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Addresses

Editorial Office
Prof. Dr. Mehdi Zoghi
Ege University, Faculty of Medicine Internal Medicine,
Department of Cardiology
Bornova, 3100, İzmir - Turkey
Telephone: +90 232 - 3905458
E-mail: mehdi_zoghi@hotmail.com

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Review Article

Exercise Training in Heart Failure: High-intensity Interval Training versus Moderate-intensity Continuous Training

Raymond Pranata, Emir Yonas[1], Bambang Budi Siswanto[2], Budhi Setianto Purwowiyoto[2]

Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village - Faculty of Medicine, Universitas Pelita Harapan, Tangerang, [1]Medical Intern, Department of Cardiology, Gatot Soebroto Central Hospital, Jakarta, [2]Department of Cardiology and Vascular Medicine, National Cardiovascular Centre Harapan Kita, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Abstract

Prevalence of heart failure (HF) increases over time and is associated with high mortality. Shortness of breath, exercise intolerance, and low quality of life related to health are the common problems in HF patients despite optimum pharmacological therapy. Exercise training counteracts the progression of devastating compensatory mechanisms of HF, leading to improvement in functional capacity and quality of life. Resistance training improves peak oxygen uptake, quality of life, and walking performance in HF patients. Adherence is central to training for the best result. Any exercise training program whether continuous or interval training is sufficient to improve the prognosis, quality of life, and anatomic function.

Keywords: Exercise, heart failure, oxygen uptake, rehabilitation, training

Introduction

Prevalence of heart failure (HF) increases over time and is associated with high mortality (5-year survival rate of 35%–55%).[1-4] Shortness of breath, exercise intolerance, and low quality of life related to health are the common problems in HF patients despite optimum pharmacological therapy.[5]

Various studies indicated that physical fitness is a prognostic factor for HF patients, in which low physical fitness is associated with high mortality rate.[6,7] Previous studies indicated that physical training increases physical fitness, cardiovascular function, and quality of life.[8-12] Peak aerobic capacity can be directly measured by peak oxygen uptake (VO_2 peak) and is the best predictor of cardiovascular and all-cause mortality in cardiovascular patients.[13,14]

Physical training is recommended for HF patients.[15] However, there are differences regarding which level of intensity and exercise formats leads to best results.

Exercise training

Mechanism

Exercise training reverses autonomic dysfunction in patients with HF, which shifts from predominantly sympathetic to vagal activity and reduces circulating renin-angiotensin-aldosterone system neurohormones,[16] resulting in improved cardiac function, reduced vasoconstriction with better peripheral and skeletal blood delivery, and improved exercise tolerance. It also produces antioxidative effects (through reduction of vascular expression of NADPH oxidase and AT1) which decrease reactive oxygen species production, resulting in improved acetylcholine-mediated coronary vasodilatation and reduced Ang-II-induced vasoconstriction.[16]

Regular exercise training can have an anti-inflammatory effect marked by increased plasma levels of the anti-inflammatory cytokine interleukin 10 and can modulate the innate immune system, influencing macrophage and lymphocyte function.[16] Exercise affects skeletal muscle's oxygen use and oxidative capacity, which are improved by increased activity of oxidative enzymes and mitochondrial content, leading to improvement in

Address for correspondence: Dr. Budhi Setianto Purwowiyoto, Department of Cardiology and Vascular Medicine, National Cardiovascular Centre Harapan Kita, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
E-mail: heybudhi@gmail.com

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peak VO_2 and lactate threshold and delayed onset of anaerobic metabolism.

Exercise training improves heart function by restoring cardiomyocyte contractility and calcium sensitivity.[16] It may minimize the stunning effects and maximize the preconditioning effects of brief ischemic episodes. All these training-induced changes can effectively counteract the progression of deleterious compensatory mechanisms of HF, leading to improvement in functional capacity and quality of life.[16]

Principles of exercise regiment(s)

Continuous training regiment(s)

Continuous training (CT) is typically performed at moderate-to-high exercise intensities in steady-state conditions of aerobic energetic yield, which allows the patient to perform prolonged training sessions (up to 45–60-min duration).[15] It is safe, efficient, and well tolerated by patients, and hence it is recommended by the Heart Failure Association guidelines.

High-intensity training

In interval training (INT) protocol, an alternate short bout (10–30 s) of moderate-to-high intensity (50%–100% peak exercise capacity) exercise, with a longer recovery (80–60 s) phase, is performed at low or no workload. Recent trials demonstrated INT, especially high-intensity INT (HIIT), to be more effective.[15]

High intensity or continuous training?

Some evidences supported that INT is more effective to improve left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter.[17] A recent meta-analysis showed that an increase in exercise capacity, represented by the peak VO_2, was similar between training modalities and the influence of a certain training modality on ventilation over carbon dioxide (VE/VCO_2) slope was not found to be significantly different from other training modalities. VO_2 efficiency slope seemed to improve significantly with INT compared to CT (only one study). Quality of life seems to improve significantly with combined INT and strength training.[17] Another meta-analysis showed that in clinically stable HF with reduced ejection fraction patients, INT is more effective than CT for improving peak VO_2, but not the LVEF at rest.[18] Adherence to exercise training is very important and this is often problematic in HF due to time constraints and lack of energy.[19,20] A HIIT training with lower training frequency and high-intensity intervals of moderate duration might address these two major factors of noncompliance, hence improving adherence. A low-frequency high-intensity training (HIT) with high-intensity intervals of moderate duration is feasible and successful in improving fitness. These might be a component of optimal exercise protocol for HF patients to achieve long-term benefits and adherence in the future.[20]

The risk of cardiovascular events concerning HIT has been demonstrated to be low in patients with coronary artery disease; however, its safety has not been confirmed in those with HF with reduced EF (HFrEF) in a large-scale investigation.[21] Most patients with HFrEF have relatively impaired exercise hemodynamic in the initial sessions of exercise training.[21] There was a trial evaluating modified HIT (CT in the first 12 sessions followed by 24 HIT sessions) compared to optimal medical treatment only, in which supervised continuous aerobic training at ventilator anaerobic threshold for 50 min/day, 3 days/week for 4 weeks, and then 3-min intervals at 40% and 80% VO_2 reserve for 50 min/day, 3 days/week for 8 weeks, demonstrated an improved peak cardiac-pumping capacity with reduced cardiac afterload which simultaneously increases ventilation efficiency during exercise in patients with HFrEF, giving time for adaption in initial sessions before proceeding to HIIT.[21] Any exercise training program seems sufficient to improve the prognosis, quality of life, and anatomic function.[17]

Despite concerns regarding patient adherence, several studies have shown irrefutable advantages of HIT in patients with cardiac failure. It is interesting that HIT protocols, the total exercise volume, and time commitment have been significantly lower compared to moderate-intensity training, and yet its use still shows various positive physiological benefits that are at least comparable with moderate-intensity protocols. It is also important to note that HIT has been shown to be safe, tolerable, and enjoyable for patients with cardiovascular disease, eliminating any major concerns of an increase in adverse effect risk.[22]

However, several trials have failed to show any comparable benefit of HIT compared to continuous moderate-intensity training [Tables 1 and 2]; however, the authors of these trials stated that the lack of comparable evidence resulted from the small sample.[20,23]

In one randomized trial of 27 patients with stable, postinfarction HF who received optimal medical therapy, aerobic INT at high intensity (at 95% of peak heart rate) reversed left ventricular remodeling and improved left ventricular relaxation; these benefits were not observed with moderate CT (at 70% of peak heart rate). At this trial, reversal of left ventricular remodeling and improved left ventricular relaxation were observed. In addition, HIT was associated with a greater increase in peak exercise levels.[24]

A Cochrane database review revealed that patients who undergo HIT showed an increase in 6-min walk distance mean of 41 m; this increase in functional capacity means that patients may be able to participate in their routine daily activities more easily and comfortably.[25]

A meta-analysis including seven randomized trials comparing HIT to moderate-intensity CT in clinically stable patients with HF with reduced ejection fraction revealed greater improvements in exercise tolerance with HIT.[18]

Two studies by Benda *et al*. and Ellingsen *et al*. failed to show statistically significant differences between CT and HIT in terms of physical fitness improvement [Table 3].[26] Exercise in patients with HF is indeed associated with beneficial cardiac remodeling; however, after 12 h of

Table 1: Maximal incremental cycling test

Parameter	CT (*n*=10)		HIT (*n*=10)		*P*		
	Post	Pre	Post	Time	Time	Group	Time*group
VO_2 peak (mL/min)	1881±214	1887±27	1662±562	1792±559	0.06	0.44	0.08
VO_2 peak (mL/min/kg)	21.2±3.6	21.3±3.7	19.1±4.1	20.4±4.3	0.10	0.14	0.09[#]
VO_2 peak (percentage predictor VO_2 peak)	86±8	87±10	79±17	85±16	0.044	0.48	0.08
Maximal workload (watt)	145±22	152±26	126±38	142±45	<0.001	0.24	0.07
Maximal heart rate (/min)	129±19	132±24	126±16	125±15	0.78	0.30	0.51
VE/VCO_2 slope	32.2±3.3	32.7±5.8	28.7±5.8	29.4±7.7	0.52	0.18	0.91
VO_2 at AT (mL)	1030±287	1248±388	1033±319	1090±225	0.041	0.54	0.22
Maximal O_2/HR (mL)	16.2±2.2	16.7±2.8	14.0±4.0	15.4±3.8	0.006	0.25	0.13

Data are presented as mean±SD. *P* values refer to a two-way repeated measures ANOVA between the two training groups. One participant in the CT group did not reach VO_2 peak, and therefore only VE/VCO_2 slope and VO_2 at AT could be determined. [#]For statistical reasons, data were analyzed with three separate tests to determine time, group, and time*group *P* values. SD: Standard deviation, CT: Continuous training, HIT: High-intensity training, VE/VCO_2: Ventilation over carbon dioxide, VO_2 peak: Peak oxygen uptake

Table 2: Echocardiographic left ventricular volumes, systolic function, and strain and diastolic function

	CT (*n*=10)		HIT (*n*=10)		*P*		
	Pre	Post	Pre	Post	Time	Group	Time*group
Systolic function							
LVEDV (ml)	154±24	159±28	194±39	204±44	0.26	0.002	0.64[#]
LVESV (ml)	98±14	102±19	134±32	132±40	0.87	0.037	0.63
Stroke volume (ml)	56±13	57±13	61±14	72±16	0.06	0.16	0.12
LVEF (%)	36±4	36±5	32±7	36±9	0.09	0.57	0.07
Cardiac output (L/min)	3.5±0.6	3.4±0.7	3.5±0.8	4.3±1.0	0.20	0.21	0.07
Cardiac index (L/min/m^2)	1.7±0.3	1.6±0.3	1.7±0.4	2.1±0.5	0.22	0.14	0.08
Longitudinal strain (%)	−9±3	−9±3	−9±3	−8±3	0.60	0.47	0.38[#]
Circumferential strain (%)	−10±2	−10±3	−9±3	−8±3	0.22	0.43	0.19
Radial strain (%)	23±7	22±6	23±8	20±8	0.13	0.71	0.48
Area strain (%)	−17±4	−15±6	−17±5	−14±5	0.044	0.73	0.97
IVCT-L (ms)	52±7	50±10	49±12	58±7	0.18	0.56	0.029
IVCT-S (ms)	57±14	59±11	53±9	56±11	0.35	0.46	0.87
Diastolic function							
IVRT-L (ms)	145±32	149±27	142±27	159±27	0.13	0.75	0.38
IVRT-S (ms)	160±36	148±22	164±41	170±37	0.60	0.45	0.22[#]
E/A	1.15±0.71	1.17±0.89	1.53±1.42	1.60±1.53	0.49	0.36	0.59[#]
S/D	1.38±0.74	1.17±0.34	1.00±0.40	1.26±0.59	0.85	0.48	0.14
E/E'-L	6.8±1.9	6.7±1.9	10.3±4.4	9.8±6.3	0.71	0.07	0.74
E/E'-S	10.1±4.1	11.1±5.2	12.6±9.8	11.8±11.2	0.93	0.67	0.42

Data are presented as mean±SD. *P* values refer to two-way repeated measures ANOVA between the two training groups. [#]For statistical reasons, data were analyzed with three separate tests to determine time, group, and time*group *P* values. Four-dimensional data were available for seven patients in the CT group and eight patients in the HIT group. IVCT-l, IVRT-C, IVRT-S, and E/E'-L were available for nine patients in the HIT group. IVCT-S and E/E'-S were available for eight patients in the HIT group. IVCT-L and S/D ratio were available for nine patients in the CT group. IVRT-L and E/A ratio was available for eight patients in the CT group. LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, IVCT-L/S: Isovolumetric contraction time, lateral/septal, IVRT-L/S: Isovolumetric relaxation time, lateral/septal, E/A ratio: Peak mitral flow velocity during early filling/peak mitral flow velocity during atrial contraction, S/D: Systolic flow velocity pulmonary vein/diastolic flow velocity pulmonary vein, E/E'-L/S: Peak mitral flow velocity during early filling/peak mitral annulus velocity during early filling, lateral/septal, SD: Standard deviation, CT: Continuous training, HIT: High-intensity training

training regiment(s) by Benda *et al*., no improvements in cardiac structure and function at rest were found. Although increase in maximal oxygen pulse suggests an increase in stroke volume during exercise, it is to be noted that previous studies that reported significant structural and functional changes were generally using training periods that exceed 6 months. These studies also failed to show a superior effect of HIT to improve vascular function, which contrasts the other studies. Improvement was indeed found in the subscale for physical functioning after exercise training, but not for the total quality of life. The lack of improvement in quality of life may relate to the relatively "good" quality of life at baseline on patients at these trials, which was well above that of other studies, and consequently provides a little space for further improvement. Quality of life in these studies was assessed using the SF-36 questionnaire. However, this

Table 3: Main echocardiography and cardiopulmonary testing measures at baseline, 12 weeks, and 52 weeks with unadjusted changes

	RRE (*n*=73)			MCT (*n*=65)			HIIT (*n*=77)		
	Baseline	12 weeks	52 weeks	Baseline	12 weeks	52 weeks	Baseline	12 weeks	52 weeks
LVEDD (mm)	68 (67-69)	69 (65-71)	66 (63-67)	69 (66-72)	67 (65-70)	64 (61-70)	68 (65-70)	63 (62-68)	63 (62-66)
LVEF (%)	30 (28-32)	28 (27-30)	28 (27-32)	29 (26-32)	27 (25-31)	33 (26-37)	29 (26-31)	31 (29-31)	28 (26-32)
VO_2 peak ($mL\ kg^{-1}\ min^{-1}$)	18.4 (16.8-19.6)	17.4 (15.7-19.8)	18.2 (15.8-20.0)	16.2 (15.3-18.7)	17.0 (15.7-19.6)	16.4 (15.0-18.6)	16.8 (15.8-17.8)	18.2 (16.3-20.0)	17.1 (15.5-18.6)
NT-proBNP (ng/L)	895 (635-1110)	821 (594-1079)	626 (419-1116)	976 (725-1348)	821 (580-1169)	698 (544-1021)	1052 (837-1472)	909 (722-1484)	813 (585-1615)
Change		Baseline-12 weeks	Baseline-52 weeks		Baseline-12 weeks	Baseline-52 weeks		Baseline-12 weeks	Baseline-52 weeks
LVEDD (mm)		0.0 (0.0-2.0)	−2.0 (−4.0-0.0)		−1.0 (−2.0-1.0)	−3.0 (−7.0-−1.4)		−2.0 (−3.6-−1.0)	−3.0 (−5.0-−1.0)
LVEF (%)		−0.6 (−2.4-1.4)	1.1 (−0.8-3.0)		0.7 (−1.8-2.6)	0.7 (−1.5-4.4)		1.7 (0.0-4.5)	−0.2 (−3.1-2.8)
VO_2 peak ($mL\ kg^{-1}\ min^{-1}$)		−0.1 (−0.9-0.4)	−0.4 (−1.3-0.4)		1.1 (0.5-1.7)	1.2 (−0.2-1.4)		0.9 (0.0-1.4)	0.1 (−0.4-1.0)
NT-proBNP (ng/L)		9 (−43-112)	−25 (−108-76)		2 (−91-97)	−101 (−130-30)		19 (−76-129)	112 (−24-236)

Values are median with 95% CI of the median. There were no differences between the groups at baseline (Kruskal–Wallis test, *P*=0.68, 0.83, 0.21, and 0.30). HIIT: High-intensity interval training, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, MCT: Moderate continuous training, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, RRE: Recommended regular exercise, VO_2 peak: Peak oxygen uptake, CI: Confidence interval

caveat indicates that patients with lower quality of life prior to exercise training may demonstrate a larger benefit from the intervention.[20,26]

Conclusion

Significant differences between CT and HIT in terms of physical fitness are not demonstrable. Preference between the former two remains unresolved in patients with HF. A more conservative approach is needed to prescribe moderate-intensity CT regiment(s) and switch to HIIT should the patient is unable to comply with the CT regiment(s).

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Glomerular Filtration Rate Calculated by Modification of Diet in Renal Disease Formula Can be an Indicator of Impaired Glucose Tolerance and Diabetes in Coronary Artery Disease

Sinan Varol, Okay Abaci[1], Muhsin Kalyoncuoglu[2], Vedat Sansoy[1]

Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, [1]Department of Cardiology, Institute of Cardiology, Istanbul University, [2]Department of Cardiology, Haseki Training and Research Hospital, Health Sciences University, Istanbul, Turkey

Abstract

Background: There is an increased risk for coronary artery disease (CAD) at modestly elevated levels of blood glucose which is still below the present threshold for type 2 diabetes mellitus (T2DM). In the present study, we aimed to define impaired glucose tolerance (IGT) and T2DM in patients with stable CAD and observe the relationship between clinical and laboratory findings. **Materials and Methods:** A total of 132 patients who had stable CAD and who had not been diagnosed as glucose intolerance or diabetes were enrolled. In one of the groups, there were patients with IGT or T2DM results and the other one consisted of patients with normal oral glucose tolerance test (OGTT) results. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was investigated in patients with fasting plasma glucose (FPG) <100 mg/dl. **Results:** The prevalance of IGT and T2DM was 30.3%. In IGT + T2DM group, waist/hip ratio and creatinin level were significantly higher and estimated glomerular filtration rate (eGFR) was low. Only eGFR calculated by Modification of Diet in Renal Disease (MDRD) formula was a reliable parameter. MDRD eGFR ≤70 ml/dk/m² independently predicted IGT + T2DM diagnosis with 50% sensitivity but with 82% specificity. Although it is insufficient to use it as an optimal screening test because of lower sensitivity, it can be a reliable indicator of IGT + DM in patients who had eGFR ≤70. Insulin resistance was diagnosed in 29% of patients whose pretest values were FPG <100 mg/dl. **Conclusion:** MDRD eGFR can be an indicator for IGT + T2DM. OGTT irrespective of FPG level should be used to determine the presence of IGT + T2DM in stable CAD.

Keywords: Coronary artery disease, diabetes mellitus, estimated glomeruler filtration rate, glucose intolerance, Modification of Diet in Renal Disease

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular (CV) morbidity and mortality.[1] There is an increased risk for coronary artery disease (CAD) at modestly elevated levels of blood glucose which is still below the threshold for T2DM.[2-5] At diagnosis, there is one or more complication in more than half of the patients. CAD mortality is two times higher in patients with high glucose levels measured at the 2nd hour.[6-8]

Impaired glucose tolerance (IGT), but not impaired fasting glucose (IFG), was determined as a risk factor for CAD,[7,9] and it is related to CV and CAD mortality.[2,8,10-12] Early diagnosis and treatment improves glucometabolic state, mortality, and morbidity.[13-16]

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Materials and Methods

A total of 132 patients were enrolled who had fasting plasma glucose (FPG) <126 mg/dl and who had not been diagnosed as glucose intolerance (GI) or T2DM before and who had documented myocardial infarction (MI) and presence of coronary stenosis >50% of the luminal diameter or documented coronary revascularization [Tables 1 and 2]. Patients with a history of acute coronary syndrome in 6 months were excluded

Address for correspondence: Dr. Sinan Varol, Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, Istanbul, Turkey.
E-mail: sinanvarol@gmail.com

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Table 1: Demographic and clinical characteristics of all patients

	n	Percentage	Mean±SD
Age (years)	132		58±9
Sex			
Male	115	87.1	
Female	17	12.9	
Presence of cardiac risk factors			
Hypertension	104	78.8	
Dyslipidemia	115	87.1	
Smoking status			
Active		16.7	
Former		52.3	
Nonsmoker		31	
Waist circumference (cm)			100±7
WHR			0.97±0.04
Height (cm)			1.68±8
Weight (kg)			82±13
BMI			29±3.8
Creatinine (mg/dl)			1±0.1
MDRD GFR (ml/dk)			80±16
Cockroft GFR (ml/dk)			93±25
Duration of CAD (month)			58±56
Number of involved coronary artery			
One vessel		28.6	
Two vessels		32.4	
Three vessels		28.6	
Unknown		10.4	

BMI: Body mass index, MDRD: Modification of Diet in Renal Disease, GFR: Glomerular filtration rate, CAD: Coronary artery disease, WHR: Waist/hip ratio, SD: Standard deviation

Table 2: Distribution of fasting plasma glucose levels

	n	Percentage	Mean±SD
FPG (mg/dl)			99±11
FPG <100 mg/dl	64	48.5	
FPG: 100-125 mg/dl	68	51.5	

SD: Standard deviation, FPG: Fasting plasma glucose

from the study. Oral glucose tolerance test (OGTT) was performed as it was defined by the World Health Organization. According to the procedure, patients were instructed not to limit carbohydrates 3 days before the procedure (daily <150 mg/dl carbohydrates) and to perform daily physical activities. They were advised to give up eating and smoking after 10 PM the night before the test. 75 g glucose in 300 ml water in 5 min was administered after giving the fasting blood sample. The blood sample was repeated at 120 min.

In patients whose FPG level was <100 mg/dl, insulin levels were analyzed using the chemimmunesance method (IMMULITE 1000 system, Siemens GmbH, Germany). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) values were calculated via appropriate formulas. HOMA-IR ≥2.18 was defined as the threshold for insulin resistance.

OGTT results were categorized based on the criteria which were defined by the American Diabetes Association Guidelines. 2nd hour blood glucose (2-h BG) >200 mg/dl was diagnosed as T2DM. Levels within the range of 140–199/dl were classified as IGT. For the levels below the value of 140 mg/dl; IFG were diagnosed if FPG ≥100 mg/dl. Otherwise they were considered as normal test result.

IGT and T2DM patients were classified as one group and patients with normal result were classified as the control group. Patients who were diagnosed as IFG were excluded from the study. Waist circumference (WC); body mass index (BMI); estimated glomerular filtration rate (eGFR); and CAD severity assessed as one-, two-, or three-vessel disease; functional capacity, and Angina score were compared between the two groups. All patients were informed about the purpose of the study and OGTT test. Informed consent was obtained. All procedures and study design were approved by the local ethical committee.

Statistical analysis

Data from patients were assessed by SPSS v20 for Windows software (SPSS Inc, Chicago Ill, USA). Appropriate tests were used to decide the distribution of values in both the groups. *t*-test, one-way ANOVA, Mann–Whitney U-test, Kruskal–Wallis test, and Chi-square test were used for comparisons. Risk factors were analyzed by the appropriate correlation analysis methods. Logistic regression analysis was used for obtaining independent predictors.

Results

After the OGTT test, it was found that 65 (49.2%) patients were normal, 27 (20.5%) patients had IFG, 34 (25.8%) patients had IGT, and 6 (4.5%) patients had T2DM [Table 3]. Patients in both groups were young (control: 57 ± 10, IGT + T2DM: 61 ± 9, $P = 0.095$) and a male predominance was observed. Waist/hip ratio (WHR) was significantly higher in IGT + T2DM group (control: 0.96 ± 0.04 and IGT + T2DM: 0.98 ± 0.04). Smoking status, presence and duration of hypertension, dyslipidemia, functional status and Angina class, history of MI, duration and severity of CAD, presence of MI, number of vessels revascularized, presence of coronary artery bypass graft, and drug usage were similar between the groups. The prevalence of IGT + T2DM was 30.3% in the whole population. Table 4a and b summarizes the demographic and clinical characteristics of the study cohort.

Logistic regression analysis showed that Modification of Diet in Renal Disease (MDRD) eGFR predicted the presence of IGT or T2DM. Age, sex, WHR, WC, BMI, and beta-blocker usage had no predictive values. After receiver operating characteristic (ROC) curve analysis, MDRD eGFR ≤70 ml/min/m² significantly predicted the presence of IGT or T2DM with 50% sensitivity and 82% specificity [Figure 1].

Insulin levels in patients with normal OGTT results were determined with respect to 0-h FPG levels. Based on the

Table 3: Distribution of fasting plasma glucose

	FPG <100 mg/dl		FPG ≥100 mg/dl		Total	
	n	Percentage	*n*	Percentage	*n*	Percentage
OGTT result						
Normal	43	32.6	22	16.6	65	49.2
IFG	10	7.6	17	12.9	27	20.5
IGT	10	7.6	24	18.2	34	25.8
DM	1	0.8	5	3.7	6	4.5
Total	64		68		132	

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus, OGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose

Table 4a: Demographic and clinical characteristics of the study cohort

	Normal (*n*=65)		IGT + DM (*n*=40)		*P*
	Percentage	Mean±SD	Percentage	Mean±SD	
Age		57±10		61±9	0.095
Sex					
Male	88 (*n*=57)		88 (*n*=35)		
Female	12 (*n*=8)		12 (*n*=5)		
Waist circumference (cm)		99±8		102±6	0.107
WHR		0.96±0.04		0.98±0.04	0.019
Weight (kg)		82±13		84±12	0.477
BMI		28.8±3.9		29.7±3.7	0.226
BUN (mg/dl)		16±5		16±4	0.167
Creatinine (mg/dl)		0.9±0.16		1.0±0.17	0.003
Cockroft GFR (cc/min)		97±27		86±21	0.03
MDRD GFR (cc/min)		85±19		74±13	0.002
EF%		48±9		44±14	0.184
CAD duration (month)		56±55		68±63	0.319
HT presence	72		87		0.068
HT duration (month)		47±55		70±73	0.110
HL presence	91		85		0.367
HL duration (month)		45±49		66±75	0.479
Smoking status					
Active		27	11		>0.05
Former		53	63		>0.05
Nonsmoker		20	26		>0.05
Smoking duration		27±22		27±26	>0.05
NYHA class					
NYHA I	94		85		>0.05
NYHA II	9		15		>0.05
NYHA III	0		0		>0.05
NYHA IV	0		0		>0.05
CCS class					
No angina	80		82		>0.05
CCS I	5		0		>0.05
CCS II	15		15		>0.05
CCS III	0		3		>0.05
CCS IV	0		0		>0.05
MI presence					
None	14		15		>0.05
Subendocardial	12		5		>0.05
Nonanterior	26		35		>0.05
Anterior	39		30		>0.05
Unknown	9		15		-

IGT: Impaired glucose tolerance, DM: Diabetes mellitus, SD: Standard deviation, WHR: Waist/hip ratio, BMI: Body mass index, MDRD: Modification of Diet in Renal Disease, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society

results, HOMA-IR values were calculated. Patients with insulin resistance were compared to others. Hypertension prevalence, BMI, and WHR were significantly higher in the insulin resistance group. The other parameters which showed significant differences are listed in Table 4. IGT + T2DM prevalence was similar between the two groups. Nearly 29% of patients who had normal OGTT results were found to have insulin resistance [Table 5].

Discussion

It was known that the presence of GI increases CAD mortality independent of developing T2DM.[17-19] It is also important because of the increasing CAD risk factors[6,20] and the development of coronary slow flow.[21] Furthermore, it was found that negative effects on reperfusion in acute coronary events increased mortality due to heart failure and cardiogenic shock.[22] Many clinical trials showed that increased CV risk was more associated with postprandial glucose levels than FPG. Hence, IGT patients have more CV risks compared to patients who have IFG.[7,23] Early diagnosis is important because it was demonstrated that the risk of acute cardiac event and T2DM development was lowered with lifestyle modifications[24-27] and pharmacological therapy with metformin, acarbose, and rosiglitazone.[25,28]

In patients with IFG, CV risk increase and risk reduction by treatment were controversial.[23] Hence, we compared

Table 4b: Demographic and clinical characteristics of the study cohort

Parameter	Normal ($n=65$)		IGT + DM ($n=40$)		*P*
	Mean±SD	Percentage	Mean±SD	Percentage	
Number of involved coronary artery					
One vessel		31		25	>0.05
Two vessels		35		28	>0.05
Three vessels		29		27	>0.05
Unknown		5		20	-
Number of revascularized vessel					
None		3		15	>0.05
One vessel		58		55	>0.05
Two vessels		25		15	>0.05
Three vessels		11		5	>0.05
Unknown		3		10	-
CABG presence					
None		85		78	>0.05
Positive		15		22	>0.05
Family history of CAD		55		50	>0.05
Family history of premature CAD		21		21	>0.05
Family history of DM		19		31	>0.05
Duration of drug usage (month) (%)					
ACE inhibitor	31±48	54	54±61	72	>0.05
ARB	14±33	23	11±28	16	>0.05
Beta-blocker	38±47	81	49±55	75	>0.05
Calcium channel blocker	11±28	17	11±27	22	>0.05
Statin	40±45	90	50±57	75	>0.05

ARB: Angiotensin receptor blocker, ACE: Angiotensin-converting enzyme, CABG: Coronary artery bypass graft, CAD: Coronary artery disease, DM: Diabetes mellitus, IGT: Impaired glucose tolerance

Table 5: Comparison of groups according to Homeostasis Model Assessment of Insulin Resistance value

	HOMA-IR <2.18 ($n=54$)		HOMA-IR ≥2.18 ($n=22$)		*P*
	Percentage	Mean±SD	Percentage	Mean±SD	
Duration of HT (months)		45±54		78±68	0.013
Waist circumference (cm)		98±7		105±6	0.0001
WHR (cm)		0.97±0.04		0.98±0.05	0.332
Weight (kg)		78±10		90±15	0.0001
BMI		27.6±3.0		31.8±4.3	0.0001
IGT + T2DM prevalence	15		23		0.327
Patients with FPG <100 mg/dl	71		29		-

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, SD: Standard deviation, BMI: Body mass index, T2DM: Type 2 Diabetes Mellitus, IGT: Impaired Glucose Tolerance, FPG: Fasting plasma glucose, WHR: Waist/hip ratio, SD: Standard deviation

IGT + T2DM group with patients with normal results. In our study, IGT was 25.8% and T2DM was 4.5%. Large-scale studies such as Euro Heart Survey (EHS), China Heart Survey (CHS) and GAMI study were conducted for revealing GI in CAD patients.[29-31] They concluded higher prevalance of GI and diabetes [Figure 2]. Taubert *et al*. demonstrated that new onset of T2DM was 32% in patients who had been directed to elective angiography.[32] EHS, CHS, and GAMI were conducted in patients who had been asked for angiography. However, our study involved patients who were on routine follow-up program. These patients had stable CAD levels with low New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) class. This could be a reason of lower prevalance of IGT and T2DM. On the other hand, the duration of CAD was 56 months in the normal group and 68 months in IGT and T2DM groups. It could be possible that IGT or T2DM development had been detected in these patients and they were already diagnosed as GI and diabetes. As a result, lower incidence was found in the rest of the patients. However, patients were younger in our study (mean age in our study: 58 ± 9, EHS: 66 ± 9, and CHS: 68 ± 9 years).

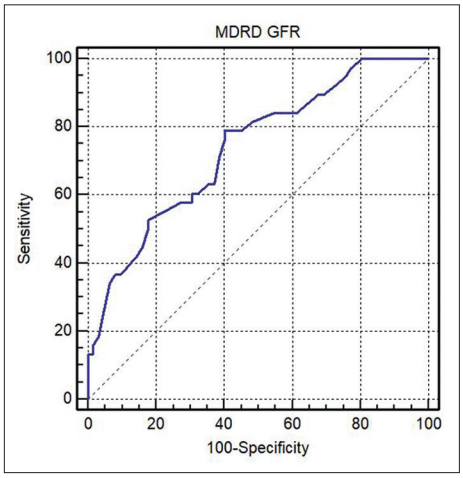

Figure 1: Receiver-operating characteristic curve of Modification of Diet in Renal Disease glomerular filtration rate exhibits the specific threshold value as ≤70 ml/min/m² for maximized predictive value for the presence of impaired glucose tolerance or diabetes mellitus with 50% sensitivity and 82% specificity (area under the curve: 0.736; 95% confidential interval: 0.639–0.819)

Age and sex were similar between the groups. Although Gunner *et al*. observed that BMI >30 kg/m² was a positive predictive value,[32] patients in our study had high values of WC and BMI, which did not differ between the groups. However, in patients with insulin resistance, these two parameters were significantly high compared to those who did not have it. It seems that it can be transformed into GI in the future as had been expected. IGT + T2DM group had significantly higher WHR. Moreover, logistic regression analysis displayed that WHR could be predictive. Renal function parameters were more deteriorated in the IGT + T2DM group. It could be interpreted as the effect of impaired glucose control. It is known that microalbuminuria is related to GI.[33] Stages of nephropathy in diabetic patients were defined as normoalbuminuria, microalbuminuria, macroalbuminuria, and reduced GFR.[34] The occurrence of an isolated reduction in GFR without antecedent microalbuminuria in patients with biopsy-proven diabetic kidney disease was also documented.[35] Another study confirmed this finding with the absence of albuminuria and retinopathy.[36] This finding confirms the presence of nonalbuminuric alternate pathway.[34] A large-scale study confirmed lower eGFR values even in newly diagnosed prediabetic patients.[37] Lower GFR is also found to be associated with insulin resistance.[38,39]

In logistic regression analysis, only MDRD eGFR was an independent predictor of IGT + T2DM. ROC analysis showed that MDRD eGFR ≤70 ml/min/m² criteria had 50% sensitivity, but 82% specificity for predicting IGT + T2DM. It is not suitable for screening test, but low eGFR values could indicate the presence of IGT + T2DM. Hence, these patients should be directed to take the OGTT test.

The relationship between insulin resistance and increased CV mortality has already been demonstrated.[40-43] In CAD patients,

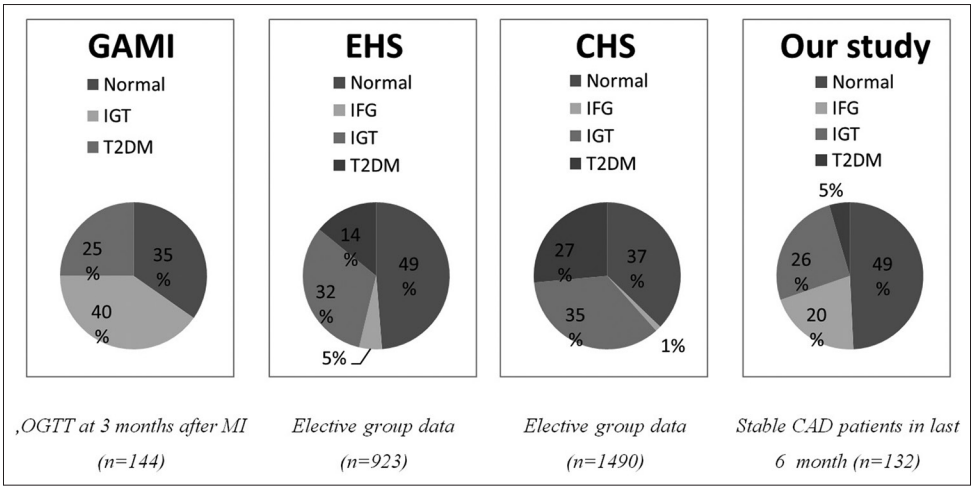

Figure 2: GAMI: Glucose tolerance in patients with acute myocardial infarction Study, EHS: Euro Heart Survey, CHS: China Heart Survey

insulin resistance prevalence is common (s41), and there is a significant relationship between and Gensini score.[44] In our study, 76 patients who had FPG <100 mg/dl results underwent the measurement of insulin levels. HOMA-IR values were calculated. The prevalence of insulin resistance was 29%. Weight, BMI, and WC were significantly higher in patients who had insulin resistance. There is no statistically significant difference between creatinine, Cockroft eGFR, and MDRD eGFR values. Nearly 27% of patients who had new-onset IGT or T2DM had FPG <100 mg/dl. This is one of the important results of our study. In EHS, Two-thirds of the patients would be undiagnosed if the OGTT test had not been performed. Similar results have been increasingly obtained in recent years.[40,29]

Our study was conducted on "functionally good" patients who planned to undergo coronary angiography. Serum creatinin values were between 0.6 and 1.4 mg/dl. They had low CCS and NYHA class. Echocardiographic ejection fraction% values were high. Perhaps, more strong relationships could be detected if they were older or had severe renal dysfunction. Nevertheless, the presence of a significant relationship between eGFR and IGT + DM status is a good finding. Nevertheless, further large-scale studies are needed to confirm this result.

Conclusion

GI and T2DM in CAD patients are common. Conventional cardiac risk factors, drug use, WC and BMI, and CAD duration and severity could not predict IGT + T2DM. Only MDRD eGFR was found to be an independent predictor. Insulin resistance calculated as HOMA-IR was high. OGTT should be performed irrespective of FPG.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Prevalence of Metabolic Syndrome in Young Patients with ST-Elevation Myocardial Infarction

Tugba Kemaloglu Öz, Nazmiye Özbilgin[1], Aylin Sungur[1], Elif Gülsah Bas, Ahmet Zengin[1], Tayfun Gürol, Özer Soylu, Bahadir Dagdeviren

Department of Cardiology, Faculty of Medicine, Bahcesehir University, [1]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Center, Istanbul, Turkey

Abstract

Background: Atherosclerotic cardiovascular disease influences young patients as well as the elderly. A large proportion of patients with coronary artery disease (CAD) have metabolic syndrome (MS), although the frequency and association of its different components are not clear. To the best of our knowledge, there is no any study about the prevalence of MS among young patients with ST-elevation myocardial infarction (STEMI). We sought to determine the prevalence of MS in patients below 46 years of age who presented with STEMI and underwent primary percutaneous coronary intervention. **Methods:** In the present prospective study, 141 consecutive patients with STEMI <46 years of age admitted to intensive coronary care unit. STEMI was defined according to the ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. All patients were grouped presence of MS. In the second step, the components of MS were analyzed, excluding patients with diabetes mellitus (DM). **Results:** The total prevalence of MS was 46.8% ($n = 66$). In MS group, the most frequent component of MS was low high-density lipoprotein (HDL) levels (84.8%), followed by elevated triglycerides (TGs) (78.1%). A total of 121 patients did not have DM and 51 (42.1%) of these patients presented with MS. **Conclusions:** The prevalence of MS in young patients with STEMI is high. Low HDL cholesterol (HDLc) concentrations and high TG levels are cardiovascular risk factors, regardless of low-density lipoprotein cholesterol levels and they are found too often in our study. These results highlight the need to implement preventative strategies for reducing overall cardiovascular risk in young patients as well as elderly.

Keywords: Acute coronary syndrome, coronary artery disease, metabolic syndrome, ST-elevation myocardial infarction, young patients

Introduction

Metabolic syndrome (MS) is a clinical and biological entity of lipid and nonlipid factors of metabolic origin, which places subjects at risk for cardiovascular and cerebrovascular diseases. It has been previously defined by 3rd Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP-III).[1]

Worldwide, coronary artery disease (CAD) is the single most frequent cause of death.[2] The atherosclerotic cardiovascular disease is a chronic disorder developing insidiously, and it remains as the major cause of premature death. Importantly, evidence revealing that increased cardiovascular risk starts to develop at a very young age has accumulated over the past decades.[3] Acute myocardial infarction (AMI) among adults aged <46 is unusual, comprising 2%–10% of all cases.[4]

Some studies have analyzed the prevalence of MS in patients with the acute coronary syndrome (ACS) but with mix populations including both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), also all age groups.[5-7]

To the best of our knowledge, this is the first study to determine the prevalence of the MS in patients <46 years of age who presented with STEMI and underwent primary percutaneous coronary intervention (PCI).

Methods

In the present prospective study, 141 consecutive patients with STEMI <45 years of age admitted to intensive coronary care unit. STEMI was defined according to the ESC guidelines

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Address for correspondence: Dr. Tugba Kemaloglu Öz, Kadiköy, E5 Üzeri 23, Nisan Sok Merdivenköy No: 17, 34732 Kadiköy, Istanbul, Turkey.
E-mail: Tugbakemalogluoz@gmail.com.

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for the management of AMI in patients presenting with ST-segment elevation.[8]

For the diagnosis of MS at baseline, we used the NCEP-ATP III criteria. MS was defined as having three or more of following criteria:[1]

1. Abdominal obesity: Waist circumference (WC) >102 cm for men and >88 cm for women
2. Elevated Triglycerides (TGs) of ≥150 mg/dl
3. Low high-density lipoprotein (HDL) <40 mg/dl for men and <50 mg/dl for women
4. Elevated blood pressure ≥130/85 mmHg
5. Elevated fasting blood glucose ≥110 mg/dl.

Patients who were not diagnosed with STEMI or had incomplete data or who used antilipidemic drugs were excluded from the study.

All patients underwent coronary angiography and results were analyzed. A coronary lesion was defined as significant if at least 70% of lumen diameter was reduced, except culprit lesion.

All patients were grouped first based on the presence of MS and then grouped again after excluding patients with diabetes mellitus (DM).

Demographic and clinical data were obtained from histories: age, sex, smoking, alcohol consumption, family history (premature coronary heart disease at 55 and 65 years of age in male and female first-degree relatives, respectively), and previous lipid-lowering treatment.

The diagnosis of DM was made by a fasting blood glucose level of 125 mg/dl or a history of DM, including those treated with diet control, oral medications, or insulin.

Blood pressure was determined in both arms after a 5-min rest. Patients were diagnosed with high blood pressure for an average (of 3 values) blood pressure during admission ≥130/85 mm Hg or if a previous diagnosis of hypertension had been made and/or treatment had already been prescribed at the time of admission.

The heights and weights of all patients were taken before discharge. The weight in kilograms (kg) was measured using a calibrated scale with capacity for 180 kg and increments of 100 g. The height, in meters, was measured using anthropometric scale. The body-mass index (BMI) was calculated using the formula: Body weight (kg)/heigt² (m²). We used the international classes of BMI: Obesity (BMI ≥30 kg/m²), overweight (BMI 25–29.9 kg/m²), normal (BMI 18.5–24.9 kg/m²), and underweight (BMI <18.5 kg/m²).

Waist and hip circumferences (HC) were recorded. WCs were measured at the level midway between the lowest rib and the iliac crest, the thinnest part of abdomen and HC were measured at the maximum circumference between the hips and buttocks.

Plasma samples were obtained after at least 12 h of fasting. Total cholesterol and TG levels were measured using an automated enzyme analyzer, and low-density lipoprotein (LDL) concentrations were calculated using the Friedewald formula whenever plasma TG concentrations were <400 mg/dl (Advia Systems, Siemens, Australia). D-dimer was estimated using automatic latex immunoassay (HemosIL™, Instrumentation Laboratory, USA). Fibrinogen-C was measured according to the method of Class (HemosIL^{R}, Instrumentation Laboratory, USA). C-reactive protein was measured using latex-enhanced immunotubidimetry (Advia System, Siemens, Australia).

Transthoracic echocardiography was performed in all patients before discharge.

Quantitative variables were expressed as a mean ± standard deviation, median (interquartile range) and qualitative variables as absolute and relative frequencies. Normally distributed data were analyzed using the Student's *t*-test to compare means; otherwise, the Mann–Whitney U-test (MWU) was used. The Chi-square test was used to analyze differences between qualitative variables. A two-sided $P < 0.05$ was used as a cut-off for statistical significance. Results of x^2 test were expressed as Chi-square (degrees of freedom, sample size) = Pearson's Chi-square value, *P* value. Results of Student's *t*-test were expressed as *t* (degrees of freedom) = *t* value, *P* value, 95% confidence interval (CI). Results of MWU-test were expressed as MWU value, *P* value. The SPSS software version 17.0 (SPSS science, Chicago, IL, USA) was used for statistical analyses.

Institutional Review Board approved this study for research, and all patients gave written informed consent before the study.

Results

The present study included a total of 141 consecutive patients with STEMI. The majority of the admitted patients were men (87.9%), and the mean age was 38.3 ± 4.6, ranging from 26 to 45 years. Table 1 shows the demographic and clinical characteristics of the patients stratified by MS status, and we compared the baseline characteristics of patients with and without MS. BMI was significantly higher in the MS group (χ^2 [2, 139] = 19.17, $P < 0.001$). Waist and HC were also significantly higher in the MS group (t [138] = −4.24, $P < 0.001$, 95% CI [−10.39, −3.79] and t [138] = −3.24, $P < 0.001$, 95% CI (−6.91, −1.67); respectively). Systolic and diastolic blood pressures were significantly elevated in the MS group (t [137] = −3.61, $P < 0.001$, 95% CI [−14.78, −4.33] and t [137] = −3.78, $P < 0.001$, 95% CI [−9.57, −2.99]; respectively). Fasting plasma glucose was significantly higher in the MS group; t (138) = −3.92, $P < 0.001$, 95% CI (−46.26, −15.23). Total cholesterol and TG showed significantly higher levels in the MS group (t [138] = −2.23, $P = 0.02$, 95% CI [−27.88, −1.66] and t [136] = −6.19, $P < 0.001$, 95% CI [−147.08, −75.87], respectively). Fibrinogen was also found to be significantly higher in the patients with MS; t (128) = −2.17, $P = 0.01$, 95% CI (−69.49, −3.3). However, HDL cholesterol (HDLc) and LDL cholesterol (LDLc) levels did not significantly differ between the groups.

Table 1 Demographic and clinical characteristics of the patients stratified by metabolic syndrome status

Variable	MS		*P*
	Positive (*n*=66: 46.8%)	Negative (*n*=75: 53.2%)	
Age (years)	39.0±4.0	37,7±5.1	0.12
Men, *n* (%)	55 (83.3)	69 (92.0)	0.11
Smoker, *n* (%)	55 (83.3)	64 (85.3)	0.74
Alcohol consumer, *n* (%)	12 (18.2)	6 (8.1)	0.07
Drug abuser, *n* (%)	1 (1.5)	1 (1.3)	0.95
Family history, *n* (%)	21 (31.8)	18 (24.0)	0.30
BMI (kg/m^2), *n* (%)	29.3±4.1	26.4±3.6	
<25	11 (16.7)	28 (37.3)	<0.001
25-29.9	22 (34.8)	36 (48.0)	
>30	32 (49.2)	11 (14.7)	
Waist circumference (cm)	98.4±11.3	91.5±8.3	<0.001
Hip circumference (cm)	105.3±8.5	101.1±7.1	<0.001
Blood pressure (mmHg)			
Systolic	128.2±17.4	118.6±13.5	<0.001
Diastolic	78.2±11.4	72.0±7.9	<0.001
Fasting plasma glucose (mg/dl)*	47 (113)	14.2 (94)	<0.001
Total cholesterol (mg/dl)	196.5±39.8	181.7±38.5	0.02
LDL-C (mg/dl)	117.7±31.5	121.7±36.1	0.50
HDL-C (mg/dl)	35.1±11.8	35.1±9.0	0.99
Triglycerides (mg/dl)*	107 (190)	62.2 (110)	<0.001
CRP (mg/dl)*	3.4 (4.2)	1.0 (3.4)	0.15
Fibrinogen (mg/dl)	389.3±110.5	348.3±78.9	0.01
D-dimer (ng/ml)*	136.0 (123.0)	135.2 (117.5)	0.52
Ejection fraction (%)	51.7±8.6	52.5±9.1	0.60

*Values expressed as median (interquartile range). Values are mean±SD or *n* (%). BMI: Body mass index, CRP: C-reactive protein, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, MS: Metabolic syndrome, SD: Standard deviation

The total prevalence of MS using ATPIII criteria was 46.8% (*n* = 66). In MS group, the most frequent component of MS was low HDL level (84.8%), followed by elevated TG (78.1%), elevated blood pressure (63.6%), carbohydrate metabolism disorder (59.1%) and in the last place, abdominal obesity (46.%) [Figure 1]. We found no MS components in 11 patients (7.8%). 15 patients with MS (22.7%) had DM.

In total, MS was not found in 75 (53.2%) patients. The most frequent component was among the patients without MS was low HDLc level (67.6%), followed by elevated blood pressure (25.7%), elevated TG (23.0%), carbohydrate metabolism disorder (21.3%), and abdominal obesity (8.0%). Five patients without MS (6.7%) had DM.

In this study, 121 patients did not have DM and 51 (42.1%) of these patients presented with MS [Table 2]. The most prevalent component of MS was low HDLc (73.6%), followed by elevated TG (45.5%), elevated blood pressure (43.0%), carbohydrate metabolism disorder (30.6%) and, finally, abdominal obesity (23.1%) [Figure 1]. In this substudy prevalence of alcohol consumption was significantly higher in patients with MS than patients without MS;

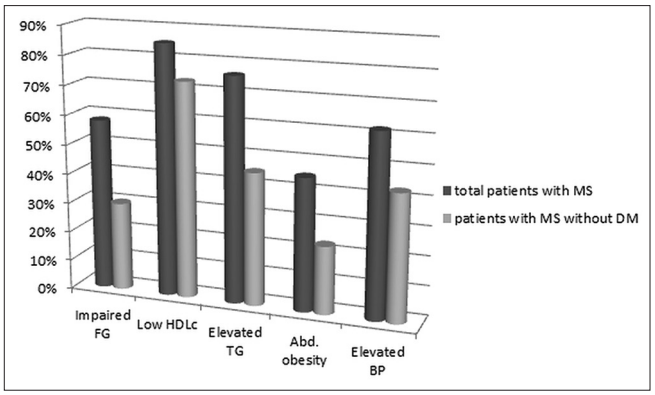

Figure 1: Distribution of metabolic syndrome criterias in all patients with metabolic syndrome and after excluding patients with DM. Abd: Abdominal, BP: Blood pressure, DM: Diabetes mellitus, FG: Fasting glucose, HDLc: High-density lipoprotein cholesterol, TG: Triglycerides

χ^2 (1, 120) = 4.09, P = 0.04. BMI was higher in the MS group; χ^2 (2,120) = 15.33, P < 0.001. Waist and HC were also significantly higher in patients with MS (t [119] = −3.53, P < 0.001, 95% CI [−10.24, −2.88] and t [119] = −2.57, P = 0.01, 95% CI [−6.83, −0.88], respectively). Systolic and diastolic blood pressures were significantly elevated in the MS group (t [118] = −3.94, P < 0.001, 95% CI [−15.76, −5.21] and t [118] = −3.72, P < 0.001, 95% CI [−10.05, −3.07]; respectively). Fasting plasma glucose was significantly higher in the MS group (MWU = 1046, P < 0.001). Total cholesterol showed significantly higher levels in patients with MS; t (118) = −2.03, P = 0.04, 95% CI (−28.78, −0.36). TG levels was significantly higher in the MS group (MWU = 636.5, P < 0.001). Fibrinogen was also found to be significantly higher in the patients with MS; t (109) = −3.01, P < 0.001, 95% CI (−84.97, −17.49).

When we assessed the most prevalent combination of ATPIII factors in the patients with MS, 12 patients (18.2%) fulfilled the triad of low HDLc levels, elevated TG and carbohydrate metabolism disorder. The most prevalent tetrad was (*n* = 9, 13.6%) low HDLc levels, elevated TG, carbohydrate metabolism disorder and elevated blood pressure. In the patients without DM the most prevalent triad of MS was low HDLc levels, elevated TG and elevated blood pressure (*n* = 10, 19.6%). The most prevalent tetrad was found same in two groups.

Single-vessel involvement with left anterior descending artery (LAD), as the culprit lesion, was the most frequent presentation and followed by the circumflex artery and right coronary artery. Distribution of vascular lesions in patients with MS was compared to patients without MS, and no significant difference was observed among the groups.

Discussion

In the present prospective study, 141 consecutive patients with STEMI < 45 years of age who were treated with primary PCI were evaluated. Only a few studies have evaluated the prevalence of MS, as defined by the nonmodified NCEP-ATP

Table 2: Demographic and clinical characteristics of the patients stratified by metabolic syndrome status, after excluding patients with diabetes mellitus

Variable	MS		*P*
	Positive (*n*=51: 42.1%)	Negative (*n*=70: 57.9%)	
Age (years)	38.3±4.1	37.4±5.0	0.35
Men, *n* (%)	41 (80.4)	64 (91.4)	0.61
Alcohol consumer, *n* (%)	10 (19.6)	5 (7.2)	0.04
Drug abuser, *n* (%)	1 (2.0)	1 (1.4)	0.82
Family history, *n* (%)	16 (31.4)	17 (24.3)	0.38
BMI (kg/m^2), *n* (%)	28.9±4.0	26.3±3.6	
<25	10 (20.0)	28 (40.0)	<0.001
25-29.9	17 (34.0)	32 (45.7)	
>30	23 (46.0)	10 (14.3)	
Waist circumference (cm)	97.7±12.0	91.1±8.4	<0.001
Hip circumference (cm)	105.0±9.1	101.2±7.3	0.01
Blood pressure (mmHg)			
Systolic	128.5±16.3	118.0±12.8	<0.001
Diastolic	78.4±11.2	71.8±8.0	<0.001
Fasting plasma glucose (mg/dl)*	24.0 (110.0)	22.2 (97.5)	<0.001
Total cholesterol (mg/dl)	196.5±40.2	181.9±37.8	0.04
LDL-C (mg/dl)	118.0±32.2	122.0±36.0	0.53
HDL-C (mg/dl)*	9.0 (36.0)	13.0 (34.5)	0.52
Triglycerides (mg/dl)*	103.5 (190.0)	89.7 (140.0)	<0.001
hsCRP (mg/dl)*	3.5 (2.1)	3.8 (1.5)	0.22
Fibrinojen (mg/dl)	401.4±100.3	350.2±78.9	<0.001
D-dimer (ng/ml)*	106.0 (110.0)	119.0 (115.5)	0.59
Ejection fraction (%)	51.7±8.5	52.9±8.6	0.50

*Values expressed as median (interquartile range). Values are mean±SD or *n* (%). BMI: Body mass index, CRP: C-reactive protein, DM: Diabetes mellitus, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SD: Standard deviation, MS: Metabolic syndrome

III criteria and to the best of our knowledge, there is not any study about the prevalence of MS among young patients with STEMI.

The present study found that patients with STEMI had a high prevalence of MS (46.8%). In two previous studies, patients aged <45 years with STEMI or NSTEMI were evaluated, and the prevalence of MS was 40.4%[9] and 46.0.[10] In a previous Turkish study, 217 patients (mean age at baseline 49.1 ± 13 years) with CAD, the prevalence of MS was reported 53%.[11] The other studies reported the prevalence of MS in ACS 29%–66%.[5,6,12-14] In a cross-sectional study, prevalence of MS was found 49.7% among adult patients who admitted to cardiology department.[14] In another study, 1255 patients aged 65 years old and over without any acute illness were evaluated, and prevalence of MS was reported 23.8%.[15]

When the twenty patients with DM were excluded, 51 of the remaining 121 (42.1%) have >3 criteria for MS. The other studies found the prevalence of MS among the patients with ACS without DM, 34%[5] and 42%.[10]

The average value for criteria of MS (TG, systolic and diastolic blood pressure, fasting plasma glucose, and WC) were all significantly higher in patients with MS compared with those without but no significant difference was observed between two groups for HDLc and LDLc levels. Multiple epidemiological studies have demonstrated that HDLc concentrations are inversely and independently associated with the development of ischemic heart disease,[2] and hence, in our study prevalence of low HDLc level was seen very common in all groups. Statistical significance between patients with and without MS was maintained even when patients with known or newly diagnosed DM excluded. At the same time, low HDLc level was most frequent component of MS, followed by elevated TG [Figure 1]. The ATPIII concluded that low HDLc concentrations and high TG levels are cardiovascular risk factors, regardless of LDLc levels.[1] And, they are found very common in young patients with STEMI, but the first target is LDLc level according to current guidelines in all ages.[2,16]

The most frequent triad combination of MS was impaired glucose tolerance, low HDLc level and elevated TG in the MS group without excluding DM. In a retrospective study of 574 patients with ACS, low HDLc, elevated blood pressure and impaired glucose tolerance were found to be the most frequent triad of MS.[5]

Perez *et al*. reported that fibrinogen and C-reactive protein (CRP) levels were significantly higher in adults with MS than without MS.[17] Differently, in this study fibrinogen levels were found significantly higher in patients with MS and there was no significant difference between two groups in the level of CRP and D-dimer. But, in our study, all patients with STEMI and CRP and D-dimer levels could be increased due to STEMI in both groups. In a case–control study, 220 patients with ACS were compared with 116 healthy volunteers, and ACS cases showed 4-fold higher median CRP concentration on admission than healthy controls.[18] However, the d-dimer level was found to be higher among patients with ACS.[19-24] In another previous study, 2722 nondiabetic men aged 60–79 years with no history of CAD were determined, and insulin resistance was found significantly associated with increased CRP, but the association with fibrinogen and fibrin d-dimer were found weak.[25]

Among our patients, single-vessel involvement with LAD was the most frequent culprit lesion within both groups. Colkesen *et al*. reported characteristics of STEMI in young patients aged <35. They reported that young patients with acute STEMI showed a preponderance of single-vessel disease and acute anterior STEMI owing to occluded LAD artery.[26]

In our study, there was no relationship between MS and the number of vessels affected. However, Marso *et al*. determined plaque composition of 673 patients with ACS and lesion length, plaque burden, necrotic core, and calcium content were significantly greater among nonculprit lesions of patients with diabetes or MS.[27] Furthermore, Yoon *et al*. found relationship between MS score and severity of coronary atherosclerosis.[28]

In both studies, the assessment of vessels was different and more detailed than our study.

Another study included 100 patients with STEMI, and 40% of these patients have MS based on Consensus statement for diagnosis of MS for Asian Indians, 49% had anterior wall MI and 37% had inferior wall MI.[29] In the different data that study population consisted of 467 men admitted with ACS. A total of 324 (69.37%) patients fulfilled the criteria stated in the latest joint statement for the definition of MS.[8] Among them, STEMI was present in 178 (54.9%) patients and NSTE-ACS in 146 (45.1%) patients (*P* value, nonsignificant). There was also no significant difference in the prevalence of different types of ACS between the MS and non-MS groups (STEMI, 54.9% vs. 51.7%; NSTE-ACS, 45.1% vs. 48.3%, respectively; $P = 0.294$ for both).[30]

Conclusions

This study revealed that the prevalence of MS in young patients with STEMI is high. Moreover, the most common criteria of MS are low HDLc and followed by elevated TG. Finally, the prevalence of MS is increasing worldwide, and it influences all age groups, and hence, these results highlight the need to implement preventative strategies for reducing overall cardiovascular risks in young patients as well as elderly.

Limitations

The study had several limitations. First, this is a single-center study. Moreover, second, unfortunately, we could not sought to examine the long-term clinical outcomes of all patients. Moreover, third, in our study, the assessment of vessels lesions was not detailed in both groups.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Congenital and Acquired Lutembacher's Syndrome Presenting in Two Adults

Umut Kocabas, Ugur Onsel Turk[1]

Department of Cardiology, Edremit State Hospital, Balikesir, [1]Center for Drug Research and Development and Pharmacokinetic Applications, School of Medicine, Ege University, Izmir, Turkey

Abstract

The coexistence of atrial septal defect (ASD) and mitral stenosis (MS) is defined as Lutembacher's syndrome (LS). LS was originally defined as the development of MS in a patient having a congenital ASD diagnosis. However, as the percutaneous interventions for MS have become widespread, the persistence of associated iatrogenic ASDs caused has given rise to a different form of the disease. LS may occur as spontaneous or iatrogenic ASD concomitant with acquired MS; this form is known as "acquired LS." This report presents two cases illustrating congenital LS and "acquired LS."

Keywords: Atrial septal defect, congenital heart disease, Lutembacher's syndrome, mitral stenosis, valvular heart disease

Introduction

Lutembacher's syndrome (LS) occurs as a rare combination of congenital secundum atrial septal defect (ASD) and an acquired mitral stenosis (MS).[1] Alternatively, LS may occur as spontaneous or iatrogenic ASD concomitant with acquired MS; this form is known as "acquired LS".[2] The literature also describes "reverse LS," which is characterized by a predominant pulmonary-to-systemic or right-to-left shunting of blood in the context of an ASD and severe tricuspid stenosis.[3] This report presents two cases illustrating congenital LS and "acquired LS."

Case Reports

Case presentation 1

A 53-year-old female was referred to our cardiology clinic with shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea. The patient history showed percutaneous mitral balloon valvuloplasty (PMBV) for rheumatic MS in 1998. Physical examination revealed a systolic murmur in the mesocardiac area and a diastolic murmur in the apical area. The 12-lead electrocardiography showed atrial fibrillation with rapid ventricular response. Transthoracic echocardiography found that the left ventricular ejection fraction was preserved and revealed calcified and thickened mitral valve with giant left atrium, severe mitral regurgitation, severe eccentric tricuspid regurgitation with a pulmonary systolic pressure of 80 mmHg and a 5-mm sized, and mild left-to-right shunting across an ostium secundum ASD [Figure 1a-e]. The Qp/Qs ratio was 1.48. Mitral valve area (MVA) was 1.1 cm^2 according to the pressure half-time (PHT) method [Figure 1f], and the mean diastolic transvalvular mitral valve gradient was 13 mmHg. To minimize the risk of miscalculations due to decreased left atrial pressure and diastolic mitral pressure gradient, which is characteristic of ASD, MVA was also calculated as 0.9 cm^2 with the planimetry method. The patient having no ASD in previous echocardiography reports and having a history of PMBV was diagnosed with "acquired LS." This is thought to have arisen iatrogenically due to PMBV in 1998 and/or spontaneously due to extreme tension of the left atrium. Following refusal of cardiac surgery, the patient was discharged with warfarin, bisoprolol, digoxin, and furosemide therapy and a program of intensive follow-up. In follow-up program, warfarin dose titrated according to international normalized ratio and

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Address for correspondence: Dr. Umut Kocabas, Department of Cardiology, Baskent University Faculty of Medicine, Istanbul, Turkey.
E-mail: umutkocabas@hotmail.com

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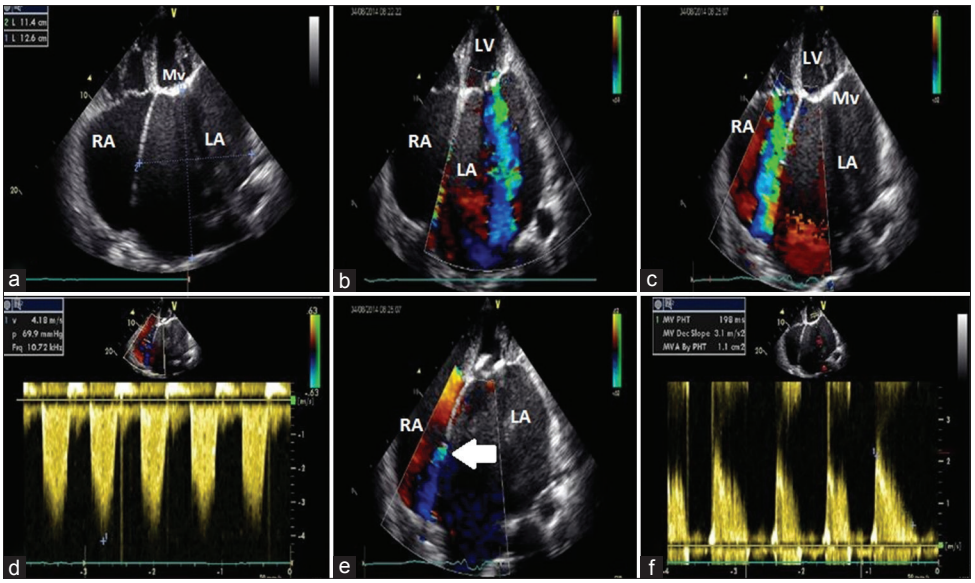

Figure 1: Transthoracic echocardiography apical 4-chamber view image showing calcified and thickened mitral valve with giant left atrium (a), severe mitral regurgitation (b), severe eccentric tricuspid regurgitation with a pulmonary systolic pressure of 80 mmHg (c and d) and mild left-to-right shunting across an ostium secundum atrial septal defect (e, arrow) and mitral valve area was 1.1 cm^2 according to the pressure half-time method (f). RA: Right atrium, La: Left atrium, LV: Left ventricle, MV: Mitral valve

bisoprolol and digoxin doses titrated according to heart rate, blood pressure, and serum digoxin level in every 3 weeks.

Case presentation 2

A 48-year-old female patient was referred to our cardiology clinic with palpitation and dyspnea. Her medical history was unremarkable. On physical examination, a diastolic murmur of 2/6° in the apical area and a systolic murmur in the mesocardiac area were auscultated. The 12-lead electrocardiography showed sinus rhythm with frequent atrial premature complexes, and *P* wave morphology was consistent with "P mitrale." Transthoracic echocardiography showed thickened, fibrotic mitral valves with a valve area of 1.6 cm^2 using the planimetry method [Figure 2a and b]. Doppler echocardiography revealed mild mitral and tricuspid regurgitation, a 4-mm sized, left-to-right shunting across an ostium secundum ASD [Figure 2c and d]. The patient was diagnosed with LS with the coexistence of MS and ASD. The Qp/Qs ratio was 1.22 and systolic pulmonary arterial pressure was 38 mmHg. The patient was discharged with metoprolol therapy and a program of echocardiographic follow-up in every 6 months.

Discussion

The coexistence of congenital ASD and acquired MS is defined as LS.[1] LS is a rare condition with a reported incidence of 0.001 in one million. Since both ASD and MS are frequently found in women, LS also occurs more commonly among women.[4] Hemodynamic interactions between ASD and MS are challenging. As in LS, one lesion can alter the clinical and hemodynamical effects of the other lesion. Clinical and hemodynamic interactions are dependent on three of the following properties: the diameter of ASD, severity of MS, and compliance of the right ventricle.[5] In a patient with MS, a large ASD provides an additional outflow point for the left atrium. The left atrium is decompressed via ASD, resulting in decreased left-atrial and pulmonary capillary pressures. Consequently, symptoms observed in isolated MS patients, such as exertional dyspnea, orthopnea, and paroxysmal dyspnea, occur in the later phases of the disease. Blood flow through the mitral valve is decreased due to an increase in the left-to-atrial shunt. The result of this effect is a decrease in the severity of mitral murmur and presystolic accentuation in patients having sinus rhythm, and the opening snap cannot be auscultated.[6] On the other hand, increased left-atrial pressure due to MS progressively increases the left-to-right shunt via ASD. In particular, in the presence of a large ASD, the right ventricular volume and pressure overload will increase over time, causing the right ventricle to dilate, leading to pulmonary hypertension and right-heart failure.[2] In summary, the coexistence of MS and ASD has a distinct course as compared with isolated MS. The existence of ASD in an MS patient can mimic the symptoms and auscultatory findings of the disease. Increased left-atrial pressure due to MS increases the left-to-atrial shunt, causing early right-heart failure and pulmonary hypertension.

LS was originally defined as the development of MS in a patient having an ASD diagnosis. However, as the percutaneous interventions for MS have become widespread, the persistence of associated iatrogenic defects caused has given rise to a different form of the disease. This condition, "acquired LS," may result from two different scenarios. In the first scenario, in isolated MS patients, an "iatrogenic ASD" may occur due to PMBV, which is performed through atrial septal puncture by

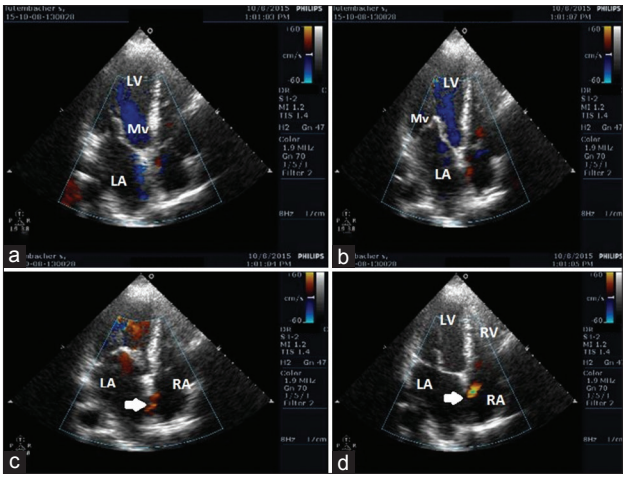

Figure 2: Transthoracic echocardiography apical 4-chamber view image showing thickened, fibrotic, and stenotic mitral valves (a and b), Doppler echocardiography revealed left-to-right shunting across an ostium secundum atrial septal defect (c and d, arrow). RA: Right atrium, LA: Left atrium, RV: Right ventricle, LV: Left ventricle, MV: Mitral valve

the transseptal approach.[2] In a trial by Yoshida *et al*., within the first 24 h of the procedure, 50% of the patients had ASD in transthoracic echocardiography, and 87% of the patients had ASD in transesophageal echocardiography.[7] Iatrogenic ASD, which occurs after PMBV, usually has a diameter of 0,0.5–1 cm. Defects that are >1 cm rarely occur and are associated with large left-to-right shunts. Iatrogenic defects that are <0.7 cm have a tendency to close spontaneously within 24 h.[8] The second scenario for "acquired LS" is spontaneous secundum type ASD development due to progressive left-atrial enlargement and pressure overload in the presence of severe MS.[2]

The parameters used to assess the severity of MS are as follows: MVA, mitral valve mean diastolic gradient, and pulmonary arterial pressure. The most commonly used echocardiographic methods for calculating MVA are PHT, planimetric MVA calculation, and continuity equation.[9] In LS patients, the existence of ASD directs blood flow from the left-to-right atrium, causing diminished blood flow through the mitral valve in the diastole. Diminution of blood flow decreases PHT, causing an underestimation of the severity of MS. For this reason, PHT is inappropriate and not recommended for calculating MVA in LS patients. The appropriate choices for calculating MVA are planimetry and continuity equation. However, in patients with atrial fibrillation, MVA cannot be calculated via continuity equation.[10]

LS has a good prognosis if it is diagnosed early. In patients who are diagnosed before the development of right-heart failure or pulmonary hypertension, survival is excellent following mitral valve replacement and ASD closure. However, prognosis will be poor if pulmonary hypertension and right-heart failure exist at the time of diagnosis.

Conclusion

The purpose of this report is to review the clinical characteristics, echocardiographic diagnosis, and prognosis of LS. LS is a rare diagnosis for most adult cardiologists. This report seeks to help clinicians to better grasp the clinical and echocardiographic characteristics of "acquired LS" presenting in older patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Double Orifice Mitral Valve: An Incidental Finding

Bhavin Brahmbhatt, Nikunj Vaidhya, Vaibhav Jain, Mrinal Patel, Amit Mishra[1]

Departments of Cardiovascular and Thoracic Surgery and [1]Pediatric Cardiovascular and Thoracic Surgery, U. N. Mehta Institute of Cardiology and Research Center, (Affiliated to BJ Medical College), Ahmedabad, Gujarat, India

Abstract

A double orifice mitral valve (DOMV) represents a rare congenital malformation characterized by two valve orifices with two separate subvalvular apparatus. We present an interesting case of an asymptomatic 1 year and 8 months old male child with DOMV who successfully underwent surgery.

Keywords: Congenital heart disease, double orifice mitral valve, echocardiography, mitral valve

Introduction

A double orifice mitral valve (DOMV) is an uncommon anomaly that was first described by Greenfield in 1876. DOMV represents a rare congenital malformation characterized by two valve orifices with two separate subvalvular apparatus.

Case Report

We report a case of an asymptomatic 1 year and 8 months old male child, referred to our department by a pediatric cardiologist. His echocardiography finding suggestive of partial atrioventricular (AV) canal defect with DOMV with the small mitral annulus [Figure 1]. Tricuspid annulus was 14 mm whereas mitral annulus was 9 mm.

During surgery, DOMV anatomy was assessed [Figure 2], the valve area was adequate for his body surface area without any regurgitation. At this moment, recognition of DOMV has no impact on the patient's management. It might, however, be of importance at the time of a further follow-up where he can develop regurgitation. The patient is on regular follow-up without any mitral valve regurgitation or stenosis for 6 months, and he is doing well.

Discussion

A DOMV is an uncommon anomaly that was first described by Greenfield in 1876.[1] DOMV represents a rare congenital malformation. Characterized by two valve orifices with two separate subvalvular apparatus.[2,3] The natural history of DOMV with intact AV septum is not known.

This case reveals the necessity of careful imaging of the mitral valve apparatus, not only in patients with AV septal

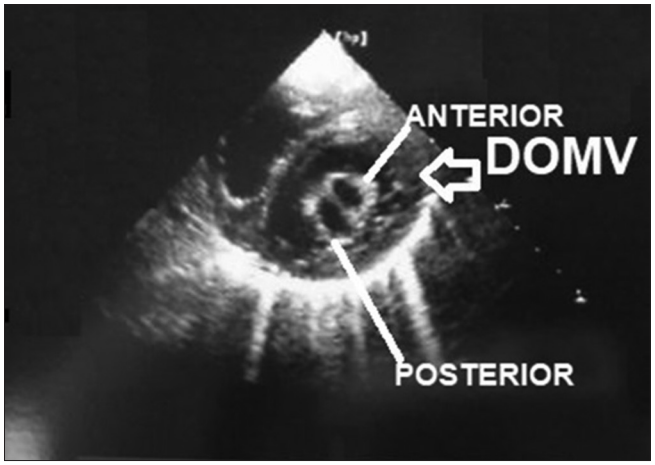

Figure 1: Parasternal short axis view at the level of the mitral valve demonstrating the two separate orifices of the double orifice mitral valve

Address for correspondence: Dr. Amit Mishra,
Department of Pediatric Cardiovascular and Thoracic Surgery,
U. N. Mehta Institute of Cardiology and Research Center,
(Affiliated to BJ Medical College),
Ahmedabad - 380 016, Gujarat, India.
E-mail: drmishraamit@gmail.com

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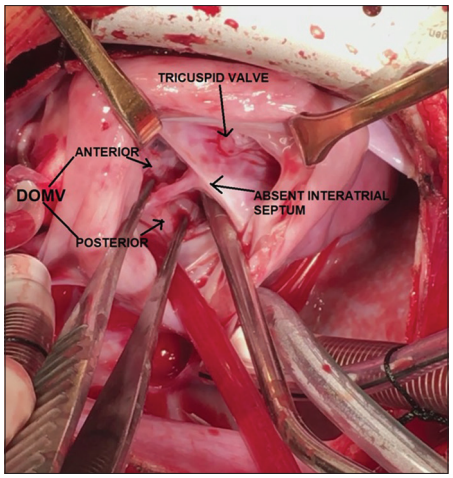

Figure 2: Operative finding

defects but also in patients with congenital left obstructive heart disease.

It is most often associated with AV septal defects (it has been found in as many as 4.9%–17.9% of cases in necropsy studies),[4] but may also be present together with other congenital heart defects such as left-sided obstructive lesions, ventricular septal defects, or cyanotic lesions. Rarely, patients with isolated DOMV are reported. However, even in the modern era of echocardiography DOMV often remains unrecognized. The hemodynamic impact of DOMV varies from a normally functioning valve to (less frequent) significant mitral regurgitation (with or without cleft) or stenosis. Surgical correction of DOMV is indicated in a minority of patients undergoing repair of associated lesions. However, these patients need regular follow-up to know any change in morphology and function of the left AV valve in the near future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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