Prognostic Implications of Left Ventricular Dilation in Patients With Nonischemic Heart Failure: Interactions With Restrictive Filling Pattern and Mitral Regurgitation

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The aim of this study was to evaluate whether small left ventricular (LV) volumes increase the negative prognostic impact of a restrictive filling pattern (RFP) and that of mitral regurgitation (MR) in patients with nonischemic heart failure (HF). The Meta-analysis Research Group in Echocardiography (MeRGE) is a meta-analysis that collated individual patient data from several prospective echocardiography outcome studies. This analysis was restricted to 10 studies and 601 patients with nonischemic HF. The role of MR was tested in a subgroup of 252 patients. A total of 106 deaths occurred during a median follow-up of 32 months. At multivariate analysis, RFP (hazard ratio [HR], 4.16; 95% confidence interval [CI], 1.54–11.23; *P*=.005) and New York Heart Association class III or IV (HR, 2.15; 95% CI, 1.33–3.47; *P*=.001) were the independent predictors of poor prognosis, and there was no statistically significant interaction between LV dilation and RFP. Moderate/severe MR was associated with poorer outcome in the group of patients with normal volumes, whereas it was not a significant predictor of mortality in patients with any degree of LV dilation. In patients with nonischemic HF, RFP is the most important indicator of poor prognosis, irrespective of the degree of LV dilation. Normal LV volumes increase the negative prognostic impact of moderate to severe MR. *Congest Heart Fail.* ****;**:**–**. ©2012 Wiley Periodicals, Inc.

It has been known since the 1980s that patients with heart failure (HF) as a result of dilated cardiomyopathy may present with end-stage HF despite having only mild left ventricular (LV) dilation.[1–4] The clinical and prognostic significance of this finding was found to vary. In fact, although a small left ventricle might be considered an indicator of early stage of disease, these patients generally exhibit somewhat poorer prognosis compared with those with conventional dilated cardiomyopathy.[1,2] From a pathophysiologic point of view, it is reasonable to hypothesize that a smaller forward cardiac output due to the small LV volumes might increase the negative prognostic impact of a restrictive LV filling pattern (RFP) and/or moderate to severe mitral regurgitation (MR).[5–8] A collaborative group, the Meta-analysis Research Group in Echocardiography (MeRGE), was recently established to test the independent prognostic significance of RFP in patients after acute myocardial infarction and in patients with HF.[9,10] Using the large dataset provided by this collaborative group, we sought to evaluate the prognostic implications of LV size and the interplay between LV size, LV filling, and MR in patients with nonischemic HF.

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METHODS

Study Design

The MeRGE HF study design has been previously described in detail.[9] Briefly, prospective studies that enrolled consecutive HF patients and included comprehensive echocardiography and outcome data were identified through online searches of several medical databases and through personal communication. Using a standard systematic review approach,[9] all prospective outcome studies in HF patients that included comprehensive echocardiographic assessment of diastolic filling were identified and the investigators were invited to submit their individual patient databases to a central site. Data were checked for consistency, range checks were performed, and clustering by the individual sites was evaluated. Overall, the MeRGE HF study encompasses more than 80% of the available prospective data that included comprehensive echocardiographic data as well as outcome data in well-characterized HF patients and demonstrated that RFP was associated with a 2-fold increase in the risk of death independently of LV ejection fraction (LVEF).[10]

Patients

The present analysis was restricted to patients with HF of nonischemic etiology and it includes data from 10 prospective studies (9 published[6,11–18] and 1 unpublished) with quantitative LV volume analysis and grading of mitral regurgitation. In such studies, ischemic heart disease was diagnosed on the basis of documented previous myocardial infarction or of significant coronary artery disease on coronary arteriography, and nonischemic heart disease was diagnosed in all other cases. Wall motion abnormalities were never considered a marker of ischemic heart disease. All patients with nonischemic HF were included, except in cases where the primary cause was valvular heart disease. Since this is a study of diastolic function, patients with atrial fibrillation/flutter or a paced rhythm were also excluded. In addition, none of the studies enrolled patients with specific restrictive cardiomyopathies such as cardiac amyloidosis. The individual patient data from each study were merged into a single database (demographic, clinical, echocardiographic, and outcome). Patients were recruited and echocardiography was performed in stable outpatients or at the time of hospital discharge in inpatients.

Echocardiography

The definition of LVRFP is a dichotomous variable based on the individual site definition (based on high E:A ratio and shortened deceleration time) (n=351) or by a predetermined cut-off value for transmitral E-wave deceleration time (<140 ms) (n=250). LV function variables included in the study were end-diastolic and end-systolic volume, LV ejection fraction (LVEF) and the degree of MR as graded by the individual site using a combination of visual assessment and quantitative methods. LVEF was estimated using validated quantitative methods (Simpson biplane method of discs or area-length method).

Statistical Methods

All data were collected and analysed by the MeRGE Coordinating Centre at the University of Auckland. The primary end point was all-cause death (or cardiovascular death where all-cause death was unavailable). All-cause death was the primary end point in a total of 430 patients and cardiovascular death was the primary end point in 171 patients. The Cox proportional hazard model, stratified by study, was used to investigate the univariate association of RFP and outcome as well as to determine independent predictors of mortality in all patients from: RFP, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), age, sex, New York Heart Association (NYHA) class, and the interaction of RFP and LVEDV. Patients were divided into different groups according to the sex-specific limits for LVEDV suggested by the American Society of Echocardiography (ASE).[19] Group 1 included patients with normal volumes (ASE group 1). Group 2 included patients with either mild or moderate dilation (ASE groups 2 and 3). Group 3 included patients with severe LV dilation (ASE group 4). Kaplan-Meier survival analyses comparing RFP vs non-RFP for each LV volume group were performed and the Cox proportional hazards model was reapplied within each volume group, this time omitting LVEDV and the interaction term from the model. As the subset of patients with information on MR was relatively small and a potential interaction between MR and volume was of interest, a Cox proportional hazards model, stratified by study, was performed that contained LVEDV categorized as normal (ASE group 1) or dilated (ASE groups 2, 3, or 4), MR categorized as none/mild or moderate/severe, and the interaction between MR and volume. Kaplan-Meier survival analyses comparing moderate/severe MR with normal/mild MR within each of the two LV volume groups were also performed. Procedures of SAS v9.1 (SAS Institute, Cary, NC) were employed. A P value $<.05$ was considered significant.

RESULTS

A total of 601 patients were included. The clinical characteristics of the study population as a whole and across LVEDV-based groups are shown in Table I. The average age of the patients was 56 years, approximately three quarters were men, and mean LVEF was 27%. RFP was present in 251 patients (42%). These patients were not different from the main MeRGE cohort of patients with HF from which they were selected. According to the sex-specific limits for LVEDV suggested by the ASE, 97 patients (16%) had normal volumes (group 1), 98 patients (16%) had mild or moderate LV dilation (group 2), and 404 patients (68%) had severe LV dilation (group 3). Age, EF, E/A ratio, deceleration time of mitral inflow, and the proportion of RFP and death were similar in all groups, but there was a greater proportion of women in group 3 (Table I). In a subset of 252 patients, information was available on the degree of MR at echocardiography. As shown in Table II, the characteristics of these patients were similar to those of the entire population, with the exception of younger age.

Survival

During a median follow-up period of 32 months, 106 deaths occurred: 67 (27%) in the RFP group and 39 (11%) in the non-RFP group (univariate hazard ratio [HR], 2.99; 95% confidence interval [CI], 1.98–4.51).

Prognostic Indicators According to LV Dilation

In the whole population, the univariate HR of RFP tended to be greater in patients with normal end-diastolic volumes (HR, 8.3; 95% CI, 2.1–32.6) (Figure 1A) than in patients with mild to moderate (HR, 3.0; 95% CI, 1.1–8.3) (Figure 1B) or severe dilation (HR, 2.3; 95% CI, 1.4–3.7) (Figure 1C). However, at multivariate analysis, RFP (HR, 4.16; 95% CI, 1.54–11.23; P=.005) and NYHA III or IV (HR, 2.15; 95%

TABLE I. Clinical and Echocardiographic Characteristics in the Whole Population and According to LV Dilation

	All Patients N=601	Group 1 (Normal EDV) n=97	Group 2 (Mild to Moderate Dilation) n=98	Group 3 (Severe Dilation) n=404
Age, y (mean±SD)	55.5±15.3	59.4±14.9	57.6±15.9	54.0±15.1
Male, n (%)	442 (74)	84 (87)	81 (83)	277 (69)
NYHA I/II/III/IV, n	75/263/220/32	12/56/22/5	15/40/37/6	48/166/161/20
Aetiology (DCM/HT/other[a]), n	548/36/17	82/8/6	86/10/3	378/18/8
EF, %	27, 21–33	30, 23–35	28, 22–33	25, 20–32
LVEDV, mL	211, 157–287	123, 98–144	173, 160–188	255, 210–313
LVESV, mL	149, 111–217	87, 65–104	127, 106–137	188, 142–242
E/A ratio	1.2, 0.7–2.1	1.2, 0.6–1.9	1.5, 0.8–2.8	1.2, 0.7–2.1
DT, ms	150, 110–209	150, 115–200	150, 110–203	150, 110–210
RFP, n (%)	251 (42)	38 (39)	44 (45)	169 (42)
Deaths, n (%)	106 (18)	15 (15)	20 (20)	71 (18)

Abbreviations: DCM, dilated cardiomyopathy; HT, hypertensive; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; E/A, ratio of early to late left ventricular filling waves; DT, deceleration time of E wave; RFP, restrictive filling pattern. Continuous variables are presented as median, IQR unless otherwise stated. [a]Other indicates mixed or undefined aetiology.

TABLE II. Clinical and Echocardiographic Characteristics of the Patients with Information on the Degree of MR

	All Patients N=252	Group 1 (Normal EDV) n=60	Group 2 (Mild to Moderate Dilation) n=47	Group 3 (Severe Dilation) n=144
Age, y (mean±SD)	48.2±14.3	53.9±12.3	48.8±13.2	45.6±14.9
Male, n (%)	199 (79)	57 (95)	42 (89)	100 (69)
NYHA I/II/III/IV, n	24/120/91/17	6/40/10/4	9/18/18/2	9/62/63/10
EF, %	25, 20–30	25, 19–30	27, 22–31	25, 19–29
LVEDV, mL	201, 147–285	123, 100–144	173, 162–187	277, 221–325
LVESV, mL	148, 111–212	94, 71–107	128, 118–136	200, 161–251
E/A ratio	1.3, 0.8–2.5	1.2, 0.7–1.9	1.8, 0.9–3.0	1.4, 0.8–2.6
DT, ms	121, 90–170	150, 110–183	140, 90–170	110, 85–150
RFP, n (%)	138 (55)	26 (43)	23 (49)	89 (62)
Deaths, n (%)	46 (18)	9 (15)	9 (19)	28 (19)

Abbreviations: NYHA, New York Heart Association; HT, hypertensive; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; E/A, ratio of early to late left ventricular filling waves; DT, deceleration time of E wave; RFP, restrictive filling pattern.

CI, 1.33–3.47; *P*=.001) were the only independent predictors of poor prognosis and the interaction between LVEDV and RFP was not statistically significant in the model (Table III). In the subset of 252 patients with information on the degree of MR, moderate/severe MR was associated with poorer outcome in the group of patients with normal volumes (n=60; univariate HR, 12.1; 95% CI, 1.4–101) (Figure 2A), whereas it was not a statistically significant predictor of mortality in patients with dilation (n=191; univariate HR, 0.6; 95% CI, 0.3–1.4) (Figure 2B). At multivariate analysis, RFP (HR, 4.6; 95% CI, 2.1–10.4; *P*=.0002), LV dilatation (HR, 6.01; 95% CI, 1.16–32.2; *P*=.04), and the interaction between LVEDV and moderate/severe MR (HR, 0.17; 95% CI, 0.03–0.97; *P*=.046) were statistically significant (Table IV).

DISCUSSION

The present study shows that the degree of LV dilation is not per se a determinant of prognosis in patients with nonischemic HF. However, we noticed that LV dilation interacts with other LV functional parameters, indirectly impacting prognosis. The risk associated with moderate/severe MR was in fact significant only in patients with normal LVEDV, and the risk associated with RFP tended to be higher, albeit nonsignificantly, in patients with normal end-diastolic volumes than in those with mild to moderate or severe LV dilation. These findings are particularly important since patients with small LV cavities might be thought to have less advanced disease, whereas they indeed have similar prognosis as patients with dilated LV cavities, and especially so in the presence of restrictive filling.

Different Presentation of LV Dilation in Patients With Nonischemic HF

In the present study, a wide spectrum of LV size was observed among patients with nonischemic HF, with a substantial proportion (24%) having either normal sex-specific LVEDV or mild LV dilation. Such a high prevalence of patients with mildly dilated cardiomyopathy is remarkably similar to that reported in previous small single-center studies, suggesting that it could be an intrinsic characteristic of about one

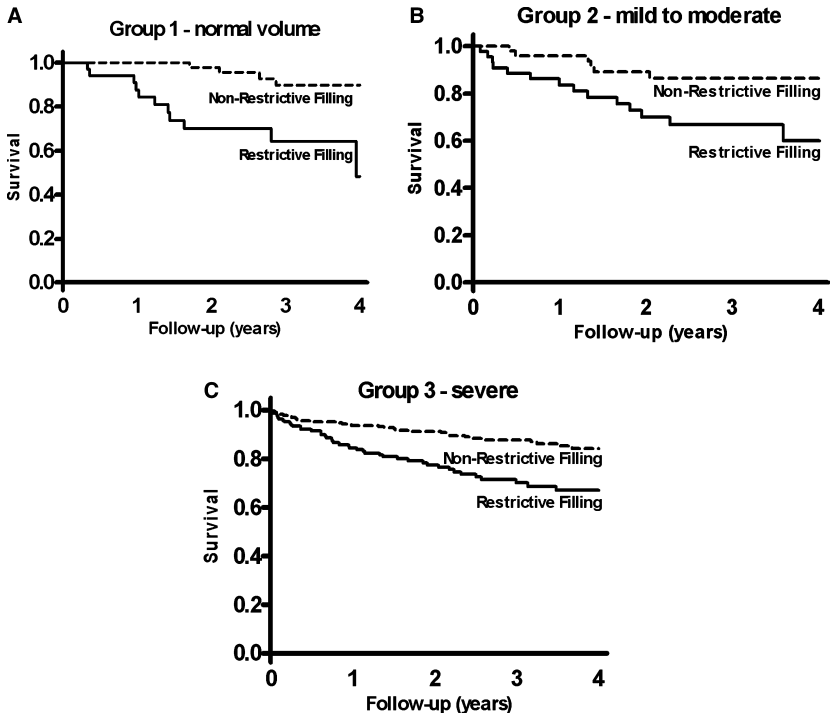

FIGURE 1. Kaplan-Meier survival curves in patients with restrictive filling pattern (RFP) (continuous line) or without RFP (dashed line) for each volume category. See text for statistical significance. (A) Patients with normal left ventricular (LV) end-diastolic volumes. (B) Patients with mild to moderate LV dilation. (C) Patients with severe LV dilation.

TABLE III. Multivariable Predictors of Outcome

Characteristic	Hazard Ratio	95% Confidence Interval	*P* Value
All patients (n=594)			
RFP	4.16	1.54–11.23	.005
LVEDV, mL	0.998	0.988–1.01	.62
LVESV, mL	1.01	0.997–1.02	.14
Age, y	1.01	0.997–1.03	.11
Gender, male	1.10	0.67–1.80	.71
NYHA III or IV	2.15	1.33–3.47	.001
RFP*LVEDV	0.997	0.994–1.00	.13

Abbreviations: RFP, restrictive filling pattern; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RFP*LVEDV, interaction between RFP and LVEDV.

quarter of patients with nonischemic HF.[3,4] Whether mild LV dilation depends on specific biologic characteristics of the disease is as yet unknown. Previous studies have attempted to utilize myocardial biopsy data to clarify this issue without success, and genetic data are not available at present.[1,2]

Echocardiographic Predictors of Prognosis in Patients With Nonischemic HF

In the present population of nonischemic HF patients, RFP of the left ventricle was the strongest echocardiographic indicator of poor prognosis. This confirms the results of several important studies that concluded that RFP is the most important predictor in chronic HF patients with different etiologies.[5,6,18] On the contrary, the degree of LV dilatation and LVEF were not independent predictors of mortality. This observation is seemingly in contrast to the notion that the beneficial effects of renin-angiotensin-aldosterone system inhibitors and β-blocking agents in HF patients are in great part mediated by drug effects on LV volumes and function. In the Studies of Left Ventricular Dysfunction (SOLVD) echocardiographic substudy,[20] enalapril significantly reduced EDV and ESV over 12 months as compared with placebo. Carvedilol has been shown to reduce volumes and increase EF in the echocardiographic substudy of the Australia-New Zealand Heart Failure Research Collaborative Group.[21] The Valsartan Heart Failure Trial (Val-HeFT) echocardiographic substudy[22] showed a reduction in LV end-diastolic dimensions and an increase in EF during treatment with valsartan as compared with placebo. In the Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalization in Seniors With Heart Failure (SENIORS) echocardiographic substudy,[23] LVESV decreased and EF increased after 12 months of therapy with nebivolol. Although these studies convincingly showed that pharmacotherapy can have favorable effects on LV remodeling in patients with HF and that reverse remodeling is associated with improved

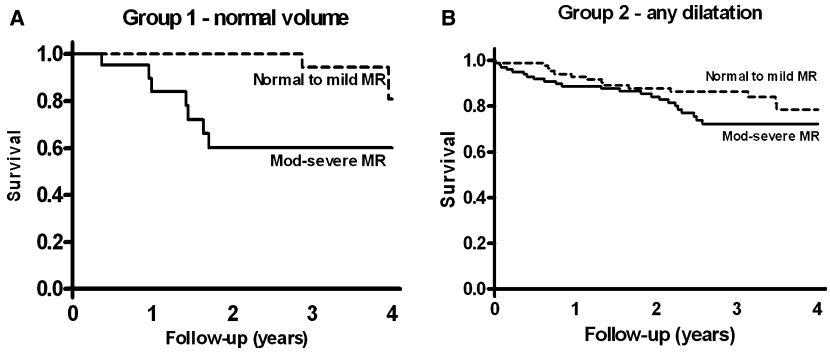

FIGURE 2. Kaplan-Meier survival curves in patients with moderate to severe mitral regurgitation (MR) (continuous line) or absent to mild MR (dashed line) for each volume category. See text for statistical significance. (A) Patients with normal left ventricular (LV) end-diastolic volumes. (B) Patients with any LV dilation.

TABLE IV. Multivariable Predictors of Outcome in Subset with Information on the Degree of MR, n=251

Characteristic	Hazard Ratio	95% Confidence Interval	*P* Value
Restrictive filling pattern	4.6	2.1–10.4	.0002
Dilated LV[a]	6.01	1.12–32.2	.04
Moderate/severe MR	2.84	0.57–14.2	.20
Moderate/severe MR*dilated LV	0.17	0.03–0.97	.05

Abbreviations: LV, left ventricle; MR, mitral regurgitation. [a]Any degree of dilatation above ASE normal reference range.

survival, much less attention has been paid to the original relationship between LV geometry, systolic and diastolic function, and outcome. The influence of LVEF on cardiovascular outcomes was evaluated in the Candesartan in Heart Failure Reduction in Mortality (CHARM) program,[24] but no further volumetric data or other echocardiographic prognostic parameters were available. The only study that included data on LV volume, LV filling, and degree of MR was the β-Blocker Evaluation of Survival Trial (BEST),[25] which found LVEDV to be an independent predictor of prognosis. Furthermore, most of these studies enrolled patients with HF of both ischemic and nonischemic etiology. Thus, the issue of the prognostic role of LV dilation in patients with nonischemic HF has not yet been fully addressed in large trials. One could hypothesize that improvements in LV geometry and function due to medical therapy have positive effects on prognosis regardless of the degree of LV dilatation and dysfunction at baseline. In addition, it could be argued that patients with mild LV dilatation may be misconstrued as being in the early stage of disease and be denied therapy with a clinically important negative outcome.

Although the degree of LV dilation was not per se a determinant of prognosis in this series of patients with nonischemic HF, we noticed that LV dilation interacts with mitral regurgitation, indirectly impacting prognosis. In the subset of patients in whom a quantification of the degree of MR was available, moderate/severe MR was found to be a significant predictor of mortality in those with normal volumes but not in those with LV dilation. These findings could be explained considering that, for any degree of MR volume, the reduction of stroke volume is greater in patients with normal LV volumes than in patients with dilated hearts. Additionally, although the risk associated with an RFP was not statistically different among patients with different LVEDV, it tended to be greater in patients with normal sex-related LVEDV than in patients with mild to moderate dilation and even lower in patients with severe dilation. The reason might be that a normal-sized LV has to contend with greater wall stress compared with a dilated LV in the presence of RFP, ie, of elevated filling pressures. This may induce greater neurohormonal activation and subsequent poorer prognosis. The findings of the present study have relevant clinical implications, since patients with nonischemic HF and small LV cavity size might be considered at lower risk, whereas they might need more aggressive therapy to revert an LVRFP pattern and to reduce the degree of MR.

Limitations

The present analysis includes only part of the original MeRGE database, since the entry criteria here were restricted to patients with nonischemic etiology and systolic LV dysfunction. We also acknowledge the lack of quantitative grading of MR and the relatively small number of patients in the MR subanalysis. In addition, prognosis in HF patients is related to many clinical factors that could not be considered in the present meta-analysis.[26] These limitations partly relate to the way in which the data were collated; for example, quantitative MR data were not an entry criterion of the main MeRGE HF study, so that when considering MR, we were only able to compare none/mild vs moderate/severe MR. The main MeRGE database has some limitations also. In order to gather as many data

(and events) as possible, some compromises were made. We do not have extensive clinical data (such as etiology, treatment, prior admissions) and we acknowledge that many of these parameters may contribute to mortality in these patients. However, inclusion in a multivariable model of all relevant data with known prognostic impact in HF patients would be an extremely challenging objective. Nevertheless, we feel that the omission of these data is partially balanced by the large sample size and number of events when compared with previous studies in this area. We have used two different end points in this study: all-cause death and cardiovascular death, in order to increase the available sample size. These are both very common end points in HF studies, and other studies have shown that <10% of deaths in HF patients are non-cardiovascular,[27] and in our study only 171 (28%) patients originated from studies with total mortality data only, and since our overall number of deaths was 106 (18%), we estimate that the number of additional deaths that might have been included in this group could be no more than 2 to 4 events. Finally, with a few exceptions, patients in the general population differ from those enrolled in HF trials usually by being older and more frequently having a preserved LV function.[28] This is a limitation that also applies to the present meta-analysis. There may be slight differences in both HF and echocardiographic diagnostic algorithms between sites. We used the original definition of RFP at the recruiting hospital, and while there may have been subtle differences in the definition of RFP, the methods were all well accepted in both the literature and clinical practice and reflect normal variation in clinical practice.

CONCLUSIONS

Although patients with HF and small LV cavities might be anticipated to be those with less advanced disease, they have a similar prognosis as patients with dilated hearts, and especially so in the presence of restrictive LV filling. In fact, the risk associated with RFP tended to be slightly, albeit not significantly, higher in patients with normal end-diastolic volumes than in patients with LV dilation. Interestingly, LV cavity size indirectly impacts the relationship between prognosis and moderate to severe MR. In addition, MR was not a significant predictor of outcome in patients with dilated LV cavities. These findings support the integration of several echocardiographic parameters, including diastolic parameters, LV volumes, and the severity of MR, for predicting outcome in individual patients with HF.

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