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EC CARDIOLOGY
Research Article

Secondary Mitral Regurgitation Impact on Symptoms and Prognosis in a Moroccan Population of Heart Failure with Reduced Ejection Fraction Patients

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Received: July 12, 2020; **Published:** September 30, 2020

Abstract

Introduction: Secondary mitral regurgitation (SMR) occurs in 20% to 30% of patients with heart failure and reduced left ventricular ejection fraction (HFrEF). There is conflicting evidence regarding its prognostic significance. The aim of this study is to report the impact of SMR on Moroccan HFrEF patients symptoms and prognosis.

Methods: Transversal retrospective study conducted between May 2006 and June 2019 including all patients with HFrEF, followed-up in the therapeutic unit of HF of our department. We studied 2 groups of patients: group 1 with SMR and group 2 without SMR. Data were collected on Excel and analyzed using SPSS 2.0 software. Differences were considered statistically significant when $p < 0.05$.

Results: Among 3412 patients, 42.6% had SMR. Mean age was 66.68 ± 12.78 years in group 1 versus 63.86 ± 12.62 years in group 2 ($p < 0.001$). History of arterial hypertension in 40.4% versus 38.5% ($p < 0.001$), diabetes mellitus in 30.8% versus 32.3% ($p < 0.001$), tobacco use in 30.2% versus 37.6% ($p < 0.001$). Regarding etiologies: ischemic heart disease in 54.5% versus 63.5% ($p < 0.001$). Regarding NYHA functional class: class I in 11.7% versus 22%, class II in 59.8% versus 60.5%, class III in 26.5% versus 15.5%, class IV in 2.1% versus 2% ($p < 0.001$). Signs of left HF in 11.2% versus 6.8% ($p < 0.001$), signs of right HF in 8.8% versus 4.2% ($p < 0.001$), mean HR was 79.39 ± 16.82 bpm versus 76.07 ± 16.72 bpm ($p < 0.001$). Persistent atrial fibrillation was present in 13.1% versus 9.4% ($p < 0.001$). Echocardiographic data: mean LVEF was 34.69 ± 13.19% versus 33.90 ± 14.19% ($p = 0.488$), mean LVEDD was 59.21 ± 9.33 mm versus 56.12 ± 8.21 mm ($p < 0.001$), elevated left ventricle filling pressures in 26.7% versus 16.8% ($p < 0.001$), SPAP was 39.20 ± 15.17 mmHg versus 35.16 ± 15.74 mmHg ($p < 0.001$), significant functional tricuspid regurgitation in 12.6% versus 3.9% ($p < 0.001$), RV systolic longitudinal dysfunction in 47.6% versus 40.8% ($p < 0.001$). HF hospitalization rates were 29.6% versus 20.3% ($p < 0.001$). Mortality rates were 3.1% versus 1.5% ($p = 0.012$).

Conclusion: In patients with HFrEF, SMR impacts NYHA functional class, and is associated with hospitalisation for HF and mortality.

Keywords: *Secondary Mitral Regurgitation; Heart Failure with Reduced Ejection Fraction; NYHA Functional Class; Hospitalisation for Heart Failure; Mortality*

Abbreviations

SMR: Secondary Mitral Regurgitation; HFrEF: Heart Failure with Reduced Ejection Fraction; HF: Heart Failure; NYHA: New York Heart Association; LVEF: Left Ventricle Ejection Fraction; LVEDD: Left Ventricle End Diastolic Diameter; SPAP: Systolic Pulmonary Artery Pressure; RV: Right Ventricle; IHD: Ischemic Heart Disease; DCM: Dilated Cardiomyopathy; VHD: Valvular Heart Disease; HR: Heart Rate; LVFP: Left Ventricle Filling Pressures; TR: Tricuspid Regurgitation; ACE-I: Angiotensin Converting Enzyme Inhibitors

Introduction

Secondary mitral regurgitation (SMR) occurs when normal or almost normal mitral leaflets are prevented from adequate coaptation by underlying left ventricular (LV) dysfunction, mitral annular dilation, or both. It is the most common valve disease, with an incidence of less than 1% before age 55 years but reaching 9% after age 75 years. Secondary mitral regurgitation is generally divided into SMR due to ischemic heart disease or nonischemic cardiomyopathies, although it can also be a consequence of chronic atrial enlargement [1]. SMR in heart failure with reduced ejection fraction (HFrEF) reflects primarily the severity of LV dysfunction and is not related to structural alterations of the mitral valvular apparatus [2].

Independently of the etiology of (HFrEF) and its underlying mechanisms, SMR is a common finding, it occurs in 20 to 30% of patients with HFrEF and portends a poor clinical outcome despite Guideline Directed Therapy (GDT) [3]. However, other studies did not confirm these results [4,5].

Aim of the Study

This study is aiming to report the impact of SMR on symptoms and prognosis in a population of HFrEF Moroccan patients.

Materials and Methods

We conducted a transversal retrospective study between May 2006 and June 2019 including all patients beyond the age of 14 with HFrEF, followed-up in the therapeutic unit of HF of our department.

We studied 2 groups of patients: group 1 with secondary mitral regurgitation and group 2 without secondary mitral regurgitation.

We compared clinical and prognostic features, echocardiographic and electrical data.

Data were collected on Excel and analyzed using IBM SPSS 2.0 software.

Differences were considered statistically significant when $p < 0.05$.

Results

Among 3412 patients, 1454 (42.6%) had secondary mitral regurgitation (mild in 19.7%, moderate in 21.3% and severe in 1.6%). Mean age was 66.68 ± 12.78 years in group 1 versus 63.86 ± 12.62 years in group 2 ($p < 0.001$). Regarding cardiovascular risk factors: history of arterial hypertension was found in 40.4% versus 38.5% ($p < 0.001$), diabetes mellitus in 30.8% versus 32.3% ($p < 0.001$), dyslipidemia in 12% versus 13.2% ($p < 0.001$), tobacco use in 30.2% versus 37.6% ($p < 0.001$). Regarding comorbidities: history of stroke was found in 16.5% versus 7.6% ($p < 0.001$). Regarding etiologies of heart failure: ischemic heart disease was represented in 54.5% versus 63.5%, dilated cardiomyopathy in 7.9% versus 8.7%, valvular heart disease in 4.6% versus 3.3%, chemotherapy induced cardiomyopathy in 2.2% versus 2.4% ($p < 0.001$). Demographics, cardiovascular disease risk factors, comorbidities and etiologies of HF are represented in table 1.

	Group 1 (n = 1454)	Group 2 (n = 1958)	p
Age	66.68 ± 12.78	63.86 ± 12.62	< 0.001
History of arterial hypertension	40.4%	38.5%	< 0.001
History of diabetes mellitus	30.8%	32.3%	< 0.001
Dyslipidemia	12%	13.2%	< 0.001
Smoking	30.2%	37.6%	< 0.001
History of stroke	16.5%	7.6%	< 0.001
Etiologies of HF:			
IHD	54.5%	63.5%	< 0.001
DCM	7.9%	8.7%	
VHD	4.6%	3.3%	
Chemotherapy induced cardiomyopathy	2.2%	2.4%	

Table 1: *Demographics, cardiovascular disease risk factors, comorbidities and etiologies of heart failure.*
HF: Heart Failure; IHD: Ischemic Heart Disease; DCM: Dilated Cardiomyopathy; VHD: Valvular Heart Disease.

Regarding NYHA functional class: class I in 11.7% versus 22%, class II in 59.8% versus 60.5%, class III in 26.5% versus 15.5%, class IV in 2.1% versus 2% ($p < 0.001$). Signs of left HF in 11.2% versus 6.8% ($p < 0.001$), signs of right HF in 8.8% versus 4.2% ($p < 0.001$), mean heart rate was 79.39 ± 16.82 bpm versus 76.07 ± 16.72 bpm ($p < 0.001$). Persistent atrial fibrillation was present in 13.1% versus 9.4% ($p < 0.001$). Clinical and electrical data are reported in table 2.

	Group 1 (n = 1454)	Group 2 (n = 1958)	p
NYHA			
Class I	11.7%	22%	< 0.001
Class II	59.8%	60.5%	
Class III	26.5%	15.5%	
Class IV	2.1%	2%	
Signs of left HF	11.2%	6.8%	< 0.001
Signs of right HF	8.8%	4.2%	< 0.001
Mean HR	79.39 ± 16.82 bpm	76.07 ± 16.72 bpm	< 0.001
Persistent atrial fibrillation	13.1%	9.4%	< 0.001

Table 2: *Clinical and electrical data.*

HR: Heart Rate.

Echocardiographic data: Mean LVEF was 34.69 ± 13.19% versus 33.90 ± 14.19 ($p = 0.488$), mean LVEDD was 59.21 ± 9.33 mm versus 56.12 ± 8.21 mm ($p < 0.001$), elevated left ventricle filling pressures in 26.7% versus 16.8% ($p < 0.001$), SPAP was 39.20 ± 15.17mmHg vs 35.16 ± 15.74 mmHg ($p < 0.001$), significant functional tricuspid regurgitation in 12.6% vs 3.9% ($p < 0.001$), RV systolic longitudinal dysfunction in 47.6% versus 40.8% ($p < 0.001$). Transthoracic echocardiography data are reported in table 3.

	Group 1 (n = 1454)	Group 2 (n = 1958)	p
Mean LVEF	34.69 ± 13.19%	33.90 ± 14.19%	0.488
Mean LVEDD	59.21 ± 9.33 mm	56.12 ± 8.21 mm	< 0.001
Elevated LVFP	26.7%	16.8%	< 0.001
Mean SPAP	39.20 ± 15.17 mmHg	35.16 ± 15.74 mmHg	< 0.001
Significant functional TR	12.6%	3.9%	< 0.001
RV longitudinal systolic dysfunction	47.6%	40.8%	< 0.001

Table 3: *Transthoracic echocardiography data.*

LVEF: Left Ventricle Ejection Fraction; LVEDD: Left Ventricle End Diastolic Diameter; LVFP: Left Ventricle Filling Pressures; SPAP: Systolic Pulmonary Artery Pressure; TR: Tricuspid Regurgitation; RV: Right Ventricle.

Regarding pharmacotherapy prescription: a betablocker was prescribed in 84.2% versus 90.8% ($p < 0.001$), ivabradine in 5.5% versus 2.7% ($p < 0.001$), loop diuretics in 52.6% versus 36.1% ($p < 0.001$), spironolactone in 63.7% versus 51.8% ($p < 0.001$), ACE-I in 80.3% versus 86.8% ($p < 0.001$). Pharmacotherapy prescription data are represented in table 4.

	Group 1 (n = 1454)	Group 2 (n = 1958)	p
Beta-blockers	84.2%	90.8%	< 0.001
Ivabradine	5.5%	2.7%	< 0.001
Loop diuretics	52.6%	36.1%	< 0.001
Spironolactone	63.7%	51.8%	< 0.001
ACE-I	80.3%	86.8%	< 0.001

Table 4: *Heart failure medical therapy.*
ACE-I: Angiotensin Converting Enzyme Inhibitors.

HF hospitalization rates were 29.6% vs 20.3% (p < 0.001). Mortality rates were 3.1% vs 1.5% (p = 0.012). Hospitalisation and mortality rates are reported in table 5.

	Group 1 (n = 1454)	Group 2 (n = 1958)	p
HF Hospitalisation	29.6%	20.3%	< 0.001
Mortality rate	3.1%	1.5%	= 0.012

Table 5: *HF hospitalization and mortality rates.*

Discussion

Secondary MR in HFrEF reflects primarily the severity of LV dysfunction and is not related to structural alterations of the mitral valvular apparatus. Nevertheless, mitral valves from hearts collected at the time of cardiac transplantation are biochemically different from those from normal hearts. Mitral valve remodeling resulting from increased deoxyribonucleic acid, glycosaminoglycan and collagen concentration develops in patients with LV systolic dysfunction [6]. Mitral valve area increases over time as the left ventricle remodels in an experimental model of inferior myocardial infarction [7]. This suggests that secondary MR in these HF patients may not be purely functional. Apical displacement of the papillary muscles due to eccentric global and local LV remodeling and segmental wall motion abnormalities associated with papillary muscle dysfunction increase the tethering forces acting on the mitral valve. Reduced LV contractility, LV dyssynchrony and reduced mitral annular contractility decrease the LV systolic pressure that in turn results in reduced mitral valve closing forces. Importantly, the hallmark of secondary MR in HFrEF is the formation of mitral valve tenting (a more apical position of the leaflets and their coaptation point during the systolic phase) that may be asymmetric if the tethering forces predominate on the posterior mitral leaflet [8]. It is currently accepted that the mitral valve tenting results from an imbalance between these increased tethering forces and reduced closing forces [9,10].

In the present study, we found that secondary mitral regurgitation was a frequent finding (42.6% of patients) in a cohort of heart failure with reduced ejection fraction patients. In addition, and most importantly, secondary mitral regurgitation was associated with a worse clinical status, more hospitalization for acute decompensated heart failure and mortality.

Previous authors have reported that SMR is present in about 50% of patients with HFrEF [11] with conflicting evidence regarding its prognostic significance. Although many studies have shown a significant worsening of survival in patients with SMR, other studies did not. According to Patel and al, in a study published in 2004, among patients with advanced HFrEF, hemodynamically significant SMR is common. The severity of SMR did not provide independent prognostic information in this group recognized to have uniformly high mortality [4]. Moreover, according to Boriani., *et al*. the use of CRT-D has favorable outcomes in HF patients with clinically significant SMR but

the presence of SMR had no major influence on patient outcome [5]. Otherwise, a strong association between SMR severity and both all-cause mortality and HF hospitalizations has been reported. SMR increases left ventricular (LV) end-diastolic pressure, contributes to LV remodeling, increases pulmonary hypertension, and worsens right ventricular function, all of which are associated with poor prognosis in HF [3]. According to Carmena., *et al*. in a letter to the editor published in 2017, the presence of SMR in HfrEF was associated with higher prevalence of decompensated HF, with associated increased natriuretic peptides, hypotension and renal failure. Prognosis was worse in patients with SMR as median survival at 5 years was significantly lower due to mortality from refractory HF [12].

The management of SMR presents significant challenges. Because this type of MR is largely related to a disease process in the LV (and not the mitral valve), therapy is primarily directed toward the underlying LV disorder. The optimal use of neurohormonal antagonists and resynchronization devices can lead to reversal of the adverse remodeling process; the resulting reduction in LV volumes can ameliorate the severity of MR in a large proportion of patients [13-15]. Recently, with the development of interventional therapy, the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial [16] did not show any difference in the risk of death or the risk of hospitalization for HF after 12 months follow-up. However, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial [17] reported a lower risk of death from any cause and a lower risk of hospitalization for HF in patients who were assigned to mitral valve repair after a 2 years follow-up. A meta-analysis of both trials reported that patients with chronic heart failure respond favorably to transcatheter mitral valve repair if they exhibit degrees of MR that are disproportionately greater than might be expected from the degree of LV chamber enlargement [18].

Conclusion

Secondary mitral regurgitation is associated with higher NYHA functional class, higher hospitalization for HF rates and mortality rates. Optimizing heart failure medical therapy, cardiac resynchronization therapy and transcatheter mitral valve repair are available options to improve prognosis.

Conflict of Interest

None.

Bibliography

1. Anna Sannino, Survival and Cardiovascular Outcomes of Patients with Secondary Mitral Regurgitation: A Systematic Review and Meta-analysis". *JAMA Cardiology* 2.10 (2017): 1130-1139.

2. Hung J., *et al.* "Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target". *Circulation* 110 (2004): 1185-1190.

3. Rossi A., *et al.* "Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1,256 patients with ischaemic and non-ischaemic dilated cardiomyopathy". *Heart* 97 (2011): 1675-1680.

4. Patel JB., *et al.* "Mitral regurgitation in patients with advanced systolic heart failure". *Journal of Cardiac Failure* 10.4 (2004): 285-291.

5. Boriani G., *et al.* "InSync/InSync ICD Italian Registry Investigators. Impact of mitral regurgitation on the outcome of patients treated with CRT-D: data from the InSync ICD Italian Registry". *Pacing and Clinical Electrophysiology* 35.2 (2012): 146-154.

6. Grande-Allen KJ., *et al.* "Apparently normal mitral valves in patients with heart failure demonstrate biochemical and structural derangements: an extracellular matrix and echocardiographic study". *Journal of the American College of Cardiology* 45 (2005): 54-61.

7. Chaput M., *et al.* "Leducq Foundation MITRAL Transatlantic Network: Mitral leaflet adaptation to ventricular remodeling: prospective changes in a model of ischemic mitral regurgitation". *Circulation* 120 (2009): S99-S103.

8. Agricola E., *et al.* "Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern". *European Journal of Echocardiography* 5 (2004): 326-334.

9. Magne J., *et al.* "Ischemic mitral regurgitation: a complex multifaceted disease". *Cardiology* 112 (2009): 244-259.

10. Lancellotti P., *et al.* "European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2. Mitral and tricuspid regurgitation (native valve disease)". *European Journal of Echocardiography* 11 (2010): 307-332.

11. Pu M. "The frequency, impact, and management of mitral regurgitation in patients with heart failure". *Current Cardiology Reports* 8 (2006): 226-231.

12. Garcı´a-Cosı´o Carmena MD., *et al.* "Prognostic Implications of Functional Mitral Regurgitation in Patients With Heart Failure and Reduced Ejection Fraction". *Revista Española de Cardiología* (2017).

13. Martens P., *et al.* "The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction". *Cardiovascular Therapeutics* 36 (2018): e12435.

14. Nasser R., *et al.* "Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction". *Journal of the American College of Cardiology* 5 (2017): 652-659.

15. Stolfo D., *et al.* "Early improvement of functional mitral regurgitation in patients with idiopathic dilated cardiomyopathy". *The American Journal of Cardiology* 115 (2015): 1137-1143.

16. Obadia JF., *et al.* "Percutaneous repair or medical treatment for secondary mitral regurgitation". *The New England Journal of Medicine* (2018).

17. Stone GW., *et al.* "For the COAPT Investigators. Transcatheter mitral valve repair in patients with heart failure". *The New England Journal of Medicine* (2018).

18. Paul A Grayburn. "Proportionate and Disproportionate Functional Mitral Regurgitation A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials". JACC (2018).

Volume 7 Issue 10 October 2020