

Evaluation of the Clinical Relevance of Baseline Left Ventricular Ejection Fraction as a Predictor of Recovery or Persistence of Severe Dysfunction in Women in the United States With Peripartum Cardiomyopathy

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ABSTRACT

Background: Baseline left ventricular ejection fraction (LVEF) has been shown to be associated with likelihood of recovery in patients with peripartum cardiomyopathy (PPCM). The clinical relevance of this association for individual patients is unclear.

Methods and Results: We analyzed baseline parameters of LVEF in 187 PPCM patients with ≥ 6 months follow-up data in an attempt to detect the value of baseline LVEF as a predictor of early recovery or persistence of severe LV dysfunction. Recovery of LV function (LVEF $\geq 50\%$) at 6 months after diagnosis was found in 115 patients (61%). Multivariate analysis identified baseline LVEF $> 30\%$ as a significant predictor for recovery (odds ratio 5.2, 95% confidence interval 1.96–7.70; $P > .0001$). Recovery of LV function was 6.4-fold higher in women with baseline LVEF $\geq 30\%$ (group III) and 3.9-fold higher in women with LVEF 20%–29% (group II) compared with those with LVEF 10%–19% (group I). Failure to achieve full recovery was seen in 63% of group I patients, 32% of group II ($P = .03$), and 21% of group III ($P = .02$ vs group I). Failure to achieve LVEF $\geq 30\%$ was seen in 30% of group I patients and 13% of group II ($P = .09$).

Conclusions: Early recovery in patients with PPCM is significantly related to the degree of myocardial insult at time of diagnosis. Baseline LVEF however, has a limited sensitivity for prediction of failure to improve in individual patients and can not be used as an indication for premature use of aggressive therapy including devices or cardiac transplantation. (*J Cardiac Fail* 2011;17:426–430)

Key Words: Peripartum, cardiomyopathy, left ventricle, function, recovery, predictors.

Peripartum cardiomyopathy (PPCM) is a disease of unknown etiology that affects women during pregnancy or post partum and characterized by the development of heart failure due to marked left ventricular (LV) systolic

dysfunction.^{1–3} PPCM remains an important cause of pregnancy-related maternal morbidity and mortality in the USA.^{4–7} Early reports as well as recent studies have revealed strong relationships between the degree and persistence of LV dysfunction and the incidence of major complications.^{7,8} The ability to identify predictors for early recovery or persistent LV dysfunction would have important implications in the management strategies of this condition and could possibly alter its prognosis by allowing early interventions. A number of studies have suggested a relationship between the degree of LV dysfunction at the time of diagnosis and the likelihood of recovery.^{9–11} Those studies have been limited, however, by a relatively small number of patients or information obtained in other countries where clinical presentation and outcome may be different.^{2,10,11}

Although the disease is uncommon, its incidence has been increasing¹⁴ and is estimated to involve between 1,000 to

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2,000 new cases per year in the USA alone.^{12–16} The condition usually presents with a marked depression of LV systolic function, and recent data have clearly demonstrated a strong relationship between the severity and persistence of LV dysfunction and the incidence of morbidity and mortality due to progressive heart failure and sudden death.^{7,8,12,17} The ability to predict early recovery of LV function or persistent dysfunction could therefore have an important impact on early management strategy of these patients. The present analysis was performed in an attempt to further evaluate whether baseline LVEF at the time of diagnosis is predictive of persistent dysfunction in a large number of patients with PPCM diagnosed in the USA.

Methods

Data Collection

The patient population included 217 women diagnosed with PPCM defined as: 1) development of heart failure in the last part of pregnancy or within 5 months postpartum; 2) absence of demonstrable cause of heart failure; 3) absence of demonstrable heart disease before last part of pregnancy; and 4) LVEF <45%.³ Exclusion criteria were patients with an identifiable etiology for their heart failure and patients who were unable to provide both initial and subsequent echocardiogram reports. Baseline and ≥ 6 -month values of echocardiographic LVEF were available in 187 women and were used for the purpose of this study.

Patients were included from 3 different sources to represent a wide spectrum of patients with PPCM diagnosed and treated in the USA from 1994 to 2004. One hundred fifty-three patients were part of the data base established at the University of Southern California (1994–2004),^{6,7} 34 patients were diagnosed and cared for at Louisiana State University Health Science Center, Shreveport, Louisiana (1993–2000), and 30 patients were recruited via the internet (1997–2007) as part of a web-based registry in collaboration with PPCM education and support (www.amothersheart.org [AMH]).¹² A detailed description of the study was featured on the AMH website describing the purpose, methods, and goals of the study, and prospective subjects initiated the enrollment process by downloading informed consent and health insurance forms. After signing the consent and insurance documents, patients were enrolled. Each patient was required to complete standardized questionnaire via website or in paper format detailing information, including echocardiography reports.

All patients were divided into 2 groups: the recovery group and the nonrecovery group with persistent LV dysfunction. We defined recovery as LVEF $\geq 50\%$, which has been used in earlier studies of patients with PPCM.^{2,6,7} We further divided the patients arbitrarily into 3 groups: group I: LVEF 10%–19%; group II: LVEF 20%–29%; and group III: LVEF 30%–45%.

This retrospective study was conducted with approval of the respective Institutional Review Boards.

Statistical Analyses

Variables of interest were selected a priori for their potential to be predictive factors of LVEF recovery which was defined as LVEF $\geq 50\%$ at ≥ 6 months after the diagnosis. Continuous variables were examined in their continuous form and as grouped terms based on their distribution in

the population. The variables examined included baseline LVEF (continuous; <30% vs $\geq 30\%$), race (black vs other), age at diagnosis (continuous; <30 y vs ≥ 30 y), gravidity (continuous; 1 vs ≥ 2), multiple pregnancy (yes vs no), history of hypertension (any vs none), tocolysis (yes vs no), delivery mode (cesarean section vs vaginal delivery); baseline LV diastolic diameter (LVDD) (continuous; ≥ 55 mm vs <55 mm) and diagnosis of PPCM at the antepartum versus postpartum period. Complete information on medical therapy was not available in many of the patients and therefore was not included in the analysis. Simple analyses using chi-square tests for categorical variables and *t* tests for continuous variables were used to evaluate associations between each variable and LVEF recovery. Variables with *P* values of <.10 were retained for further examination in a multivariable model. Pairwise correlation coefficients and corresponding *P* values were computed to determine whether potentially related clinical variables identified by the simple analyses were significantly correlated. A backward stepwise approach to model building was used to identify the best predictive model of LVEF recovery while examining multiplicative interactions between variables. Logistic regression methods were used to model the outcome “recovery” by the predictor variables. LVDD was not available in all patients and was not evaluated in the main stepwise multivariable Cox proportional hazards model. Variables were retained in the multivariable model with a Wald *P* value of <.05.

In addition, recovery of LVEF to >30% or $\geq 50\%$ in the various subgroups of patients were analyzed using the Fisher exact test, and *P* <.05 was considered to be statistically significant.

Results

Clinical Characteristics of All PPCM Patients

Clinical characteristics of the entire group are presented in Table 1. The average age was 30 ± 6 years, 64% of the patients were caucasian, 25% were African American, and the remainder were Hispanic, Native American, or Asian. The average gravidity was 2.7 ± 2.0 pregnancies, 18% of patients had either twin or triplet pregnancies, gestational hypertension was present in 41%, tocolysis was used in 13%, and 44% of the patients had cesarean delivery. Mean baseline LVEF was $28 \pm 10\%$ and LVDD (92 patients) 58 ± 8 mm; at ≥ 6 months, mean LVEF was $47 \pm 14\%$ and LVDD 49 ± 17 mm. Some data on medical treatment were available in 143 patients: 118 (82.5%) were treated with angiotensin-converting enzyme inhibitors; 83 (58.0%) with β -blockers; 12 (8.3%) received anticoagulation, and 37 (25.8%) were on digitalis.

Differences in Baseline Clinical Characteristics Between Patients With LV Recovery and Those With Persistent LV Dysfunction

Mean echocardiographic follow-up was 8.8 ± 4.9 months (6–12 months follow-up in 181 patients, 20–48 months in 6 patients). Of the 187 patients with PPCM, 115 (61%) demonstrated recovery of LV function (LVEF

Table 1. Clinical Characteristics of All Patients Included and Comparison Between Patients With (Recovery group) and Without Left Ventricular Recovery (Nonrecovery Group)

	All PPCM Patients (n = 187)	Recovery Group (n = 115)	Nonrecovery Group (n = 72)	P Value
Age, y (n = 186)	30 ± 6	30 ± 6	29 ± 6	.4
Age >30 y (n = 186)	94 (51%)	60 (52%)	34 (48%)	.6
Black (n = 182)	45 (25%)	21 (19%)	24 (34%)	.02
Gravida (n = 175)	2.7 ± 2.0	2.4 ± 1.9	3.1 ± 2.1	.009
Gravida ≥2 (n = 175)	111 (63%)	61 (58%)	50 (72%)	.05
Twin or triplet pregnancy (n = 184)	34 (18%)	23 (20%)	11 (15%)	.4
Gestational hypertension (n = 184)	75 (41%)	49 (43%)	26 (37%)	.4
Tocolysis (n = 178)	24 (13%)	18 (16%)	6 (9%)	.2
Cesarean delivery (n = 181)	80 (44%)	50 (45%)	30 (43%)	>.9
PPCM diagnosed postpartum (n = 178)	112 (63%)	72 (65%)	40 (59%)	.4
LVEF at diagnosis, % (n = 187)	28 ± 10	31 ± 10	23 ± 10	<.0001
LVEF ≤30%	98 (52%)	45 (39%)	53 (73%)	<.0001
LVDD at diagnosis, mm (n = 97)	58 ± 8	55 ± 7	61 ± 8	.002
LVDD >55 mm (n = 97)	58 (60%)	24 (46%)	34 (75%)	.004
LVEF at ≥6 months, % (n = 187)	47 ± 14	53 ± 9	34 ± 12	<.0001
LVDD at ≥6 months, mm (n = 61)	49 ± 17	45 ± 17	55 ± 7	.0002

PPCM, peripartum cardiomyopathy; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter. Data are presented as mean ± SD or number (%). P values are for differences between the 2 groups.

≥50% at ≥6 months of follow-up; recovery group) and 72 (39%) had persistent LV dysfunction (nonrecovery group). The comparison between the 2 groups is presented in Table 1. The nonrecovery group had a significantly higher prevalence of African Americans (34% vs 19%; $P = .02$) and significantly higher mean index pregnancy (3.1 ± 2.1 vs 2.4 ± 1.9 ; $P = .009$). There was no significant difference in other characteristics, including age, gestational hypertension, use of tocolytic therapy, rate of cesarean section, and antenatal or postpartum diagnosis of PPCM between the 2 groups.

Differences in Baseline Left Ventricular Function

A comparison of the degree of LV systolic dysfunction at time of diagnosis between the 2 groups revealed a significantly lower LVEF in the nonrecovery group ($23 \pm 10\%$ vs $31 \pm 10\%$; $P < .0001$; Fig. 1), with a larger proportion of patients with LVEF <30% (73% vs. 39%; $P < .0001$) and a significantly larger LV size (LVDD 61 ± 8 mm vs. 55 ± 7 mm; $P = .002$).

Improvement of LV function occurred in both groups, but to a lesser degree in the nonrecovery group (LVEF $56 \pm 9\%$ vs $34 \pm 12\%$; $P < .0001$; Table 1; Fig. 1), and LVDD remained significantly larger in the nonrecovery group (45 ± 18 mm vs 55 ± 7 mm; $P = .0002$).

Predictors of Recovery of LV Function by Multivariable Analysis

The following variables were evaluated as potential predictors of LV recovery: age >30 years, baseline LVEF <30%, African-American background, gestational hypertension, multiparity, timing of diagnosis (antepartum vs postpartum), and cesarean delivery. The only significant predictor of recovery was baseline LVEF >30% (hazard ratio 5.2, 95% confidence interval [CI] 1.96–7.70; $P > .0001$).

Rate of Recovery of LV Function According to Baseline LVEF

We further arbitrarily divided the patients based on their baseline LVEF into 3 groups (Table 2): group I: LVEF 10%–19%; group II: LVEF 20%–29%; and group III: LVEF 30%–45%. A comparison of groups II and III with group I used as a reference group revealed 3.9- and 6.4-fold increases in recovery of LVEF to >50% (95% CI 1.8–8.4; $P = .004$; and 95% CI 2.9–13.7; $P < .0001$; respectively). Additional analysis (Fig. 2) showed a failure to achieve full recovery of LV function in 63% of group I versus 32% in group II patients ($P = .04$) and 21% in group III patients ($P = .002$ vs group I; $P = .4$ vs group II).

Rate of Persistence of LVEF ≤30%

Persistence of LVEF ≤30% (Fig. 2) was found in 20 of 67 patients (30%) of group I and in 7 of 53 patients (13%) of group II ($P = .09$).

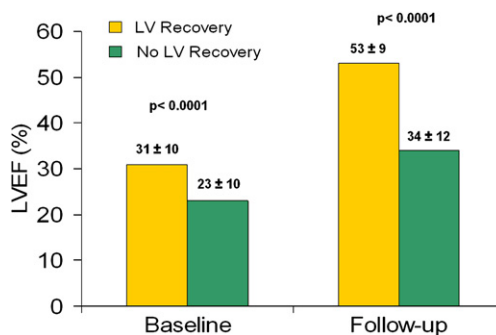


Fig. 1. Comparison of mean (±SD) left ventricular ejection fraction (LVEF) at the time of the diagnosis of peripartum cardiomyopathy and at follow-up ≥6 months between left ventricular (LV) recovery and nonrecovery groups. P values are for the comparison between the 2 groups.

Table 2. Likelihood of LV Recovery Based on Baseline LVEF

Groups Compared	Odds Ratio	P Value	Confidence Interval
Group 2 vs group 1	3.9	.004	1.8–8.4
Group 3 vs group 1	6.4	<.0001	2.9–13.7

LV, left ventricle; LVEF, left ventricular ejection fraction. Group 1: LVEF 10%–19% (n = 67); group 2: LVEF 20%–29% (n = 53); group 3: LVEF 30%–44% (n = 67).

Discussion

The present study has used a large database and a wide spectrum of patients with PPCM diagnosed in the USA and has confirmed the significant relationship between LVEF at the time of diagnosis and the likelihood of LV functional recovery. Patients with baseline LVEF $\geq 30\%$ were >5 -fold more likely to normalize their LV function (LVEF $\geq 50\%$) than those with LVEF $< 30\%$ in whom failure to achieve full recovery was seen in more than one-half of the patients: Of those, 45% showed persistent severe depression of cardiac function with LVEF $< 30\%$. Our findings support earlier studies with a smaller number of patients^{5,9–11} which showed a relationship between LVEF and LV function recovery. Witlin et al.⁵ studied a small cohort of 9 PPCM patients and had found that fractional shortening $\leq 21\%$ was related to persistent LV dysfunction. It was recently confirmed by Chapa et al.,⁹ who described 3-fold higher risk for persistent LV dysfunction in those with fractional shortening $\leq 20\%$ among 32 PPCM patients, and Duran et al.¹¹ reported an initial cutoff value of 27% for LVEF as a predictor of normalization of LV function.

These findings are clinically useful because they identify a group of patients at higher risk of complications⁷ who require a close surveillance as well as an aggressive treatment strategy. Recent preliminary reports have suggested the potential benefit of new therapy, including pentoxifylline and bromocriptine, for early recovery and prevention of complications in patients with PPCM.^{18,19} A prospective evaluation in a relatively large number of patients will be

required to establish the validity of these emerging and promising treatment modalities.²⁰ The ability to conduct such studies is limited by the small number of patients seen in most institutions and by the relatively high rate of recovery on standard therapy. The results of the present study identify patients with PPCM who are at risk for persistence of LV dysfunction that could potentially benefit from new therapy. A focus of new studies on these higher-risk patients, especially those in group I (LVEF 10%–19%), in whom failure to completely recover was documented in two-thirds of the patients, could increase the yield and lower the cost of such important and urgently needed trials. Early implantation of an implantable cardioverter/defibrillator (ICD) is often considered in patients with PPCM, because of an emotional concern for the young woman and her newborn child and because sudden death, usually occurring within the first 6 months of diagnosis, has been reported in nearly one-half of nonsurvivors.^{6,7} At the same time, however, premature implantation of an ICD in patients with high likelihood of recovery of LV function is not recommended.²¹ Can baseline value of LVEF predict failure of LV recovery and be used as an indication for early ICD implantation? Despite the strong association between LVEF at time of diagnosis and rate of recovery, 70% of patients in group I (LVEF 10%–19%) and 87% of patients in group II (LVEF 20%–29%) recovered almost beyond the “device threshold” at ≥ 6 months. These findings clearly indicate that early aggressive therapy, including implantation of ICD or cardiac transplantation, based on baseline LVEF is not advisable and that temporary measures, such as a wearable external defibrillator and assist devices, may be used in these high-risk patients as a bridge to LV recovery or to device or surgical therapy in cases that fail to recover despite optimal heart failure therapy of sufficient duration. Further research is needed to identify markers more sensitive than baseline LVEF, for recovery in all individuals with PPCM. An ongoing study is presently evaluating the relationship between systemic immune activation and myocardial inflammation as well as the development of myocardial fibrosis detected by magnetic resonance imaging and recovery of LV function in patients with PPCM.²²

Study Limitations

The results of this study may be limited by a retrospective data collection in many of the patients and reliance on information obtained from patient records that have been incomplete. In addition, analysis of echocardiographic findings was based on data provided by the interpreting physicians. Similar data, however, are available to most clinicians and provide the basis for the management of patients with LV dysfunction. Our study population represents a wide spectrum of patients with PPCM in the USA, but it should be noted that, because of potential phenotypic differences between patients with PPCM in other parts of the world, which is reflected in a lower rate and

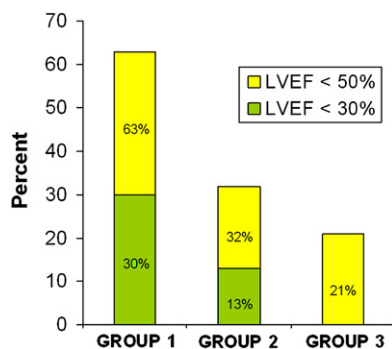


Fig. 2. Failure to achieve left ventricular ejection fraction (LVEF) of 50% and 30% at ≥ 6 month in different groups according to baseline LVEF: group I: 10%–19%; group II: 20%–29%; and group III: 30%–45%.

longer time of recovery of cardiac function,^{8,10} our findings may not be applicable to non-USA patients.

Conclusions

The present study demonstrates failure to normalize LVEF at ≥ 6 months in almost 40% of a large group of PPCM diagnosed in the USA. Persistent LV dysfunction is significantly more common in patients with severe myocardial insult at the time of diagnosis, as represented by depression of LV systolic function. These findings should be helpful in identifying high-risk patients who require close surveillance and should be useful in the design of new clinical trials for evaluation of new and promising therapies for PPCM. However, the sensitivity of baseline LVEF as a predictor of LV recovery or lack of it in an individual patient is limited and should not be used for early and premature utilization of aggressive and expensive therapy such as device implantation or cardiac transplantation.

Disclosures

None.

References

- Pearson GD, Veille JC, Rahimtoola SH, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum Cardiomyopathy. *JAMA* 2000;283:1183–8.
- Sliwa K, Fett J, Elkayam U. Current understanding of the epidemiology, aetiology, clinical profile, and management of PPCM. *Lancet* 2006;368:687–93.
- Sliwa K, Hilfiker-Kleiner D, Pieske B, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. *Eur J Heart Fail* 2010;12:767–78.
- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2008;342:1077–84.
- Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. *Am J Obstet Gynecol* 1997;176:182–8.
- Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation* 2005;111:2050–5.
- Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LS, et al. Clinical profile and predictors of complications in peripartum cardiomyopathy. *J Card Failure* 2009;15:645–50.
- Sliwa K, Forster O, Libhaber E, et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* 2006;27:441–6.
- Chapa JB, Heiberger HB, Weinert L, DeCara J, Lang RM, Hibbard JU. Prognostic value of Echocardiography in peripartum cardiomyopathy. *Obstet Gynecol* 2005;105:1303–8.
- Fett JD, Sannon H, Thélisma E, Sprunger T, Suresh V. Recovery from severe heart failure following peripartum cardiomyopathy. *Int J Gynaecol Obstet* 2009;104:125–7.
- Duran N, Günes H, Duran I, Biteker M, Ozkan M. Predictors of prognosis in patients with peripartum cardiomyopathy. *Int Gynaecol Obstet* 2008;101:137–40.
- Safirstein JG, Choi J, Ro A, Grandhi S, Hermance E, Staniloae C. Web-based recruitment facilitates collection of patients with peripartum cardiomyopathy. *J Am Coll Cardiol* 2007;272A–97A.
- Berg CJ, Chang J, Callaghan WH, Whitehead SJ. Pregnancy-related mortality in the United States, 1991–1997. *Obstet Gynecol* 2003;101:289–96.
- Mielniczuk LM, Williams K, Davis DR, Tang A, Lemery R, Green MS, et al. Frequency of peripartum cardiomyopathy. *Am J Cardiol* 2006;97:1765–8.
- Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, et al. Incidence, mortality, racial differences in peripartum cardiomyopathy. *Am J Cardiol* 2007;100:302–4.
- Kuklina EV, Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004–2006. *Obstet Gynecol* 2010;115:93–100.
- Modi KA, Illum S, Jariatul K, Caldito G, Reddy P. Poor outcome of indigent patients with peripartum cardiomyopathy in United States. *Am J Obstet Gynecol* 2009;201:171–2.
- Sliwa K, Skudicky D, Candy G, Bergmann A, Hopley M, Sareli P. The addition of Pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *Eur J Heart Fail* 2002;4:305–9.
- Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy. A proof of concept pilot study. *Circulation* 2010;121:1465–73.
- Elkayam U, Goland S. Bromocriptine for the treatment of peripartum cardiomyopathy. *Circulation* 2010;121:1463–4.
- Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. American College of Cardiology, American Heart Association Task Force, European Society of Cardiology Committee for Practice Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Death). *Circulation* 2006;114:e385–484.
- Peripartum cardiomyopathy. *ClinicalTrials.gov* identifier NCT01085955.