	.18
Culprit artery			
LAD	65 (48.5)	20 (50.0)	45 (47.9)
RCA	45 (33.6)	14 (31.1)	31 (33.0)
CX	5 (3.7)	3 (7.5)	2 (2.1)
Other	19 ()	3 (7.5)	16 (17.0)
Ψ Defined as failed to perform balloon dilatation or stent implantation			
PCI, percutaneous coronary intervention			

Most patients who developed IMR had STEMI (92%). The ST-segment elevation on ECG, KILLIP class, and infarct territory was not associated with FTR development or progression (Table 1). We did not find a significant statistical correlation between the infarct-related artery involved and the development of FTR. Our analysis did not cover the correlation of multivessel disease with the development of FTR. Pulmonary arterial pressure (mean) and left ventricular systolic function as estimated by ejection fraction appeared to have a significant effect on FTR progression ($p < 0.05$, $p < 0.02$, respectively) but did not affect FTR development ($p < 0.5$, $p < 0.54$, respectively) (Table 2s and Table 3s). The distribution of incidence events and their severity among IMR patients appear to be directly and linearly linked to FTR development and progression (Fig. 2). During follow-up, the development of new FTR was observed in almost third of the patients. FTR progressed in one-fifth of patients within 1.67 years ($1.8 \pm \text{SD}$). The development of FTR was strongly associated with elevated pulmonary arterial pressure and reduced left ventricular ejection fraction (LVEF) (Fig. 3). Atrial Fibrillation was found to be associated with TR severity 2 ($\chi^2 = 0.96$, $p > .62$).

Patients who developed FTR had a lower overall survival rate than patients who did not have FTR. Multivariable models to predict FTR in IMR patients indicated a statistically significant difference in survival between the two groups at the time to progression to severe FTR (Mantel Cox $\chi^2 = 5.02$, $p < .025$). FTR group mean survival time was 4.58 years (95% CI: 4.11–5.04 years) and the no-FTR group was 5.15 years (95% CI: 4.90–5.40 years) (Fig. 4).

FTR progression was associated with heart failure at admission. There were statistically significant greater odds of FTR progression among patients with heart failure compared to patients with no heart failure at admission (OR: 8.09; 95% CI: 3.30–19.89, $p < .001$).

Discussion

The results of our study support recent reports of bivalvular deterioration in heart failure patients with reduced ejection fraction (HFrEF) and the interconnection between the mitral and tricuspid apparatuses. Our study highlights a specific group of patients with ischemic-related mitral regurgitation and its effect on the development of functional TR.

Multivalve involvement was described in the past regarding rheumatic heart disease and congenital heart disease and not extensively in the context of ischemic heart disease.

Myocardial infarction is still the most common cause of HFrEF and until recently it was thought that its major effect was directed toward left-sided pathology through an extensive remodeling process.

IMR is a common complication after myocardial infarction that requires adequate follow-up regardless of the appearance of clinical symptoms. Mild asymptomatic IMR usually tends to be neglected; however, our study demonstrates a linear relationship between the development of mitral regurgitation and the development of functional tricuspid regurgitation as a result of myocardial infarction. This linear connection, we believe, seems to involve volume and pressure overload, shifting from the left to the right side through the pulmonary vasculature.

Nearly one-third of IMR patients developed FTR during the five-year follow-up period. Elderly patients with extensive myocardial damage were at particularly high risk. Almost one-fifth of patients who developed IMR and LV dysfunction had a significantly high risk of FTR deterioration.

Bivalvular regurgitation, particularly with involvement of the tricuspid valve, greatly influences the prognosis of heart failure, limits therapeutic options, and substantially increases the overall mortality.

IMR should be properly monitored and followed up regardless of symptoms. FTR should be assessed annually to avoid significant deterioration and to start prompt treatment for heart failure before the first signs of heart failure appear.

Limitation Of The Study

Our study is designed in a retrospective fashion. The data were analyzed retrospectively based on computerized patient medical records. Echocardiographic images were assessed according to the ASE criteria.

Quantification of the severity of mitral and tricuspid regurgitation was based on qualitative grading (visual assessment) using parameters such as color flow, jet area; CWD jet; LV and RV size, function, and volume; PA pressure; MV and TV morphology; and LA and RA size. These assessment methods may be confounded by several technical and hemodynamic factors, including the eccentricity of the jets and atrial size. However, we cannot accurately apply quantitative or semiquantitative methods because this is a retrospective study.

The influence of heart failure medical therapy and its contribution to valvular dysfunction could not be evaluated here. Larger samples are needed to evaluate these factors.

Conclusion

One-third of patients who develop ischemic mitral regurgitation (IMR) will develop functional tricuspid regurgitation (FTR) at a five-year follow-up. The incidence and severity of FTR are highly influenced by the severity of the IMR. Elderly patients with ischemic heart disease who had extensive myocardial damage and for whom revascularization failed are at high risk of IMR and FTR development. LV function significantly influences FTR deterioration.

Declarations

1. Ethics approval and consent to participate

- The study was approved by Emek Medical Center Ethics Committee in accordance with the Helsinki Convention. Informed consent was waived due to the confidentiality of the patient data and the methodology of the study.

2. Consent for publication

– N/A

3. Availability of data and materials

– The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

4. Competing interests

– The authors declare that they have no competing interests.

5. Funding

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6. Authors' contributions

– OK, HD, and ER contributed to the writing, editing, formatting of the main manuscript, and production of the figures. ER, OK, and YT provided care to the patients and revised the manuscript. OK certified that all authors have contributed and met the criteria for authorship.

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8. Authors' information (optional)

– N/A

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Figures

Figure 1

Study design

Distribution of prevalence and severity of FTR and IMR among study population

Figure 2

Distribution of prevalence and severity of valvular at indexed event

Figure 3

Distribution of FTR in relation to mean pulmonary arterial pressure and left ventricular ejection fraction progression

Figure 4

Kaplan-Mayer survival curve of FTR progression in IMR

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