EDITORIAL COMMENT

The Search for a Crystal Ball to Predict Early Recovery From Peripartum Cardiomyopathy?*

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Peripartum cardiomyopathy (PPCM) is an idiopathic myocardial disease presenting toward the end of pregnancy or in the months following delivery with heart failure secondary to left ventricular (LV) systolic dysfunction [1]. Left ventricular ejection fraction (LVEF) at diagnosis is usually markedly reduced, averaging in the published data at around 30% [2–5]. Early recovery (within 2 to 6 months) with partial or complete restoration of cardiac function is an additional characteristic of PPCM and has been described in the majority of patients diagnosed with this condition in the United States and Europe [5–7]. At the same time, however, PPCM is a leading cause of pregnancy-related nonobstetric morbidity and mortality. Markedly reduced cardiac function and failure to recover reported in 10% to 30% can be associated with major adverse events, including life threatening arrhythmias, thromboembolic complications, clinical deterioration with a need for aggressive therapy (including cardiac mechanical support and heart transplantation), and death [2,5,6]. For these reasons, the ability to identify early predictors of failure to recover in women diagnosed with PPCM is of obvious importance and can help to prevent complications and improve outcome.

In this issue of *JACC: Heart Failure*, Damp et al. [8] report that higher relaxin-2 levels (>6.4 pg/ml) soon (0 to 11 days) after delivery were associated with myocardial recovery at 2 months. The authors

postulated that higher levels of relaxin-2 may result in less LV remodeling secondary to its vasodilatory effect, as well as its effect to decrease inflammation, increase angiogenesis, and decrease fibrosis. On the basis of their findings, the authors suggest a possible role for the use of relaxin-2 (serelaxin) as a therapeutic agent in women with PPCM to increase rates of recovery. These interesting findings should stimulate further research to provide additional information regarding the potential value of relaxin-2 level as a marker for early recovery and a possible role of relaxin-2 for the treatment of women with PPCM.

Extensive evaluation of the clinical characteristics of PPCM in the last decade, both retrospectively and prospectively, have identified a number of other clinical parameters associated with recovery or its failure in women with PPCM that can be useful to the clinician caring for this patient population.

BASELINE LVEF

In a retrospective evaluation of 182 women with PPCM included in the University of Southern California database, recovery of LV function (LVEF ≥50%) at 6 months after diagnosis was demonstrated in 61% of the patients [9]. Multivariate analysis identified baseline LVEF >30% as a significant predictor of recovery. Recovery was 6.4-fold higher in women with LVEF >30% (group III) and 3.9-fold higher in women with LVEF 20% to 29% (group II) compared with women with LVEF 10% to 19% (group I). A total of 63% of group I patients failed to achieve full recovery compared with 32% of group II and 21% of group III. In addition, failure to achieve LVEF ≥30% was noted in 30% of group I and 13% of group II patients. The relation between the initial myocardial insult,

represented by the level of baseline LVEF, and early recovery has been further confirmed in more recent publications. The results of a German registry, including 96 patients with PPCM diagnosed between 2004 and 2006 and followed for 6 ± 3 months, demonstrated a baseline EF of 28 ± 9% in patients who recovered and 17 ± 5% in those who did not (p = 0.0001) (7). The recently published IPAC (Investigation of Pregnancy-Associated Cardiomyopathy) study (5), which prospectively followed 100 women with PPCM in the United States, showed a complete or partial recovery in 93% of the patients. Mean EF increased from 35 ± 10% to 51 ± 11% in 6 months and 53 ± 10% in 12 months, with EF remaining <35% in 7 patients. Full recovery (EF ≥50%) was seen in 86% of women with baseline EF >30% and in only 37% in those with baseline EF <30%. This study has also confirmed previous reports of a high risk of complications that occur almost exclusively in the latter group (6,10) and the need for close monitoring of this patient population.

LV SIZE

Goland et al. (9) compared baseline left ventricular end-diastolic dimension (LVEDD) obtained by echocardiography in 97 women with PPCM. LVEDD was 61 ± 8 mm in nonrecovered patients and 55 ± 7 mm in those who recovered (p = 0.002), and LVEDD >55 mm was found in 75% versus 46%, respectively (p = 0.04). Similar findings were reported in 66 patients included in the German registry (70 ± 8 mm in 11 nonrecovered patients vs. 59 ± 7 mm in 55 recovered patients; p = 0.01) (7). This strong association between the size of the LV at time of diagnosis and failure to demonstrate early recovery suggested by the previously mentioned retrospective studies has been recently confirmed by the prospective IPAC study (5). Women with an LVEDD >60 mm (n = 25) at study entry, when compared with those with an LVEDD <60 mm (n = 74), had a lower LVEF at baseline (31 ± 10% vs. 36 ± 9%; p = 0.04) and at 6 and 12 months (40 ± 13% vs. 55 ± 7%; p < 0.001; and 42 ± 13% vs. 56 ± 7%; p < 0.001, respectively). An attempt to combine baseline EF and LVEDD provided what seems to be an even more powerful predictor of recovery. A total of 91% of 55 women who had both a baseline EF ≥30% and LVEDD <60 mm recovered to an EF >50%, whereas in 10 patients with both EF <30% and LVEDD >60 mm, none demonstrated an early recovery, and 2 died.

ETHNIC BACKGROUND

Although PPCM can affect women of various ethnic groups, the prevalence among African-American (AA)

patients in the United States has been reported to be considerably higher. An analysis of 52 AA women diagnosed in the United States compared with 104 whites demonstrated a similar LVEF at diagnosis (28 ± 10% for both) but a significantly lower rate of recovery at an average follow-up of approximately 1 year (LVEF 39 ± 17% vs. 46 ± 14%; p = 0.02; and LVEDD 57 ± 10 mm vs. 51 ± 6 mm; p = 0.004) (11). In addition, AA women had a significantly lower rate of complete recovery to LVEF ≥50% (40% vs. 61%; p = 0.02). Similar findings were obtained in the IPAC study, in which 30 AA women presented with lower EF compared with non-AA women (31 ± 9% vs. 36 ± 9%; p = 0.009), a difference that persisted at 6 months (46 ± 14% vs. 51 ± 8%; p = 0.006) and 12 months (47 ± 14% vs. 56 ± 8%; p = 0.001) (5). These data strongly suggest that AA patients with PPCM in the United States have a different clinical profile, lower rate of recovery, and worse prognosis compared with white patients.

HYPERTENSION

Kamiya et al. (4) performed a retrospective analysis of 102 Japanese patients with PPCM. A total of 42% of the patients had a history of either chronic or pregnancy-induced hypertension or pre-eclampsia. The EF at baseline was comparable between patients with and without hypertension (32 ± 10% vs. 31 ± 13%), but it was significantly higher in the patients with hypertensive disease at the end of a 7-month follow-up. Haghikia et al. (7) reported a 49% incidence of hypertensive conditions in women who demonstrated recovery compared with only 7% in those who did not (p = 0.009); these findings, however, were not confirmed by the IPAC study, which failed to find hypertension (reported in 45% of the patients) to be a predictor of recovery.

BIOMARKERS

Hu et al. (3) (2007) reported a serum concentration of cardiac troponin T (cTnT) in 106 women obtained within 2 weeks of onset of PPCM. Serum cTnT concentration was negatively correlated with LVEF at follow-up (LVEF, r = −0.518; p = 0.0001). Analysis by receiver-operator characteristic curve yielded an area under the curve of 0.764 (p = 0.0001) for cTnT, and a cTnT concentration cut off of 0.04 ng/ml predicted persistent LV dysfunction, with a sensitivity of 55% and a specificity of 91%. The 6-month LVEF was significantly lower in 33 patients with cTnT >0.04 ng/ml compared with those with cTnT <0.04 ng/ml (35% vs. 50%; p = 0.0001). In another study, Li et al. (12) analyzed levels of baseline B-type natriuretic peptide (BNP) in 71 women presenting with PPCM

with a mean group value of 1,583 ± 1,510 pg/ml. These investigators found a marked difference in BNP levels between 40 patients who recovered and 31 patients who did not. In a multivariate analysis, LVEF <34% and BNP level >1,860 pg/ml were powerful predictors of failure to recover (hazard ratios: 3.17; p = 0.007, and 2.87; p = 0.02, respectively). These results provide even further indication for the strong relationship between the level of cardiac dysfunction at diagnosis and its ability to recover.

SUMMARY

The attempts to find useful predictors for failure to recover in patients with PPCM and severe LV dysfunction who are subjected to the risk of severe and, at times, life-threatening complications has resulted in the identification of a number of clinical parameters with strong associations with cardiac recovery. The results of these studies have clearly demonstrated a strong relationship between the initial myocardial insult, as reflected by severe depression of LVEF, and enlargement of the LV as well as increased levels of serum BNP and troponin. Increased levels of relaxin-2 may be added to the list of predictors of early recovery, which may be due to a protective effect of this hormone. AA ethnicity is also associated with a lower rate of recovery and worse outcome, which may be related to a more severe degree of myocardial insult on presentation, but can also be related to genetic and environmental factors that need further investigation. The strong association between the previously mentioned parameters and likelihood of myocardial recovery in women with PPCM should be helpful in designing treatment plans for patients with PPCM and should be useful in the design of new clinical trials for evaluating emerging new and promising therapies for PPCM. At the same time, however, because of the somewhat limited sensitivity of the previously mentioned parameters in the prediction of LV recovery (or lack of it) in individual patients, these parameters should not be used as the only reason for early and *premature* utilization of aggressive and expensive therapy, such as device implantation or cardiac transplantation. More information in a larger number of patients is needed to further determine the usefulness of the combined parameters of initial LVEF <30% and LVEDD >60 mm, which may emerge as the most powerful predictor of low likelihood of recovery and high likelihood of poor outcome.

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