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Restrictive diastolic filling predicts death after acute myocardial infarction: systematic review and meta-analysis of prospective studies

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Objective: To determine, through a systematic review and meta-analysis, the magnitude of the survival deficit associated with a restrictive filling pattern after acute myocardial infarction (AMI).

Methods: Online databases were searched for prospective echocardiography outcome studies of patients after AMI. All authors were contacted to seek confirmation of their data. Restrictive filling was compared with all non-restrictive filling patterns. Review Manager Version 4.2.7 software was used for analysis.

Results: 3855 patients in 16 studies were identified. Follow up varied from two weeks to five years (> 1 year, 10 studies; and > 4 years, four studies). 776 (20%) of patients had a restrictive filling pattern at baseline. 580 patients died (247 in the restrictive group), and the overall odds ratio for death (restrictive filling worse) was 4.10 (95% confidence interval 3.38 to 4.99).

Conclusions: Mortality is about four times higher in patients with a restrictive filling pattern than in those with non-restrictive filling patterns after AMI. Echocardiographic assessment of diastolic filling pattern is an important part of the echocardiographic assessment of patients after myocardial infarction and provides important prognostic information about such patients.

Echocardiographic Doppler indices of diastolic function have been widely used to identify subgroups of patients with different risk among patients with systolic dysfunction and heart failure (HF).¹ In particular, the presence of restrictive mitral diastolic filling (high E velocity, low A velocity and shortened deceleration time) is associated with pronounced increases in mortality in patients with HF.¹ This technique has also been widely applied in the acute coronary setting. The presence of restrictive filling, which is a sign of raised left atrial pressure, is also associated with worse survival after acute myocardial infarction (AMI).^{2–28} As in the HF cohorts, many of these studies showed significant increases in mortality with advanced filling patterns. However, these studies are somewhat heterogeneous in comparison with the HF cohorts in that baseline clinical and functional status vary greatly, in particular left ventricular (LV) function. Importantly, both systolic and diastolic dysfunction are less prevalent in this group of patients than in HF populations, as are the overall event rates.

The objective of this systematic review and meta-analysis was to combine the results of all studies investigating the relationship between prognosis and the presence of restrictive diastolic filling after myocardial infarction to estimate accurately the risk associated with this advanced diastolic filling abnormality. The hypothesis was that patients with evidence of restrictive filling after AMI may have worse long-term survival.

METHODS

Identification of studies

Published studies were identified through online searches of several medical databases: Biological Abstracts, Clinical Evidence, Current Contents, Embase, Medline, Medline In-progress and PubMed. The search terms “incidence”, “prognosis”, “outcome”, “mortality”, “clinical trials”, “echocardiography”, “ventricle”, “systolic”, “diastolic” and “myocardial infarction” were used. Papers published up until September 2005 and not restricted to the English

language were searched. The citation lists of the identified papers were also reviewed. All authors were contacted and asked to provide further data or studies (published or unpublished). All three authors developed the strategy for database searching and one reviewer primarily performed the actual searches. One other reviewer implemented some targeted review. All papers were reviewed by two reviewers, both of whom extracted and confirmed the data. Ambiguities were reconciled through consensus reached through further discussion, evaluation and confirmation by the original authors. In all but five cases, the original authors subsequently reviewed these data.

Criteria for study inclusion

From the online searches, we selected any study that included echocardiography, prognosis and AMI. In addition, studies were required to have clearly stated diagnostic thresholds for definition of AMI. Each study was then reviewed according to a predetermined protocol, which included information about patients' recruitment and follow up (prospective, retrospective, consecutive recruitment, exclusions and reason), co-morbidity, loss to follow up and completeness of data (that is, how many patients actually underwent the echocardiographic measurements). Only prospective studies that recruited patients after reaching a predetermined diagnostic threshold for AMI, with an end point of death, were included (fig 1).

Definition of a prospective study

For these analyses, we determined a prospective study to be one into which patients were enrolled and then followed up. The diastolic analysis may have been retrospectively applied, but the patients needed to be recruited at the time of their acute coronary event. Retrospective cohort studies that identified patients at the end of the follow-up period were

Abbreviations: AMI, acute myocardial infarction; HF, heart failure; LV, left ventricular

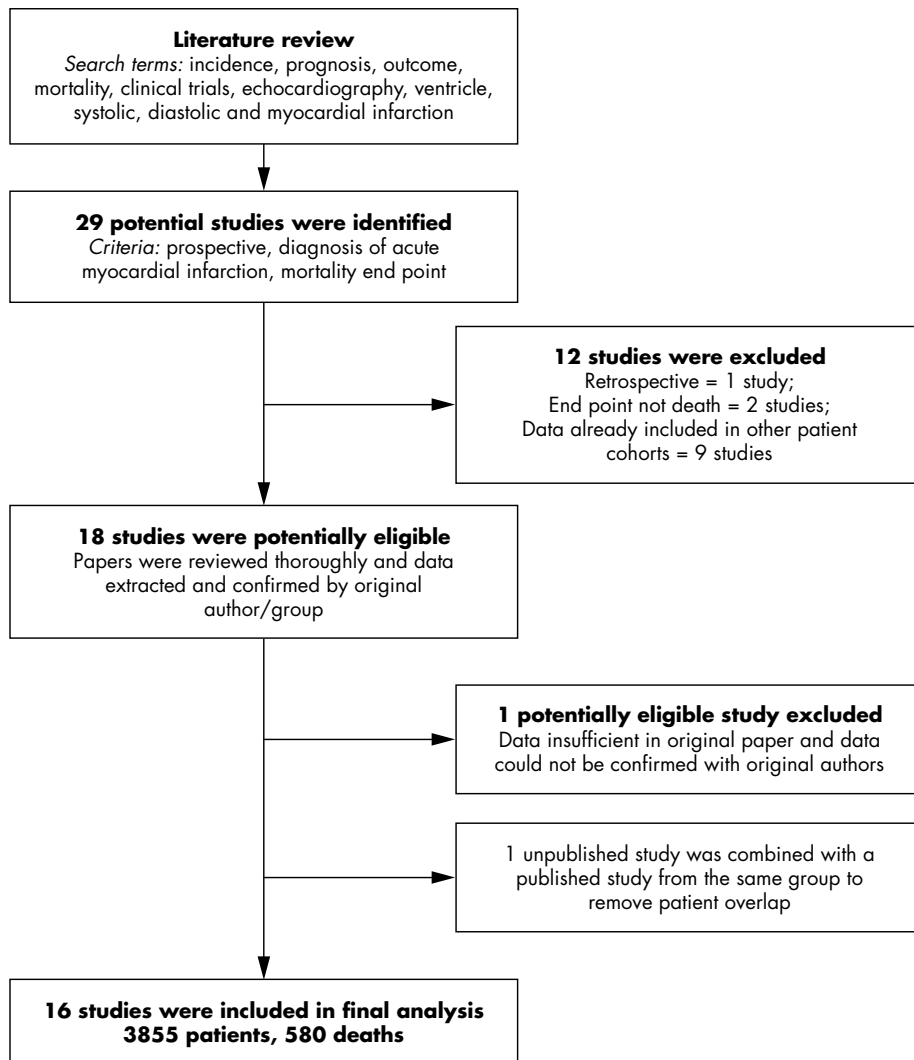


Figure 1 Review process for identification of studies of prospective echocardiography outcomes of patients after acute myocardial infarction.

excluded. Most studies recruited consecutive patients, although this was not an inclusion criterion in order to allow the exclusion of patients with incomplete data—for example, atrial fibrillation or suboptimal imaging.

Data collection

For many studies, the publication identified the numbers of patients and events in each filling pattern group. Every investigator was asked by letter or email to confirm the data we had extracted or to provide data where the paper's content was insufficient. Authors were also asked to confirm that patients were included in one publication only and to identify sources of potential patient overlap. We also sought any additional references to either published or unpublished studies. One author supplied unpublished data from a doctoral thesis²⁹ to supplement already published data.²⁷ Not all studies reported diastolic parameters as a primary end point. We contacted authors of any publications that reported outcome data and comprehensive echocardiographic examinations at baseline to determine whether patients were able to be stratified according to diastolic filling grade (fig 1).

Differentiation of restrictive filling

Restrictive filling was determined by the individual authors and clearly stated in the papers' methods. These criteria were reviewed and considered to be acceptable and in accordance

with internationally accepted standards, allowing for slight regional and institutional variation. One paper reported pseudonormal and restrictive filling pattern together, and these deaths were attributed equally between the two groups.³⁰

Statistical methods

The Cochrane Collaboration Program Review Manager V.4.2.7 (<http://www.cc-ims.net/RevMan>) was used for analysis. For each study, patients were stratified according to the individual study criteria as having restrictive or non-restrictive filling. The number of patients and the number of events allocated to each group were recorded. The odds ratio in a fixed effects model is presented, but a random effects model was also evaluated. As the random effects model was not different from the fixed effects model, we present only the fixed effects model. Each study was weighted in the model according to sample size. Standard tests for heterogeneity were used including χ^2 (presented). Funnel plots were examined for evidence of publication bias and none was observed. All-cause mortality was the primary end point.

RESULTS

Thirty-one potential studies were identified,²⁻³² of which we analysed 16^{2-7 12 13 17-19 22-27} (table 1). One author provided

Table 1 Prognosis studies on restrictive filling pattern classification after myocardial infarction

Reference (publication year)	Author confirmed data	Country	No	FU (years)	Events	Echocardiographic definition of restrictive filling
Garcia-Rubira ³ (1997)	Numbers in paper	Spain	133	In hospital	20 deaths	Non-restrictive, restrictive
Nijland ² (1997)	Numbers in paper	The Netherlands	95	3	8 deaths	E:A >2 or DT <140 ms
Sakata ⁴ (1997)	Numbers in paper	Japan	206	5	33 deaths	Low mitral A velocity
Poulsen ¹⁷ (1999)	Yes	Denmark	58	1	6 deaths (MFP 2/3)	DT <140 ms
Burgess ⁶ (2000)	Yes	UK	102	1	9 deaths	Non-restrictive, restrictive
Møller ⁷ (2000)	Yes	Denmark	125	1	33 deaths	DT <140 ms
Cerisano ¹³ (2001)	Yes	Italy	104	2.7	9 deaths	DT <130 ms
Otasevic ¹² (2001)	Yes	Yugoslavia	106	4.9	14 deaths	DT <150 ms
Møller ¹⁸ (2003)	Yes	Denmark multicentre	799	2.8	197 deaths	DT <140 ms
Møller ¹⁹ (2003)	Yes	USA	288	1.25	46 deaths	DT <140 ms
Beinart ²⁵ (2004)	Yes	Israel	371	5	63 deaths	Non-restrictive, restrictive*
Kinova ²⁷ (2004)	Yes	Bulgaria	119	0.5	12 deaths	DT <140 ms
Karvounis ²⁴ (2004)	Yes	Greece	33	1	3 deaths	E:A >2
Møller ²³ (2004)	Yes	Europe multicentre	225	2.3	23 deaths	DT <140 ms
Quintana ²⁶ (2004)	Yes	Sweden	520	2.6	57 deaths	DT <140 ms
Temporelli ²² (2004)	Yes	Italy	571	4	47 deaths	DT <130 ms

*Based on age-dependent E:A ratio and deceleration time. DT, deceleration time of passive mitral filling velocity (E); E:A, ratio of early to late mitral filling; FU, follow up; HF, heart failure; MFP, mitral filling pattern.

additional data published in thesis form only,²⁹ which were merged with another publication²⁷ to alleviate patient overlap. Initially, 12 studies were reviewed and subsequently excluded^{5 8-11 15 16 20 21 28 31 32}: one study was a retrospective cohort study; two studies reported other outcomes than death; and nine studies reported on patients who were included in other patient cohorts. Study data (number of patients and events) were confirmed by 12 of the authors. Despite repeated attempts, confirmation was not received for four studies. Of these, three studies clearly reported numbers in the publication and were included, leaving only one study that may have been eligible but was excluded.¹⁴ Thus, 16 studies and 3855 patients were included in the final analysis.^{2-4 6 7 12 13 17-19 22-27} The average follow-up time varied between two weeks and five years: follow up was six months or less in two studies; one year in five studies; 1-3 years in six studies; and 4-5 years in the remaining four studies (table 1).

Restrictive filling versus non-restrictive filling

Of the 3855 patients, 776 (20%) had a restrictive filling pattern and the remaining 3079 (80%) had a non-restrictive pattern. There were 580 deaths in total: 247 (43%) in the restrictive group and 333 (57%) in the non-restrictive group. The event rate in the whole group was 15.1%: 31.8% in the restrictive filling group and 10.8% in the non-restrictive group. The odds ratio for death associated with restrictive filling pattern was 4.10 (95% confidence interval 3.38 to 4.99, $p < 0.00001$) (fig 2). The group was significantly heterogeneous ($p < 0.00001$) but this was driven by two studies^{3 24} with unusually high odds ratio due to lower event rates in the non-restrictive group. When these studies were excluded from the analysis heterogeneity was reduced, but not eliminated. This is confirmed by inspection of the funnel plots (fig 3) and Egger test ($p = 0.023$). The odds ratio was not related to length of follow up (fig 4).

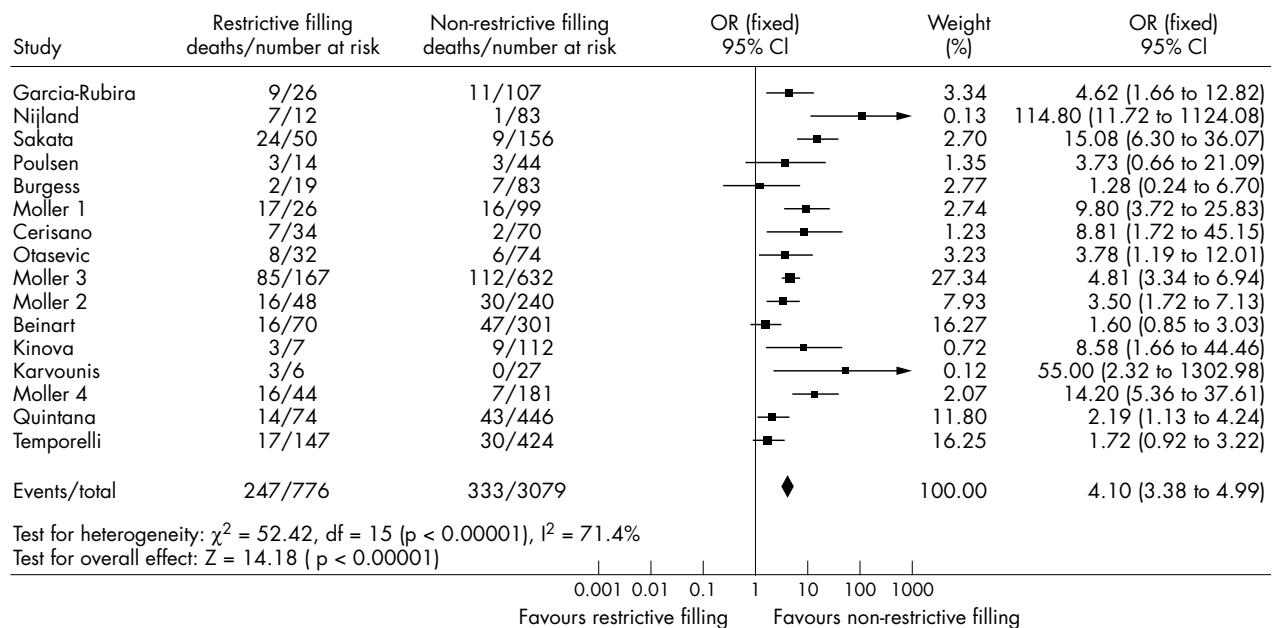


Figure 2 Meta-analysis of the restrictive filling pattern after myocardial infarction. Fixed effects model, studies weighted according to sample size. CI, confidence interval; OR, odds ratio.

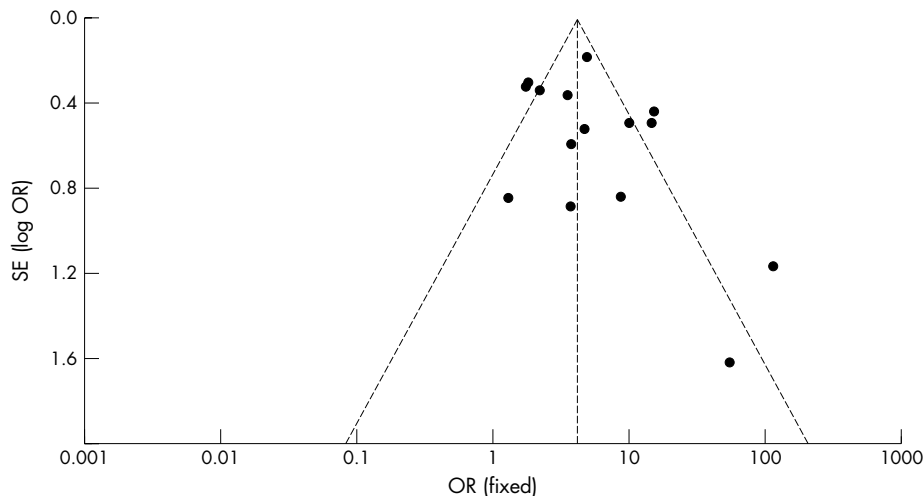


Figure 3 Funnel plot of odds ratios (OR) (fixed effects model).

Criteria for detection of restrictive filling

The criteria for restrictive filling varied between studies and usually included a shortened deceleration time (cut off ranged from 130–150 ms) (table 1). The observed odds ratio for the individual study and the deceleration time cut off used were not related.

DISCUSSION

This analysis combined the results of several studies to compare the prognostic relevance of the presence of a restrictive filling pattern with all other non-restrictive filling patterns after AMI. The presence of a restrictive filling pattern documented soon after the initial ischaemic injury was associated with four times the risk of death in this meta-analysis, which represents 3855 patients and 580 deaths, providing a robust and significant result. This risk was observed in a variety of patients with differing baseline clinical status and degrees of underlying LV systolic dysfunction. Assessment of diastolic filling is a relatively easy addition to the clinical echocardiographic examination of patients after AMI and is an important part of the information provided by echocardiography in this situation.

Restrictive filling pattern is associated with higher left atrial pressure,^{33–39} higher neurohormone concentration^{40–41} and higher New York Heart Association functional class.⁴² As neurohormonal concentration, in particular B-type natriuretic peptide, is also linked to prognosis after acute coronary events^{43–44} it may not be so surprising that patients with evidence of restrictive filling have poor prognosis, as both most likely reflect a degree of haemodynamic stress.

LV systolic impairment and clinical HF are common complications of AMI and undoubtedly explain some of the

risk observed in the patients with restrictive filling pattern. Excluding the patients who are admitted with shock, HF either is present at admission or develops during hospitalisation in 20–30% of patients after AMI.^{45–49} This number continues to rise after hospital discharge,⁴⁵ with about 40% of patients developing HF by six years.⁴⁹ LV systolic dysfunction has been considered to be one of the most important predictors of outcome after AMI and thus has been the focus of echocardiography in this setting. When LV ejection fraction is measured, patients with a low ejection fraction experience higher mortality rates than those with preserved ejection fraction.^{49–50} But, interestingly, patients whose LV ejection fraction is not measured (most patients in many acute coronary studies) experience similar mortality to those with depressed ejection fraction.^{49–50} While many of the patients who develop HF have depressed LV systolic function, the relationship between ejection fraction and outcome is biphasic, with increased risk in patients with hyperdynamic systolic function.⁴⁷ Both of these groups of high risk patients with differing systolic function may have advanced diastolic filling abnormalities, which may be associated with outcome. Patients with angiographically documented coronary artery disease but no detectable resting systolic dysfunction almost always have diastolic filling abnormalities when assessed by radionuclide techniques.⁵¹ Often patients with advanced diastolic filling abnormalities and HF have small LV cavities that appear to contract normally but, because of the reduced volume, the stroke volume is inadequate. In such patients, systolic function may be wrongly assumed to be normal. This hypothesis is supported by the many studies, and the current meta-analysis, showing increased risk associated with restrictive filling pattern.

Nevertheless, many of the patients with restrictive filling pattern also have significant systolic impairment in addition to their diastolic abnormalities. In multivariate analyses of patients with HF the presence of restrictive filling pattern, characterised by high E velocity, low A velocity and shortened deceleration time, remains one of the only independent predictors of cardiovascular outcome.^{52–54} Several of the larger studies in this systematic review and meta-analysis showed that when both diastolic and systolic measurements were available systolic measurements offered little or no additional prognostic information to diastolic filling pattern.^{18–22–25} In a multicentre study of 799 patients, wall motion score index, diastolic filling pattern and the Tei index (a measure of global systolic and diastolic LV function) all predicted outcome but, in a multivariate model, wall motion score index had no prognostic value.¹⁸ In another study of 571

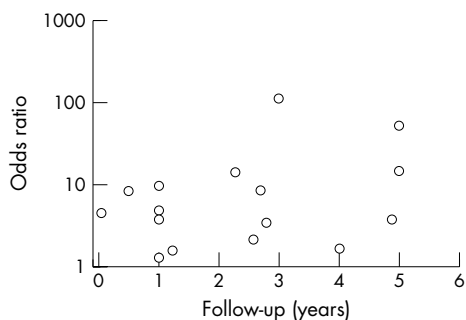


Figure 4 Odds ratio according to follow-up time of each study.

patients, predischARGE restrictive filling pattern was a very strong predictor of death and LV end diastolic index was a weaker, but still significant, predictor of death in a Cox proportional hazards model.²² These findings were confirmed in another smaller study (n = 371) where restrictive filling pattern predicted death alongside other clinical factors and left atrial size, but not systolic function.²⁵ In contrast, in a multicentre study of 520 patients, although restrictive filling pattern predicted death, it did not reach significance in a multivariate model where wall motion score index, age, history of hypertension and diabetes did.²⁶ Thus, there is lack of consensus regarding the prognostic significance of individual echocardiographic variables among the previously published studies.

It is difficult to truly evaluate the independent role and combined effects of systolic and diastolic dysfunction, and it was not within the realm of this systematic review and meta-analysis to evaluate the individual and multivariate contributions of all echocardiographic and clinical variables to overall risk. This would require a meta-analysis incorporating individual patient data from each study. Because of the similarity between the studies' designs and the total number of patients, this approach may be able to discern the relative weighting of systolic and diastolic parameters and overall risk. An individual patient meta-analysis or large individual study (sample size 1000–2000 patients, 300–500 events) would potentially have the power to discriminate between the individual echocardiographic parameters. This would be an important study that may lead to understanding of both the development of HF and the risk factors for death in patients having acute coronary events. In turn, this may lead to enhanced medical management of these patients. Nevertheless, this systematic review and meta-analysis has collated the results of 16 studies, from a wide variety of settings and more than a dozen countries, and provides an average size of the mortality risk associated with the presence of restrictive filling after AMI. Some of the larger studies provided similar results, but their effect sizes were inconsistent (with odds ratio ranging from about 2 to 15 for the five largest studies).

The importance of assessing diastolic filling pattern in the setting of AMI is often underrated. In this situation, the diagnostic role of echocardiography is of paramount importance: quantification of regional wall motion, infarct size, viable myocardium and structural trauma constitute the first goal of echocardiography in patients with an acute coronary event. However, the consistency of the findings and the size of the effect observed in this systematic review and meta-analysis suggest that it may be equally important for prognostic purposes to identify diastolic filling grades accurately, allowing a means of identifying patients who are at highest risk of death after their acute coronary event. A similar systematic review and meta-analysis of observational data evaluating the prognosis associated with higher natriuretic peptides in patients with acute coronary syndrome⁵⁵ showed that patients with higher natriuretic peptide concentrations (above the median) experienced higher mortality rates than those with lower concentrations. The odds ratio was of similar order of magnitude to that observed in the present review of restrictive mitral inflow. Both higher neurohormone concentrations and the presence of restrictive filling appear to be important cardiovascular markers that offer further prognostic information above simple clinical parameters, but their independence remains uncertain.

Most of the patients included in this analysis underwent echocardiography during their hospital admission. The timing of the echocardiography may be important. One recent study has shown that, although the filling pattern close to the ischaemic injury (1–2 days) predicts outcome, the

persistence of a restrictive filling pattern (10–12 days later) is even more ominous.²² This poses a potential conflict, given that the optimal timing of diagnostic echocardiography may be earlier in the course of the patient's admission.

Many of the studies included in this review were performed and reported before the recent redefinition of myocardial infarction and as a result may not apply to all of the patients who would now have acute coronary syndrome diagnosed. Further evaluation of the prognostic role of echocardiographic, clinical and neurohormonal factors within this new diagnostic framework is required.

Limitations

The process of meta-analysis contains many inherent biases. The first of these is publication bias. We may have omitted some unpublished data, which may or may not be in agreement with our results. Unpublished studies are often negative and their omission may lead to exaggeration of the difference between the two groups. We did contact all identified authors to request any unpublished data and did identify one further study in this way. To minimise this risk we identified all studies that included prognosis and echocardiography, but not necessarily restrictive filling pattern. These authors were contacted and asked whether their data could be broken down by restrictive versus non-restrictive filling.

A further bias may be patient overlap between studies. Because of the nature of our search strategy outlined above, we did identify several publications that reported on the same patients but were using different echocardiographic variables. In consultation with all authors, we were able to identify several studies based on the same patients and thus minimise this effect. We believe this rigorous methodological approach has minimised these potential sources of bias and error.

Lastly, the criteria used by individual investigators for classification of restrictive filling varied slightly. In most cases, the investigators predetermined this to be the best cut off for detecting at-risk patients. This may have influenced the results but we do not think this was the case for two reasons. Firstly, the deceleration time used varied little and, secondly, the analysis of odds ratio as a function of deceleration cut off showed no relationship and thus implies no bias.

The size of the risk estimates and confidence intervals around the risk estimates in the main results of this systematic review and meta-analysis, in conjunction with the sample size, suggest that these potential sources of error, although possible, are likely to have minimal effect on the overall risk estimates.

Conclusion

The assessment of diastolic filling grade confers important prognostic information about patients after AMI. In this study, about 20% of patients who had an AMI displayed a restrictive filling pattern, which was associated with a four times higher mortality. This prognostically important finding is thus not a rare phenomenon in this patient group. The findings of this study support the comprehensive echocardiographic assessment of diastolic filling pattern in patients close to the time of their ischaemic event. This important prognostic information should be considered alongside other important echocardiographic and clinical findings when managing such patients.

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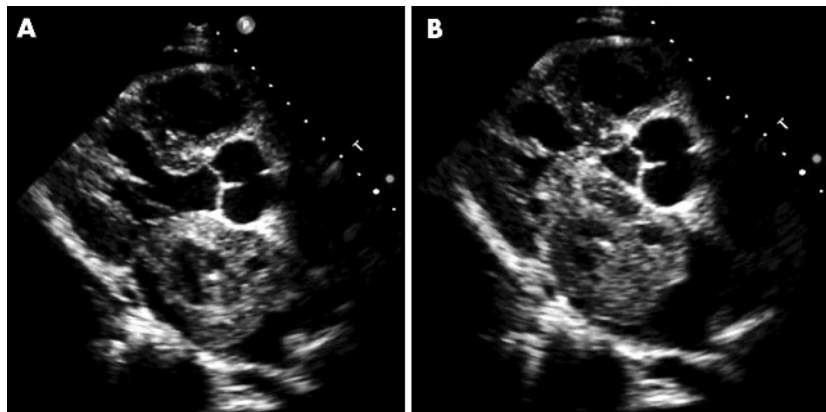
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IMAGES IN CARDIOLOGY

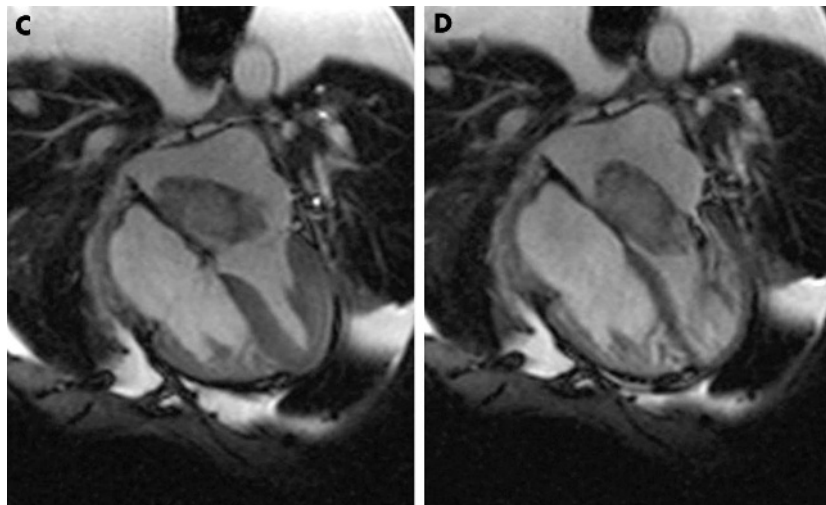
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Prolapsing left atrial myxoma causing severe pulmonary hypertension: dynamic echocardiographic and magnetic resonance imaging

A 63-year-old man presented with a 12 month history of increasing dyspnoea and lethargy. Transthoracic echocardiography (Philips IE33, The Netherlands) demonstrated a 6.2 × 3.9 cm mobile hyperechoic lesion within a dilated left atrium (panel A). This lesion occupied most of the left atrium and could be seen to be prolapsing into the left ventricle in diastole (panel B and supplemental video; to view video footage visit the *Heart* website—<http://www.heartjnl.com/supplemental>). Associated with this, moderate tricuspid regurgitation, a dilated right ventricle and notably elevated right ventricular systolic pressures (120 mm Hg) were also demonstrated. Dynamic magnetic resonance imaging (Siemens Symphony 1.5T, Germany) showed the lesion to be attached to the interatrial septum in the region of the foramen ovalis with a 2 cm pedicle (panel C) and to be prolapsing into the mitral valve orifice during valve opening, almost completely occluding the orifice and only allowing a small turbulent jet of blood into the left ventricle (panel D and supplemental video). The lesion was closely associated with but not adherent to the mitral valve leaflets and the pulmonary veins were not obstructed. Surgical excision of the lesion and post-operative recovery were uncomplicated, and associated with almost complete resolution of the pulmonary hypertension (38/18 mm Hg). Histological analysis of the lesion demonstrated typical microscopic features of a benign atrial myxoma. At two-month follow-up the patient remained well and postoperative echocardiography confirmed complete removal of the lesion with no residual atrial septal defect and good biventricular function.



Two dimensional echocardiography demonstrating hyperechoic left atrial lesion (A) attached to the interatrial septum in the region of the fossa ovalis and occupying the majority of the left atrium in systole, and (B) prolapsing into the left ventricle almost completely obstructing left atrial outflow in diastole.



Dynamic cardiac magnetic resonance images using a steady state free precession sequence (SSFP). (C) The left atrial mass is attached to the interatrial septum with a 1–2 cm pedicle and is close to but not attached to the mitral valve. (D) The mass prolapses into the mitral valve orifice during valve opening, only allowing a small turbulent jet of blood into the left ventricle in diastole.

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