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Original Research Article

A Retrospective Study Determining the Association between Echocardiographic LVFP Parameter, VMT Score and Clinical Outcomes of HFpEF

Mukesh Shandilya[1], Nirav Kumar[2]

[1]Senior Resident (Academic), Department of Cardiology, IGIMS, PATNA, Bihar, India
[2]Additional Professor, Department of Cardiology, IGIMS, PATNA, Bihar, India

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Corresponding Author: Dr. Mukesh Shandilya
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Abstract

Aim: The aim of the present study was to determine the association between the newly proposed echocardiographic LVFP parameter, visually assessed time difference between the mitral valve and tricuspid valve opening (VMT) score, and clinical outcomes of HFpEF.

Methods: This was a retrospective observational study that assessed the VMT score and clinical outcomes in patients with HFpEF in the Department of Cardiology, IGIMS, PATNA, Bihar, India. 200 patients were included in the study.

Results: Out of 200 patients, 36 patients were under VMT0, 130 in VMT1 and 34 in VMT 2 or 3. While LV volume was increased in patients with VMT 2/3, LV wall thickness and EF were similar among the groups, resulting in greater LV mass index and stroke volume in this group. Mitral E wave velocity, E/A, LA volume index, TR pressure gradient, and E/e0 were increased, and the deceleration time of the E wave and LV isovolumic relaxation time were shortened in accordance with the VMT score, resulting in the higher prevalence of elevated LVFP judged by the 2016 ASE/EACVI recommendations in VMT 2/3. There was an increase in the prevalence of significant mitral regurgitation in the higher VMT scores. RV dimensions and RA volume were also increased with the VMT score which could be associated with a higher prevalence of significant TR in VMT 2/3. While RV systolic function was similar between the groups, the VMT 2/3 was characterized by a larger IVC diameter and lower its respiratory change.

Conclusion: In patients with HFpEF, the VMT score was independently and incrementally associated with adverse clinical outcomes. Moreover, it could also predict clinical outcomes in HFpEF patients with AF.

Keywords: Echocardiography, Acute heart failure, VMT score.

Introduction

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. [1] The syndrome of HF is a common manifestation of the later stages of various cardiovascular diseases, including coronary artery disease, hypertension, valvular disease, and primary myocardial disease. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. [2,3]

Approximately 50% of HF patients present with evidence of left ventricular systolic dysfunction manifested as a low left ventricular ejection fraction. [4] HF is considered a progressive disorder that can be represented as a clinical continuum. The American College of Cardiology/American Heart Association (ACC/AHA) updated 2005 guidelines for the management of chronic HF identify 4 stages in this continuum. Stage A: risk for HF but without structural heart disease or symptoms of HF; Stage B: structural heart disease but without signs or symptoms of HF; Stage C: structural heart disease with prior or current symptoms of HF; Stage D: refractory HF. [5] The number of patients with LV systolic dysfunction in stage B is estimated to be 4 times greater than in stages C and D combined. [6]

These patients remain at risk for significant morbidity and mortality and the subsequent development of symptomatic HF. Because substantial evidence indicates that pharmacological intervention may have an effect on the risk of progression to HF and death, identification of patients who are asymptomatic would then appear to be a priority.

ACC/AHA guidelines[5] as well as ESC guidelines [7] state that echocardiography is the single most useful test in the diagnosis of heart failure since structural abnormality, systolic dysfunction, diastolic dysfunction, or a combination of these abnormalities needs to be documented in patients who present with resting or/and exertional symptoms of heart failure to establish a definitive diagnosis of heart failure. It is important to demonstrate an objective evidence of structural or functional abnormalities to explain patient's symptoms of heart failure since symptoms of heart failure are not specific and more than a third of patients with a clinical diagnosis of heart failure may not actually have heart failure. [8]

However, echocardiography represents the "gold standard" in the assessment of LV systolic dysfunction, it can certainly do better than chest x-ray for cardiac enlargement, and may also provide direct imaging of pulmonary congestion. In addition, it is important to consider the disadvantage of radiation exposure in situations, such as heart failure, when serial assessment is mandatory. [9,10] Current protection standard and practices are based on the premise that any ionising radiation dose, no matter how small, can result in detrimental health effects. [11] These include long-term development of cancer and genetic damage. [12] For the purposes of radiation protection, the dose-response curve for radiation-induced cancer is assumed to be linear at low doses, with no minimum threshold. [13]

The aim of the present study was to determine the association between the newly proposed echocardiographic LVFP parameter, visually assessed time difference between the mitral valve and tricuspid valve opening (VMT) score, and clinical outcomes of HFpEF.

Materials and Methods

This was a retrospective, observational study that assessed the VMT score and clinical outcomes in patients with HFpEF in the Department of Cardiology, IGIMS, PATNA, Bihar, India for two years. 200 patients were included in the study.

HFpEF was defined by the typical clinical symptoms of HF (exertional dyspnoea, fatigue, and oedema), EF > 50%, and evidence of elevated LVFP [invasively measured pulmonary arterial wedge pressure >15mmHg, B-type natriuretic peptide (BNP) levels >200 pg/mL or N-terminal pro-BNP >400 pg/mL, E/e0 >15, left atrial (LA) volume index >34mL/m2 (see the echocardiographic measurements section for further details), or previous HF hospitalization].[14] Subjects with (i) reduced EF (EF< 50%), (ii) recovered EF (previous EF< 40%), (iii) pulmonary arterial hypertension, (iv) significant left-sided valvular heart disease (>moderate regurgitation, >mild stenosis), (v) previous atrioventricular valve replacement, (vi) acute coronary syndrome, (vii) constrictive pericarditis, (viii) congenital heart disease, or (ix) cardiomyopathies were excluded. From this group, patients with comprehensive echocardiographic evaluation in a compensated state (outpatient or discharge from HF hospitalization) were identified. When patients had multiple echocardiograms during this period, the oldest study was used as an index echocardiographic evaluation. The study was approved by the Institutional Review Boards of the two hospitals. Data on clinical demographics, medical history, current medications, and laboratory data were extracted from a detailed chart review. Based on a previous study, we defined atrial fibrillation (AF) as AF rhythm in patients during the echocardiographic assessment, that is, current AF. [14]

Echocardiographic examination

A comprehensive echocardiographic examination was performed in accordance with the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines.[15] LV end diastolic volume, end-systolic volume, EF, and LA volume were measured using the biplane disc summation method. LV mass was calculated by using the Devereux formula. Stroke volume was calculated from the time velocity interval of the LV ejection flow and the diameter of the LV outflow tract. Peak early-diastolic velocity (E), deceleration time of E, and the ratio of the E to the peak late-diastolic velocity (E/A) were measured in the apical LV long-axis view. Early-diastolic mitral annular velocity at the septal annulus (e0) was measured from the apical four-chamber view, and the ratio of E to the septal e0 (E/e0) was calculated. LV isovolumic relaxation time was measured as the time interval between the end of ejection and the onset of the E wave. The right ventricular (RV) to right atrial (RA) pressure gradient was estimated from the peak systolic tricuspid regurgitation (TR) velocity. LV diastolic dysfunction was then segregated into three severity grades, with grades 2/3 diastolic dysfunction regarded as elevated LVFP. [15] In patients with AF, the peak systolic TR velocity >2.8 m/s and E/e0 ratio >_11 were used to determine LVFP elevation according to the previous reports. [16]

In line with our recent study[16] the VMT score was assessed as a marker of LVFP elevation. Based on

earlier opening of the MV than TV in the presence of a higher LVFP compared to RA pressure, [16] this scoring system consists of (i) visual assessment of the time sequence of atrioventricular valve openings and (ii) estimated RA pressure based on inferior vena cava (IVC) findings. Briefly, from the cine loops (6–9 beats) of the apical four-chamber view, the time sequence of the MV and TV openings was visually assessed by slow playback, if necessary, and scored into three grades: 0= TV opening first, 1= simultaneous, and 2=MV opening first. When a marker of abnormal RA pressure (the IVC dimension was >21mm and collapsed to <20% with quiet inspiration) was observed,[16] 1 point was added and the VMT score was calculated as four grades from 0 to 3. The VMT 2/3 was then regarded as elevated LVFP. [16]

Outcome assessment

All subjects were followed up from the day of echocardiographic examination. The primary endpoint of the current study was a composite of cardiac death and hospitalization for HF. The secondary endpoint was a composite of all-cause mortality and hospitalization for HF. HF hospitalization was defined as dyspnoea and pulmonary oedema on chest X-ray requiring intravenous diuretic treatment. [14] As elevated LVFP and subsequent lung congestion are associated with short-term cardiac events. [17]

Results

Table 1: Patients' demographics according to VMT score

	All patients	VMT0	VMT1	VMT2or 3	P Value
Number	200	36	130	34	
Age (years)	74 ± 12	71 ± 15	74 ± 12	75 ± 10	0.285
Female, n (%)	102	20	65	17	0.442
Body mass index (kg/m2)	22 ± 4	21±3	23± 5a	23 ± 4a	0.009
Systolic blood pressure (mmHg)	127 ± 21	129 ± 20	128 ± 21	121 ± 22	0.090
Heart rate (bpm)	74 ± 17	72 ± 16	74 ± 17	75 ± 17	0.484
History of HF hospitalization	130	19	80	30	0.344
Comorbidity, n					
Hypertension	160	22	114	24	0.895
Coronary artery disease	45	8	27	10	0.554
Current atrial fibrillation	64	1	48	15	<0.001
Diabetes mellitus	64	8	50	6	0.722
Cardiac implantable electrical devices	14	3	5	6	0.011
Medications, n					
ACEI or ARB	96	15	66	15	0.925
Beta-blocker	86	14	60	12	0.253
Diuretic	130	17	93	20	0.438
Mineralocorticoid receptor antagonists	75	12	52	11	0.563
Laboratories					
Haemoglobin (g/dL)	11.6 ± 2.3	11.3 ± 2.1	11.7 ± 2.3	11.5 ± 2.4	0.454
Albumin (g/dL)	3.7 (3.3–4.0)	3.7 (3.4–4.1)	3.7 (3.2–4.0)	3.8 (3.2–4.1)	0.685
Creatinine (mg/dL)	0.9 (0.7–1.3)	0.9 (0.7–1.1)	0.9 (0.7–1.3)	1.0 (0.7–1.5)	0.521
B-type natriuretic peptide (pg/mL)	193 (92–371)	108 (45–283)	191(100–361)a	321(163–472)a,b	<0.001
c-Glutamyl transferase (IU/L)	28 (17–52)	25 (16–43)	27 (18–51)	34 (17–72)	0.139
Total bilirubin (mg/dL)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.6–1.1)	0.035

Out of 200 patients, 36 patients were under VMT0, 130 in VMT1 and 34 in VMT 2 or 3.

Table 2: Cardiac structure and function stratified by VMT score

Left heart	N	VMT0	VMT1	VMT 2 OR 3	NA
LV end-diastolic volume (mL)	89 ± 35	94 ± 36	84 ± 32	104 ± 39	0.001
Interventricular septal thickness (mm)	10 ± 2	10 ± 2	10 ± 2	11 ± 3	0.271
LV mass index (g/m^2)	105 ± 31	107 ± 30	102 ± 32	114 ± 31	0.049
LV ejection fraction (%)	61 ± 7	60 ± 6	61 ± 7	62 ± 7	0.351
Stroke volume (mL)	52 ± 19	53 ± 18	49 ± 17	62 ± 24	<0.001
E (cm/s)	84 ± 25	60 ± 21	86 ± 25[b]	99 ± 29	<0.001
E/A	0.8 (0.7–1.2)	0.7 (0.5–0.8)	0.9 (0.7–1.3)[b]	1.2 (0.8–1.9)	<0.001
Deceleration time of E (ms)	207 ± 75	244 ± 76	202 ± 70[b]	189 ± 90	<0.001

Isovolumic relaxation time (ms)	82 ± 34	108 ± 41	78 ± 33[b]	69 ± 29	<0.001
e^0 (cm/s	5.6 ± 2.1	4.5 ± 1.6	5.8 ± 2.2[b]	5.9 ± 2.1	<0.001
E/e^0	16.2 ± 6.1	14.5 ± 5.3	16.0 ± 5.9	18.4 ± 7.6	0.005
LA volume index (mL/m^2)	50 (34–65)	38 (28–48)	51 (32–64)[b]	64 (51–76)	<0.001
Tricuspid regurgitant pressure gradient (mmHg)	27 ± 9	24 ± 7	26 ± 9	33 ± 11	<0.001
LA pressure judged by the guidelines, *n* (%)					<0.001
Elevated LA pressure	76	15	54	15	
Normal LA pressure	74	19	50	5	
Indeterminate LA pressure	50	2	40	8	
Significant mitral regurgitation, *n*	12	1	6	5	<0.001
Right heart					
RV basal diameter (mm)	36 ± 8	33 ± 6	35 ± 8	40 ± 7	<0.001
RV mid diameter (mm)	29 ± 7	27 ± 6	28 ± 7	32 ± 7	<0.001
TAPSE (mm)	18 ± 5	18 ± 5	18 ± 5	16 ± 6	0.103
RA maximum volume (mL)	38 (25–56)	25 (16–36)	37 (25–53)[b]	60 (41–93)[a,b]	<0.001
IVC dimension (mm)	16 ± 5	13 ± 4	15 ± 5[b]	19 ± 6[a,b]	<0.001
IVC respiratory change (%)	47 ± 19	53 ± 17	48 ± 18	37 ± 25[a,b]	<0.001
Significant tricuspid regurgitation, *n* (%)	63 (20)	7 (13)	37 (18)	20 (37)	0.003

While LV volume was increased in patients with VMT 2/3, LV wall thickness and EF were similar among the groups, resulting in greater LV mass index and stroke volume in this group. Mitral E wave velocity, E/A, LA volume index, TR pressure gradient, and E/e0 were increased, and the deceleration time of the E wave and LV isovolumic relaxation time were shortened in accordance with the VMT score, resulting in the higher prevalence of elevated LVFP judged by the 2016 ASE/EACVI recommendations in VMT 2/3. There was an increase in the prevalence of significant mitral regurgitation in the higher VMT scores. RV dimensions and RA volume were also increased with the VMT score which could be associated with a higher prevalence of significant TR in VMT 2/3. While RV systolic function was similar between the groups, the VMT 2/3 was characterized by a larger IVC diameter and lower its respiratory change.

Discussion

Heart failure with preserved ejection fraction (HFpEF) comprises approximately half of the cases of heart failure (HF) [18] and the morbidity and mortality in HFpEF are similar to that observed in patients with HF with reduced ejection fraction (EF). [19] With limited preferential treatment, HFpEF has been a major global public health problem. [20] Over the past decade, the pathophysiological diversity of HFpEF has been well recognized; [20] however, the presence of left ventricular (LV) diastolic dysfunction manifested by elevated LV filling pressure (LVFP) is a fundamental haemodynamic abnormality in HFpEF. [21,22]

Out of 200 patients, 36 patients were under VMT0, 130 in VMT1 and 34 in VMT 2 or 3. While LV volume was increased in patients with VMT 2/3, LV wall thickness and EF were similar among the groups, resulting in greater LV mass index and stroke volume in this group. Mitral E wave velocity, E/A, LA volume index, TR pressure gradient, and E/e0 were increased, and the deceleration time of the E wave and LV isovolumic relaxation time were shortened in accordance with the VMT score, resulting in the higher prevalence of elevated LVFP judged by the 2016 ASE/EACVI recommendations in VMT 2/3. Elevated LVFP indicates two pathophysiological abnormalities: the congestive state to be managed to reduce the cardiac overload and the severe diastolic dysfunction which requires a high filling pressure to maintain adequate cardiac output even after optimal management. Because both of these are prone to haemodynamic stress, elevated LVFP in the non-decompensated state should be a powerful indicator of worsening HF. [23,24]

There was an increase in the prevalence of significant mitral regurgitation in the higher VMT scores. RV dimensions and RA volume were also increased with the VMT score which could be associated with a higher prevalence of significant TR in VMT 2/3. While RV systolic function was similar between the groups, the VMT 2/3 was characterized by a larger IVC diameter and lower its respiratory change. Although LV isovolumic relaxation time is related to the VMT score, they might show somewhat different behaviours. In healthy individuals, a short isovolumic relaxation time is observed resulting from rapid LV relaxation, which is similar to patients with elevated LVFP. [15] The VMT score, on the other hand, conceptually shows 0 or 1 in patients with normal LVFP because the early-diastolic opening of TV usually precedes that of MV under normal

conditions because of the differences of pulmonary to systemic blood pressure.[16] Therefore, the VMT score might be considered as an indicator that escapes the pseudonormalization compared to the conventional parameters such as isovolumic relaxation time and E/A. In the present study, we applied VMT scoring, which is a novel parameter of LVFP[16] and found that VMT >_2 was associated with future cardiac events in a well-differentiated HFpEF population even after adjusting for other established risk markers. Notably, VMT >_2 was still prognostic even in the subgroup where the guideline-recommended algorithm was judged as indeterminate LVFP as well as in AF patients. As a result, VMT scoring showed an incremental prognostic value for the algorithm. Based on the substantial HFpEF population in whom the algorithm cannot be applied, VMT scoring is expected to add a diagnostic option for HFpEF patients.

Optimal reduction of LVFP with diuretics, vasodilator, and optimal neurohormonal antagonist therapies is one of the limited options for the relief of symptoms and reduced readmission in HFpEF patients. Recently developed transcatheter intracardiac shunt device showed favourable results in HFpEF patients. [25] LVFP is thus a key therapeutic target in HFpEF patients, and accurate detection of elevated LVFP is pivotal for their management. [26] The VMT score is expected to provide an accurate detection of elevated LVFP in these patients. In particular, VMT scoring could be an additional option for precise risk stratification of HFpEF patients complicating AF and those with indeterminate LVFP according to the 2016 ASE/EACVI recommendations.

Conclusion

In patients with HFpEF, the VMT score was independently and incrementally associated with adverse clinical outcomes. Moreover, it could also predict clinical outcomes in HFpEF patients with AF.

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