Angiogenic Imbalance and Residual Myocardial Injury in Recovered Peripartum Cardiomyopathy Patients

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Background—Recent studies suggest that angiogenic imbalance during pregnancy may lead to acute peripartum cardiomyopathy (PPCM). We propose that angiogenic imbalance and residual cardiac dysfunction may exist even after recovery from PPCM.

Methods and Results—Twenty-nine women at least 12 months after presentation with PPCM, who exhibited recovery of left ventricular (LV) ejection fraction (≥50%), were included in the study (mean age 35±6 years, LV ejection fraction 61.0±3.9%). The number of circulating endothelial progenitor cells (EPCs) and plasma levels of proangiogenic vascular endothelial growth factor and of soluble vascular endothelial growth factor receptor Flt1 (sFlt1) were measured. All patients underwent comprehensive cardiac function assessment, including tissue Doppler imaging and 2-dimensional (2D) strain echocardiography. All measurements were compared with healthy controls. Patients with a history of PPCM have significantly higher sFlt1 concentrations (median [25th–75th percentile]: 149.57, [63.14–177.89] versus 20.29, [15.00–53.89] pg/mL, P<0.001) and significantly decreased vascular endothelial growth factor/sFlt1 ratio (P=0.012) compared with controls, with a trend toward lower concentration of circulating CD34+/KDR+ levels. In addition, patients with PPCM had lower early velocities E′ septal (9.9±2.1 versus 11.0±1.5 cm/s, P=0.02), with a significantly lower systolic velocity S′ septal (7.6±1.2 versus 8.5±1.2 cm/s, P=0.003) by tissue Doppler imaging. Significantly lower LV global longitudinal (−19.1±3.3 versus −22.7±2.2%, P<0.001) and apical circumferential 2D strain (−16.6±4.9 versus −21.2±7.9, P=0.02) were present in patients with PPCM compared with controls.

Conclusions—Higher concentration of sFlt1 with concomitant decreased circulating endothelial progenitor cell levels along with inappropriate attenuated vascular endothelial growth factor levels may imply an angiogenic imbalance that exists even after recovery and may thus predispose to PPCM. In addition, tissue Doppler imaging and 2D strain were able to identify residual myocardial injury in post-PPCM women with apparent recovery of LV systolic function. Both angiogenic imbalance and residual myocardial injury may play an important role in the recurrence of LV dysfunction during subsequent pregnancies. (Circ Heart Fail. 2016;9:e003349. DOI: 10.1161/CIRCHEARTFAILURE.116.003349.)

Key Words: cardiomyopathy ■ circulating endothelial progenitor cells echocardiography ■ pregnancy ■ vascular endothelial growth factors ■ VEGF receptor, FLT

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease, which occurs toward the end of pregnancy or in the first postpartum months in previously healthy women.1 PPCM is characterized by the development of heart failure because of left ventricular (LV) systolic dysfunction.1–3 Recent research has suggested that PPCM is associated with vascular dysfunction, triggered by late-gestational hormonal changes. Experimental data support an important role of unbalanced oxidative stress during pregnancy that triggers the proteolytic cleavage of the nursing hormone prolactin into a vasotoxic, proapoptotic, and proinflammatory 16-kDa prolactin fragment that in turn leads to impaired endothelial function and cardiomyocyte metabolism in a STAT3 knockout mouse.4 Another antiangiogenic factor that is extensively released from the placenta during later stages of pregnancy is soluble VEGF receptor Flt1 (sFlt1), known as vascular endothelial growth factor receptor 1 (VEGF-R), which decreases the proangiogenic vascular endothelial growth factor (VEGF) and placental growth factor levels.5,6 Recently, the 2-hit hypothesis was proposed: one hit is the late-gestational hormonal changes with vasotoxic effects, including sFlt1 and prolactin, and the second hit is a predisposed inability to resist this insult in some women, probably because of some baseline altered endothelial function.7,8 In addition, a progressive increase in the number of circulating endothelial progenitor cells (EPCs) during pregnancy in healthy women has been found in most studies,9,10 but no data exist on women with PPCM.

See Clinical Perspective

Although there has been considerable progress made in our understanding of the pathogenesis and clinical course of acute PPCM, there are scarce data on status of recovered
post-PPCM population in terms of endothelial function and LV function.

Recovery of LV function (LV ejection fraction, LVEF ≥50%) is reported to occur in ≥50% of cases in the United States, with even higher rates reported by the IPAC (Investigation in Pregnancy Associated Cardiomyopathy) registry 72%. There is a single report with significantly lower rates in 40 indigent women with a recovery rate of 35% in the United States similar to those reported in South Africa and Haiti. Most of the studies suggest that improvement of LVEF occurs within 6 months of diagnosis, but delayed recovery of LV function may also occur. Although we define women with PPCM who improve their LVEF ≥50% to 55% as having achieved LV function recovery, some of them will develop relapse of the disease during subsequent pregnancies and in rare cases even spontaneous deterioration of LV function, suggesting that some patients do not reach complete LV recovery and remain with residual LV dysfunction.

In this study, we attempt to evaluate the measures of endothelial function and possible residual myocardial injury by comprehensive echocardiographic techniques in woman with apparent recovery from PPCM.

Methods

Women at least 12 months after clinical presentation with PPCM who experienced LV recovery (defined as achieving LVEF ≥50%) were included in this prospective study. The diagnosis of PPCM was defined as the development of idiopathic cardiomyopathy during pregnancy or within 5 months of delivery with LV systolic dysfunction as assessed by echocardiography with LVEF <45%. Clinical information on PPCM was collected. Blood samples were obtained for assessment of circulating EPCs (CD34+ and CD34+/KDR+) and proangiogenic VEGF and of sFlt1 from patients with PPCM. In addition, all patients underwent comprehensive echocardiography, including both LV and right ventricle (RV) function assessment, using standard echocardiography, tissue Doppler imaging (TDI), and 2-dimensional strain (2DS) techniques. Stress echocardiography to evaluate contractile reserve was done in 20 women. All laboratory and echocardiographic measures were compared with data from the control group that included healthy volunteering women who will develop relapse of the disease during subsequent pregnancies and in rare cases even spontaneous deterioration of LV function, suggesting that some patients do not reach complete LV recovery and remain with residual LV dysfunction.

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Conventional Echo and Doppler Analysis

LV dimensions and LVEF by biplane Simpson rule were measured according to the American Society of Echocardiography recommendations and the assessment by conventional and TDI. The following parameters were measured by pulse-wave Doppler: peak velocities of early (E) and late (A) diastolic filling, and deceleration time; and by TDI: early (E’) and late diastolic velocity (A’) and systolic velocity (S’). Raw data were stored digitally as DICOM cine loops and transferred for offline analysis to a workstation with the EchoPAC software (PC Dimension version 5.0.1; GE Vingmed Ultrasound, Horten, Norway). Stress echocardiography (Bruce protocol) was performed to evaluate contractile reserve, which was defined as increase in LVEF ≥5%.

Speckle-Tracking Strain Analysis

For 2D speckle tracking, the LV myocardium was imaged with a frame rate >50 Hz. Measurements of 2DS and strain rate (SR) were performed by offline semiautomated analysis. The endocardial border was semiautomatically traced, and a myocardial region of interest was then automatically identified by the software package. 2DS and SR

| Table 1. Comparison of Demographic Characteristics Between the PPCM and Controls |
|------------------------|------------------------|------------------------|
|                        | PPCM Patients          | Controls               | PValue |
| Age, y                 | 35.5±6.0               | 35.2±8.1               | 0.9    |
| Parity                 | 2.3±1.2                | 2.2±0.9                | 0.8    |
| Gravida                | 2.5±1.5                | 2.4±1.0                | 0.9    |
| Twin                   | 7 (24%)                | 4 (14%)                | 0.3    |
| Hypertension           | 6 (21%)                | 5 (17%)                | 0.7    |
| Preclampsia            | 5 (17%)                | 2 (7%)                 | 0.2    |
| Background             |                        |                        |        |
| Ethiopian              | 4 (14%)                | 2 (7%)                 | 0.4    |
| North African          | 8 (28%)                | 9 (31%)                | 1      |
| European               | 17 (59%)               | 18 (62%)               | 1      |

PPCM indicates peripartum cardiomyopathy.

were measured in the parasternal short-axis views at the papillary muscle level to determine circumferential and radial 2DS and SR and in the 3 apical views (which were then averaged) to determine longitudinal 2DS and SR. Myocardial rotation in the parasternal short-axis view was measured at the mitral valve and apical levels.

Isolation of EPCs by Fluorescence-Activated Cell Sorting and VEGF and Soluble Flt1 ELISA

Isolation of Peripheral Blood Mononuclear Cells

Human peripheral blood mononuclear cells were isolated from whole blood by ficoll gradient. peripheral blood mononuclear cells were taken for fluorescence-activated cell sorting staining, and plasma was removed and stored at −80°C for enzyme-linked immunosorbent assay (ELISA).

Determination of Circulation EPC by Fluorescence-Activated Cell Sorting

The number of circulating EPCs (CD34+ and CD34+/KDR+) was quantified by flow cytometry (fluorescence-activated cell sorting) analysis. One million cells were stained by phycoerythrin anti-CD34+ (Miltenyi Biotech) and allophycocyanin anti-VEGF receptor 2 (KDR, R&D System). The various EPC phenotypes assessed were CD34+ and CD34+/KDR+.

ELISA for VEGF and VEGF-R

Serum level of human VEGF and of sFlt1 was assessed by Quantikine ELISA kit (R&D System) according to the manufacturer’s instructions and the analysis protocol.

Statistical Methods

The mean and SDs are presented, and a 2-sided t test was performed to determine the statistical significance of differences in echocardiographic parameters between women with PPCM and controls. For comparing categorical data between the patient group and controls, Fisher exact test was used. Pearson correlation coefficient was used to compare angiogenic markers and echo measures. P value <0.05 was considered significant.

About the laboratory data analysis, after evaluation of normality by Kolmogorov–Smirnov tests, continuous variables that were not normally distributed are presented as median (25th–75th percentile) and geometric mean with 95% confidence interval. Variables with skewed distribution were transformed using a log transformation, and t test was performed to assess mean differences between PPCM and control group. Original data were also compared between the 2 groups using nonparametric Mann–Whitney U test Statistical analysis was performed using IBM SPSS version 21.0 (Armonk, NY).
Results
We evaluated 41 women (mean age 35±6 years) with post-PPCM at least 12 months after presentation. Twenty-nine (71%) of them exhibited LV function recovery (LVEF≥50%) at follow-up (mean 32 months, 12–58 months) and are included in the analysis. The control group included 29 women with mean age of 35±8 years and mean parity of 2.2±0.8. Demographic characteristics of PPCM patients and controls are presented in Table 1.

Clinical Characteristics of PPCM Patients at the Time of Diagnosis
Mean age was 29±7 years. The occurrence of symptoms before delivery was reported in 31% of women. Diagnosis was established postpartum in 77% of patients. Mean parity was 2.3±1.2 and gravidity 2.5±1.5. Hypertension during pregnancy was recorded in 17% and preeclampsia in 17% of the patients. Twin pregnancies were reported in 15%. Eighteen women delivered by caesarian section. No fetal complications were reported. The mean parity at diagnosis of PPCM was 33.2±11.1%.

Echocardiography Post-LV Recovery and Comparison With Healthy Controls
Twenty-nine patients who recovered from PPCM were included in this study. The mean age was 29±7, all of whom were asymptomatic, and the mean LVEF was 61.0±3.9%. Six women (21%) were still on a low dose of β-blocker treatment. Twenty women (69%) underwent stress echo postrecovery and showed good LV contractile reserve. No significant differences were seen between PPCM patients and controls in terms of LVEF, LV diastolic diameter, and pulmonary artery pressure (Table 2). However, patients with PPCM had lower early velocities E’ septal (9.9±2.1 versus 11.0±1.5 cm/s, P=0.02), with significantly lower systolic velocity S’ septal (7.6±1.2 versus 8.5±1.2 cm/s, P=0.003) and lower RV systolic velocity S’ (11.4±1.9 versus 12.8±2.6 cm/s, P=0.03). When analyzing 2D parameters, there was significantly lower global LV longitudinal global strain (−19.1±3.3 versus −22.7±2.2%, P<0.001) and early diastolic SR (1.35±0.32 versus1.75±0.30, 1/s, P<0.01). There were no differences in circumferential strain and SRs at papillary muscle level, however, the apical circumferential strain was significantly lower (−16.6±4.9 versus −21.2±7.9%, P=0.02; Figure 1). Lower longitudinal global strain of the RV was obtained in patients with PPCM compared with controls (−21.9±4.5 versus −24.9±3.1%, P=0.02).

Biomarkers of Endothelial Function and Comparison With Healthy Controls
VEGF and sFlt1 levels, as well as CD34+, CD34+/KDR+ numbers in PPCM and control groups, are presented in Table 3. Patients with post-PPCM have significantly higher plasma sFlt1 concentration (P<0.001) with a trend of somewhat higher levels of VEGF (P=0.1) and significantly decreased VEGF/sFlt1 ratio (P=0.01; Figures 2 through 4). There was a trend for lower numbers of circulating CD34+/KDR+ in post-PPCM women compared with controls (Figure 5). The sFlt1 levels correlated inversely with circulating CD34+/KDR+ numbers (r=−0.34, P=0.02).

In addition, we found some correlation between sFlt1 levels and apical circumferential strain (r=0.31, P=0.02), between sFlt1 and E’ by TDI (r=−0.30, P=0.02), and a trend for correlation between sFlt1/VEGF ratio and average longitudinal strain (r=0.28, P=0.08), which may suggest a potential effect of angiogenic markers on apparent LV remodeling.

Discussion
In our study, we report for the first time a higher concentration of sFlt1 with a concomitant decrease in circulating EPCs along with an inappropriate levels of VEGF in women with post-PPCM, suggesting that angiogenic imbalance may be present even after recovery from PPCM. Concomitantly, lower TDI velocities and 2D indices on echocardiography were obtained, which raises the possibility of residual myocardial injury in post-PPCM women with apparent recovery of LV systolic function.

Angiogenic Imbalance in Post-PPCM Women With LV Recovery
Oxidative stress-mediated cleavage of the nursing hormone prolactin into a smaller biologically active fragment, 16-kDa prolactin, has recently been described as a major factor potentially initiating PPCM. This 16-kDa prolactin upregulates miR-146a and exerts a toxic effect on the endothelium and on cardiomyocytes and together with a soluble sFlt1, which decreases the proangiogenic VEGF and placental growth factor levels, lead to impaired vascular and cardiac function and subsequently heart failure in late pregnancy and postpartum. The prolactin hypothesis has been developed from studies on mice. Treatment of STAT3 cardiac knockout mice with bromocriptine thus blocked prolactin production in these mice, leading to impaired cardiac function.
mice and, strikingly, completely reversed the observed PPCM. Cathepsin D as a type of substitute for measure of prolactin metabolite has been tested in women with PPCM. Haghiha et al. reported the largest series in which Cathepsin D has been measured. This recent registry from Germany found the greatest improvement occurred in patients with PPCM receiving bromocriptine on top of standard therapy. However, the percent of patients showing full recovery of LV function was similar in the 2 groups, in addition, patients with low LVEF failed to improve, suggesting that treatment with bromocriptine was not effective in sicker patients with PPCM. Therefore, it is still a matter of significant debate over the role of bromocriptine as a part of standard management of PPCM, and large-scaled controlled study has to be done to establish the efficacy of bromocriptine.

sFlt1 is capable of binding all isoforms of VEGF, inhibiting their proangiogenic function, and is particularly elevated in both PPCM and preeclampsia. To date, there are no reports on PPCM that have evaluated sFlt1 in women during pregnancy. Even in the recent prospective IPAC study of 100 patients, blood samples were drawn after the removal of the placenta postdelivery. In our study, despite a significant time elapsed since the presentation, women who had recovered from PPCM (LVEF ≥50%) exhibited a significantly higher sFlt1 serum level when compared with controls. Although sFlt1 is elaborated primarily from the placenta, it can also be produced by pericytes from multiple tissues. Increased levels of sFlt1 were recently reported in atherosclerosis, chronic kidney disease, diabetes mellitus, anti-neutrophil cytoplasmic antibody-associated vasculitis, potentially contributing to endothelial dysfunction in these patients. Similar to our results, a study on women with a history of preeclampsia reported higher sFlt1 level compared with controls.

VEGF plays a key role in EPC recruitment, enhancing mobilization and survival of EPCs, promoting vasculogenesis, and contributing to normal endothelial function. Moreover, it has been recently described that mice with PGC1-α deletion develop PPCM that is associated with an increased level of sFlt1 and insufficient upregulation of cardiac expression of VEGF blunted by sFlt1. This animal study showed lack of protection from oxidative stress and enhanced cleavage of prolactin. A partial improvement of PPCM was achieved by the addition of recombinant VEGF or bromocriptine, and a complete recovery was observed when the combination of both recombinant VEGF and bromocriptine was used. In our study, we found only a trend for higher levels of VEGF

| Table 3. Comparison Between the PPCM Patients and Controls in EPCs, VEGF, and sFlt1 |
|------------------------------------------|-------|---------|-------------|-------------|-------------|-------------|
| Group | n | GM (95% CI) | Percentile 25th | Median | Percentile 75th |
| CD34+ | PPCM | 23 | 0.56 (0.32–1.00) | 0.19 | 0.39 | 1.79 |
| Control | 23 | 0.82 (0.56–1.18) | 0.36 | 0.80 | 1.74 |
| CD34+/KDR | PPCM | 23 | 0.06 (0.04–0.10) | 0.04 | 0.06 | 0.10 |
| Control | 23 | 0.12 (0.07–0.21) | 0.04 | 0.14 | 0.34 |
| sFlt1 | PPCM | 28 | 107.45 (73.96–156.09) | 63.14 | 149.57 | 177.79 |
| Control | 29 | 26.73 (18.42–38.78) | 15.00 | 20.29 | 53.86 |
| VEGF | PPCM | 29 | 153.64 (89.82–262.83) | 48.91 | 276.64 | 440.27 |
| Control | 29 | 85.89 (52.79–139.73) | 50.27 | 116.64 | 212.09 |
| VEGF/sFlt1 | PPCM | 28 | 1.40 (0.82–2.39) | 0.77 | 1.48 | 3.43 |
| Control | 29 | 3.21 (2.13–4.84) | 1.28 | 2.63 | 8.39 |

CI indicates confidence interval; EPCs, circulating endothelial progenitor cells (CD34+ and CD34+/KDR+); GM, geometric means; sFlt1, soluble VEGF receptor Flt1; and VEGF, vascular endothelial growth factor.
but significantly higher increase in the level of sFlt yielding a decreased VEGF/sFlt1 ratio in women with post-PPCM. Similar changes have been reported in patients with pre-eclampsia, suggesting impaired endothelial function in these women.\(^{24}\)

EPCs play a critical role in adult vasculogenesis and endothelial homeostasis with an ability to repair endothelial injury. Previous studies assessing EPC number in normal pregnancy by different assays have reported contradictory results because of lack of standardized methods for EPC quantification in these studies,\(^{25}\) but most of them reported increased numbers of circulating EPCs with increasing gestational age. In contrary to normal pregnancy, a significantly lower number has been found in pregnant patients with gestational diabetes mellitus and preeclampsia.\(^{26}\) There are no previous studies looking at circulating EPCs in patients with PPCM.

We found that together with elevated sFlt1 serum levels, patients with post-PPCM showed a trend for lower numbers of circulating EPCs (CD34\(^+\)/KDR\(^+\)). Moreover, VEGF inhibitor sFlt1 levels correlated inversely with circulating EPCs numbers. To maintain and balance normal endothelial function, one would expect enhanced VEGF production; however, compared with controls, our patients with post-PPCM did not exhibit a significant increase in circulating VEGF, suggesting a potentially prominent inhibition by VEGF inhibitor sFlt1 and inappropriately low production of VEGF.

Previous studies found that endothelial dysfunction, observed in preeclampsia, can persist beyond pregnancy.\(^{27}\) In addition, the epidemiological data suggest an increased maternal risk of hypertension, coronary, and cerebrovascular disease.
in women with preeclampsia. However, to date, no study has looked at the risk of these disorders among PPCM patients.

Our finding of altered endothelial function in recovered post-PPCM women may suggest either a baseline state of endothelial dysfunction, which can lead to PPCM triggered by the oxidative stress during pregnancy or residual changes after PPCM. These changes, especially increased sPIT1, which exists even after recovery from PPCM, may potentially offer an opportunity to identify women prone to develop relapse in subsequent pregnancies and are at risk for cardiovascular events in the future.

**Residual LV Function Impairment in Post-PPCM Women With LV Recovery**

Previous studies have demonstrated LV function recovery in many women with PPCM, with the definition of complete LV recovery as achieving LVEF of $\geq 50\%$ in the vast majority of the reports. Although more than half of the women in the United States with PPCM on contemporary therapy will reach the threshold of recovery, there is still a concern of the potential risk of worsening of LV function during subsequent pregnancy. Does this mean that our definition of LV recovery using the LVEF is inappropriate? Should we use a cut-off of $\geq 55\%$ or $60\%$ for complete recovery, as has been suggested by some investigators? But even using this threshold, LV relapse has been reported. In addition, it is often difficult to distinguish between LVEF of 50% and 55% using conventional echo LVEF assessment. Therefore, the issue of complete recovery is problematic even using the so-called better indicator such as LVEF of $\geq 55\%$. Despite these limitations, there is strong evidence that the LVEF before subsequent pregnancies remains the best indicator of relapse; normalization of LVEF does not guarantee good outcome at subsequent pregnancies; and 20% of these patients still are at risk for deterioration in LV function. An attempt to look for another indicator using stress echocardiography has been made, evaluating 8 women with PPCM with recovered LV and normal contractile reserve who did not relapse during subsequent pregnancies. However, these results have not been tested in a larger cohort of patients, including patients with abnormal response to exercise.

Two recent developments in echocardiography enable a more accurate assessment of cardiac function: a relatively preload insensitive estimation of left atrial pressure using TDI in conjunction with standard Doppler$^3$ and a technique based on preload insensitive estimation of left atrial pressure using TDI compared with controls, suggesting some subtle residual changes of the RV. Altered TDI and 2DS indices suggest residual myocardial injury in recovered post-PPCM patients with the so-called complete LV function recovery.

**Conclusions**

In line with recent studies postulating that angiogenic imbalance leads to acute PPCM, the results of our study demonstrate for the first time that women recovering from PPCM may still have altered and discordant plasma concentrations of proangiogenic and antiangiogenic factors and residual cardiac impairment. More information in a larger number of patients will be required to determine the clinical importance and effect of these findings on long-term outcome and the risk of relapse during subsequent pregnancies.

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**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

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nancy or in the first postpartum months in previously healthy women. Recent research has suggested that PPCM is associated with vascular dysfunction, triggered by late-gestational hormonal changes. Although there has been great progress made in our understanding of the pathogenesis and clinical course of acute PPCM, there are scarce data on status of recovered post-PPCM population in terms of endothelial function and LV function. In our study, we evaluated biomarkers reflective of endothelial function (vascular endothelial growth factor, endothelial progenitor cells, and sFlt1) and possible residual myocardial injury by comprehensive echocardiographic techniques such as tissue Doppler and 2-dimensional strain imaging in women with apparent recovery from PPCM. In line with recent studies postulating that angiogenic imbalance leads to acute PPCM, the results of our study demonstrate for the first time that women recovering from PPCM still have altered and discordant plasma concentrations of proangiogenic and antiangiogenic factors and residual cardiac impairment. These findings may suggest an important potential effect of both angiogenic imbalance and residual myocardial injury on long-term outcome and the risk of relapse during subsequent pregnancies.
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