Functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome: contribution to congestive heart failure

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Aims Functional mitral regurgitation (MR) is a frequent complication after the acute phase of a myocardial infarction and plays an important role in the development of congestive heart failure (CHF) after a Q-wave myocardial infarction. Nevertheless, until now, the relevance of functional MR after a non-ST-segment elevation acute coronary syndrome (NSTSEACS) has been poorly addressed. Our aim was to assess the relationship between the presence or absence and the severity of functional MR after a first NSTSEACS and the development of CHF.

Methods and results Two hundred and seventy-nine patients discharged from hospital in NYHA functional classes I and II (71.7% men; mean age 66.3 ± 13.2 years) after a first NSTSEACS were studied. Every patient underwent an echocardiographic study during the first week after the index NSTSEACS and were clinically followed-up. MR was detected in 40.1% patients. Patients were followed-up for a median time of 418 days (inter-quartile range: 295–561). Six patients (3.6%) in the group without MR and 15 patients (13.4%) in the group with MR required hospitalization due to CHF during follow-up. Only MR was found as an independent predictor of CHF development (HR = 1.8; 95% CI = 1.1–3.1; \(P = 0.02\)) and CHF development or cardiac death (HR = 2.1; 95% CI = 1.3–3.3; \(P = 0.01\)) in the long-term follow-up multivariable Cox regression analysis.

Conclusion There is an increased risk for subsequent CHF in patients with MR after a first NSTSEACS. The risk of CHF is closely related to the MR presence and severity. Thus, the detection of MR by means of Doppler echocardiography after a first episode of NSTSEACS is crucial.

Keywords Mitral regurgitation; Non-ST-segment elevation acute coronary syndrome; Congestive heart failure

Introduction

Functional mitral regurgitation (MR) is a frequent complication during and after the acute phase of a myocardial infarction and it has been proved to be a predictor of long-term cardiac mortality after a Q-wave acute myocardial infarction (AMI) and after a non-ST-segment elevation acute coronary syndrome (NSTSEACS).1–9 Very recently, Grigioni et al.10 have described the role of ischaemic MR in the development of congestive heart failure (CHF) after a Q-wave myocardial infarction. Nevertheless, until now, the influence on the development of CHF of functional MR after an NSTSEACS has been poorly addressed. It is well known that functional MR after an acute coronary syndrome is an independent predictor of outcome, but the mechanism linking MR and outcome is not well understood. The development of CHF secondary to the development of functional MR might be one of the main links between both entities.

Our aim was to assess the relationship between the presence or absence and the severity of functional MR after a first NSTSEACS and the development of CHF. To establish a link between both entities could be a main step in the understanding of the relationship between functional MR and long-term outcome after an NSTSEACS.

Methods

Study population

Three hundred and eleven consecutive patients were admitted to the Coronary Care Unit of the Cardiovascular Institute of San Carlos Clinic Hospital for a first NSTSEACS between March 2003 and August 2005. Patients with mitral valve and/or subvalvular apparatus structural disease and those with acute mechanical post-acute coronary syndrome complications were not included in the cohort of study, in order to study only those with a functional cause of MR. Twenty-one patients of the study group died during hospitalization and were excluded from the analysis. Eleven patients were excluded due to the lack of an adequate acoustic window able to provide an MR assessment. The 279
remaining patients were discharged from hospital in NYHA functional classes I and II and they constituted the study group. Every patient completed all the procedures of this study. The diagnosis of NSTSEACS was based on the European Society of Cardiology criteria. Medical history, laboratory findings, and in-hospital course were collected for each patient. All the patients were prospectively selected and prospectively followed-up.

Echocardiography
All patients underwent a complete echocardiographic study before hospital discharge that included a specific evaluation of the mitral valve anatomy and function, during the first week after the NSTSEACS. The median and inter-quartile range when echo examinations were performed were 2 (1–3) days after admission. The Doppler echocardiography was performed with a Philips Sonos 5500 (Phillips; Andover, MA, USA) with 2.5 or 3.5 MHz transducers. Standard parasternal M mode register was employed to measure left atrial and left ventricular (LV) diameters. Global ejection fraction was calculated on bidimensional echocardiography from two- and four-chamber apical views by the modified Simpson’s method and systolic thickening evaluated in the 16 segments defined by the American Society of Echocardiography.

The presence and degree of MR was evaluated using the proximal isovelocity surface area (PISA) method and a validated nomogram for semi-quantitative estimation. This validated and simplified semi-quantitative method, based on PISA, has a good correlation with the angiographic degree of MR. Taking into account only the radius of the PISA and the aliasing velocity used, a nomogram is used to allow a fast semi-quantitative estimation of the degree of MR. Thus, MR was classified according to these criteria in four degrees of severity (I, mild; II, mild to moderate; III, moderate; IV, severe). Patients with trace MR were included in the group without MR. The systolic pressure of the pulmonary artery was calculated using tricuspid regurgitation and inferior cava vein diameters. Seven patients underwent transoesophageal echocardiogram to accurately assess the severity of the MR.

Cardiac catheterization
Cardiac catheterization was performed according to the treating physician’s preferences. Coronary angiography was performed using standard techniques. Significant coronary artery disease (CAD) was defined as ≥70% diameter stenosis of an epicardial coronary artery. The extent of CAD was characterized by the traditional one-, two-, or three-vessel disease classification. Percutaneous revascularization was performed according to physician’s criteria.

Follow-up
During follow-up, the development of CHF requiring hospitalization and cardiac death were considered the endpoints. After discharge, all patients were followed in the outpatient clinic. Planned timings of follow-up in the outpatient clinic were immediately after the hospital discharge, 1 month later, and for less than 6 months intervals afterwards. If a patient did not show up at outpatient clinic, medical records and phone interview were used.

Statistical analysis
Baseline characteristics are expressed as mean ± standard deviation or median (inter-quartile range) for continuous variables and absolute number (proportions) for categorical variables. Comparisons between groups were made with Pearson’s χ² test for categorical variables and the t-test or Mann–Whitney U test for continuous variables. In the statistical evaluation, MR was used as a binary (presence/absence) or as a categorical variable depending on the analysis. Sample size was estimated in the basis of a two-groups non-equality comparison test. One-year survival for patients without MR was estimated in 85%, taking into account the advanced mean age of the hospital population. Seventy percent survival at 1 year was considered as clinically relevant. Two-sided test was used with 80% power and 5% significance level. The estimated number of patients for each group was 125. Long-term follow-up survival curves for various groups were constructed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Cox’s proportional hazards regression analysis was used to select those variables independently associated with long-term events. To address over-fitting, the number of variables to be included in the multivariable analysis was reduced by using a pre-specified model including those variables known to be related to the outcome. Thus, age, diabetes mellitus, renal failure, LV ejection fraction (EF), peak troponin value, mean number of coronary vessels with significant involvement, atrial fibrillation, and MR were the variables included in the final model. Linearity assumption was assessed using the residual analysis. This assumption was satisfied by every continuous variable. For the Cox regression analysis, the proportional hazards assumption was assessed using stratified analysis and it was satisfied by every continuous variable. The time point at which the last follow-up data were obtained was 29 December 2005. Two-sided tests were used. Comparisons were considered significant in the presence of P < 0.05.

Results
Baseline characteristics
Mean age was 66.3 ± 13.2 years and 200 (71.7%) were men. The incidence of MR was 40.1% (112 patients; 79 men, mean age 70.7 ± 11.1 years). The distribution of the severity of MR was: 74 patients degree I (66.1%), 20 patients degree II (17.9%), 15 patient degree III (13.4%), and three patients degree IV (2.7%). Baseline characteristics are shown in Table 1. Mean age (63.6 ± 13.8 vs. 70.7 ± 11.1), the incidence of hypertension (61.1 vs. 73.2%), diabetes mellitus (23.4 vs. 38.4%), renal failure (7.2 vs. 16.1%), the number of coronary vessels with significant disease [1 (1–2) vs. 2 (1–3)], and the involvement of LAD coronary artery (47.3 vs. 63.4%) were significantly higher in the group with MR when compared with the group without MR. There were only three patients with severe MR. One of them with LVEF 30% and anterior wall akinesia; a second one with LVEF 37% and global depression of the systolic contraction, and the third one with LVEF 60% and inferior-posterior wall akinesia. Only eight (five in the group without MR and three in the group with MR) patients had a peak troponin value inferior to 0.1 ng/mL. Thus, only 2.9% patients suffered from unstable angina.

Table 2 describes the use of different therapies in patients with or without MR at the moment of hospital discharge. As this table shows, no statistical significant differences were found between both groups. No patient in this study was submitted to repair of the mitral valve in our study because they did not have indication for that due to the presence of contraindications or due to patient’s preferences.

Echocardiographic parameters
LV end-systolic diameters were significantly higher in the group of patients with MR (29.5 ± 9.1 vs. 33.9 ± 8.7 mm), LV performance was diminished in the group with MR (LVEF 58.5 ± 17.6 vs. 51.1 ± 15.5%) in the groups without and with MR), the prevalence of LV wall motion abnormalities in the echocardiographic study was higher in the group
with MR (47.3 vs. 61.6%), and the left atrium diameter was larger in the group with MR (37.9 ± 9.9 vs. 41.9 ± 8.6 mm). The echocardiographic results are shown in Table 3.

**Coronary anatomy**

Two hundred and sixty-three patients (94.3%) underwent coronary angiography during hospitalization. The median number and inter-quartile range of vessels with significant lesions was 1 (1–2) in the group without MR and 2 (1–3) in the group with MR (Table 1). One hundred and fifty-five patients underwent revascularization procedures (55.6% of patients; 95 patients in the group without MR and 60 patients in the group with MR). Bypass graft surgery was performed in 21 patients without MR (12.6%) and in 17 patients with MR (15.2%). Percutaneous revascularization was performed in 83 patients in the group without MR (49.7%) and in 47 patients in the group with MR (42.0%). The difference in the number of patients revascularized in each group did not reach a significant level. No patient in our series underwent mitral valve repair combined with coronary artery bypass graft.

**Incidence of congestive heart failure and long-term follow-up**

Patients were followed for a median time of 418 days (inter-quartile range: 295–561). During this follow-up period, six patients (3.6%) in the group without MR and 15 patients (13.4%) in the group with MR required hospitalization due to CHF during follow-up. Survival curves showed that the development of CHF requiring hospitalization depends on the presence or absence of MR and on its severity (Figure 1A and B). Only MR was found as a long-term independent predictor of CHF development in the multivariable Cox regression analysis (Table 4).

Furthermore, when follow-up to the development of CHF or cardiac death was analysed, MR was also related to long-term outcomes (Figure 2A and B). Cox regression analysis showed that the presence and degree of functional MR is an independent predictor of long-term outcome (Table 4).
### Table 3 Echocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No MR</th>
<th>MR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>49.3 ± 9.3</td>
<td>49.7 ± 8.8</td>
<td>0.9</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>29.5 ± 9.1</td>
<td>33.9 ± 8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.5 ± 17.6</td>
<td>51.1 ± 15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>WM abnorm. (%)</td>
<td>79 (47.3%)</td>
<td>69 (61.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>37.9 ± 9.9</td>
<td>41.9 ± 8.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral E-wave peak velocity</td>
<td>66.0 (59.0–99)</td>
<td>73.0 (59.0–99)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mitral A-wave peak velocity</td>
<td>75.0 (60–78.5)</td>
<td>85.0 (62.0–102.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>E-wave peak velocity/velocity</td>
<td>0.8 (0.6–1.1)</td>
<td>0.9 (0.7–1.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>A-wave peak velocity/velocity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>37.6 ± 14.1</td>
<td>39.5 ± 15.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; WM abnorm: wall motion abnormalities; LAD, left atrial diameter; PASP: pulmonary artery systolic pressure.


A separate analysis was performed for patients with LVEF ≥ 45% and < 45%. The results obtained for patients with LVEF ≥ 45% were log rank 8.4 (*P* = 0.07). And the results for patients with LVEF < 45% were log rank 7.5 (*P* = 0.1).

Survival analysis using the Kaplan–Meier curves and log-rank test was specifically performed to compare the long-term prognosis of patients without MR and patients with only mild MR, in order to assess if mild MR is related to outcome. As is shown in Figures 1C and 2C, even mild MR is related with long-term outcome after a first NSTSEACS, although in the follow-up to CHF the *P*-value was only 0.05, almost reaching the statistical significance level.

**Discussion**

This work is, to our knowledge, the first one to consider the influence of the presence or absence and severity of functional MR after a first NSTSEACS in the development of CHF requiring hospitalization. In a previous work by Grigioni *et al.*, the role of ischaemic MR in the development of CHF was described, but in their cohort only patients after a Q-wave myocardial infarction were enrolled. Thus, until now, the relationship between functional MR after an NSTSEACS, and in particular in the follow-up to CHF, has been poorly studied.

Our population is very similar to the population in the study by Grigioni *et al.*, with the exception of the type of acute coronary syndrome evaluated. The results in the present work also agree with their results: the presence of functional MR after a first NSTSEACS is a determinant of the occurrence of CHF requiring hospitalization in the long-term follow-up. Furthermore, our results also show that a higher severity of functional MR is associated with a higher incidence of CHF. When CHF or cardiac death is considered as a combined endpoint, the results also show that the existence of MR and its severity is related to outcome. These results are obtained in the adjusted for differences analysis between groups. Our results also agree with the results obtained in the Survival and Left Ventricular Enlargement Study (SAVE). In that study, although the authors could not establish a definitive conclusion, data showed a strong relationship between functional MR after an acute coronary syndrome and the occurrence of CHF.

After the occurrence of an acute coronary syndrome, patients are at high risk for death, development of CHF, and the need of hospitalization due to CHF. Therefore, identification of factors related to the development of CHF in patients in an adequate functional class at the moment of the hospital discharge after the acute coronary syndrome is very important in order to optimize their therapeutic management.

Functional MR occurs with a structurally normal valve as a result of an altered force balance on the mitral leaflets. Nevertheless, all the factors involved in the development of MR after AMI are not well described. We believe that segmental dysfunction, LV dilatation, and MR are consequences of severe CAD and they are factors probably related to the development of MR after an NSTSEACS. Until now, we know that functional MR after an acute coronary syndrome is an independent predictor of outcome, but the mechanism linking MR and the outcome is not well understood. Probably, the development of CHF secondary to the development of functional MR is one of the main links between both entities. Thus, the development of functional MR leads to the development of CHF and the last one to the occurrence of cardiac death.

In this work, serial echo assessment was not performed. It would have been useful because functional MR is very variable in its evolution and these changes could have had some influence on the results.

The statistical analysis used in this work provides a strong clue that the differences found in the baseline characteristics of the population enrolled do not interfere in the validity of the results regarding the prognostic implications of functional MR. The fact that we performed two survival analyses using two endpoints (CHF and the combined endpoint CHF or cardiac death) allows us to affirm that the higher rate of patients suffering from functional MR is not due to a longer time at risk because of lower cardiac mortality, as the combined endpoint was also found more frequently in patients with functional MR. These results are also in concordance with the results of the work previously reported.

Although the study was not designed for evaluating this point, a separate analysis was performed for patients with LVEF ≥ 45%. The results obtained for patients with LVEF ≥ 45% showed a trend to statistical significance in those patients with preserved LVEF and a lack of statistical significance in patients with depressed LVEF. These findings must be considered with caution due to the relatively few patients enrolled in each group, especially in the group with depressed LVEF.

Diastolic function was not specifically addressed but important parameters regarding this subject have been analysed, such as left atrial diameter and mitral E and A-waves. The only difference found was the dimension of the left atrium. It was larger in patients with MR than in patients without it. Nevertheless, the evaluated parameters are very dependent on the haemodynamic status of the patient and the presence and degree of MR might modify its interpretation as well as the load conditions. More specific parameters for the evaluation of the diastolic function should be explored in future works in order to reveal...
the contribution of diastolic dysfunction to heart failure in this subset of patients.

Clinical implications

There are two main clinical implications to enhance, following the results of the present work. The first one is the need to study every patient with an NSTSEACS by means of Doppler echocardiography to detect the presence and degree of MR because it is rarely heard clinically. In contrast, MR is an independent prognostic factor for the development of CHF. Thus, identification of factors involved in the development of CHF after an NSTSEACS represents an important factor to consider in the management of NSTSEACS patients.

Limitations

In our study, we cannot distinguish between pre-existing MR and new-onset MR. Pre-AMI MR is a recently described prognostic factor.8 It is very difficult to obtain echocardiographic data of patients before the index myocardial infarction. Nevertheless, in the studies analysing the influence of MR on the subsequent development of CHF, the presence of pre-AMI MR is not analysed. Thus, we think that this limitation is only a minor one if we keep in mind the previously published works.

Not every patient in our series had coronary arteriography but it is of note that this study is not an intervention study. Thus, the management of these patients was the standard management at that time in our institution and it depended on the physician’s preferences. Thus, in this way, our results reflect more closely the daily clinical practice.

The morphological characteristics of the mitral valve was not specifically assessed or quantified in the present work. Thus, the diagnosis of functional MR was performed excluding those patients with structural alterations at the level of the mitral leaflets or mitral subvalvular apparatus, following the methods used in previous works.6,9 In this study, no differences were found regarding the presence and/or location of wall motion abnormalities in the survival analysis. Nevertheless, the number of patients with wall motion abnormalities, although is higher in the group with MR, could be relatively small to obtain statistical significant differences in the survival assessment.

Conclusions

There is an increased risk for subsequent CHF in patients with MR after a first NSTSEACS. Furthermore, the risk of CHF is closely related to MR severity. Thus, the detection of MR by means of Doppler echocardiography after a first episode of NSTSEACS is crucial in order to optimize the management of patients with functional MR.
due to congestive heart failure or cardiac death for patients without mitral regurgitation and those with only mild mitral regurgitation.


