ORIGINAL RESEARCH

Long-Term Cardiac Function After Peripartum Cardiomyopathy and Preeclampsia: A Danish Nationwide, Clinical Follow-Up Study Using Maximal Exercise Testing and Cardiac Magnetic Resonance Imaging

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***Background*—**Long-term clinical studies of peripartum cardiomyopathy (PPCM) are few. We aimed to measure the long-term effect of PPCM on cardiac function in comparison with the long-term effects of severe preeclampsia and uncomplicated pregnancy.

***Methods and Results*—**A nationwide Danish cohort of women diagnosed with PPCM from 2005 to 2014 (PPCM group) were invited to participate in a clinical follow-up study including maximal cardiopulmonary exercise testing and cardiac magnetic resonance imaging. Matched women with previous severe preeclampsia (preeclampsia group) and previous uncomplicated pregnancies (uncomplicated pregnancies group) served as comparison groups. A total of 84 women with 28 in each group participated. Median time to follow-up after PPCM was 91 months. Most women (85%) in the PPCM group reported no symptoms of heart failure. Mean left ventricular ejection fraction in the PPCM group was normal at 62%, but significantly lower than in the preeclampsia group and the uncomplicated pregnancies group where mean left ventricular ejection fraction was 69% and 67%, respectively ($P<0.0001$). Women in the PPCM group also had impaired diastolic function with reduced left ventricular peak filling rate, left atrial passive emptying volume, and left atrial passive emptying fraction. Maximal exercise capacity (peak VO_2) was also reduced in the PPCM group compared with the preeclampsia group and the uncomplicated pregnancies group, and PPCM, high body mass index, and low left ventricular ejection fraction independently predicted reduced peak VO_2. Only 1 woman with PPCM had late gadolinium enhancement.

***Conclusions*—**Women generally recovered left ventricular ejection fraction and were asymptomatic 7 years after PPCM, but had subtle diastolic dysfunction on cardiac magnetic resonance imaging and reduced peak VO_2. Focal myocardial fibrosis assessed with late gadolinium enhancement was, however, uncommon. **(*J Am Heart Assoc*. 2018;7:e008991. DOI: 10.1161/JAHA.118.008991.)**

Key Words: diastolic function • heart failure • peripartum cardiomyopathy • preeclampsia • pregnancy

Peripartum cardiomyopathy (PPCM) is defined as idiopathic heart failure with left ventricular ejection fraction (LVEF) reduced below 45% in late pregnancy or in the first months after childbirth in women with no previous heart disease or other identifiable causes of heart failure.[1] Incidence varies greatly worldwide, most likely reflecting differences in population ethnicity, awareness of the disease, and rigor of definition.[2]

PPCM is associated with hypertensive disorders of pregnancy (HDP), including chronic hypertension, gestational hypertension, and preeclampsia.[3] Recent studies report an incidence of concomitant HDP in nearly half of PPCM cases.[4–7] This clinical association may be explained by shared pathophysiological mechanisms such as increased levels of soluble Fms-like tyrosine kinase (sFlt-1).[8,9] Higher sFlt-1 levels seem to correlate with severity of both preeclampsia[10] and PPCM,[11] and echocardiographic studies have also demonstrated subclinical cardiac dysfunction in women with preeclampsia,[12] leading to the hypothesis that preeclampsia and PPCM represent a spectrum of disease.[2,8] Some PPCM studies have reported

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Accompanying Tables S1 through S3 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008991

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Clinical Perspective

What Is New?

- In this first nationwide, long-term clinical follow-up study of women with previous peripartum cardiomyopathy, women generally recovered left ventricular ejection fraction and were clinically asymptomatic 7 years after diagnosis.
- However, they had diastolic dysfunction, reduced maximal exercise capacity, and higher body mass index compared with 2 matched groups of women with either previous preeclampsia or uncomplicated pregnancies.

What Are the Clinical Implications?

- Despite a symptomatic recovery, some degree of cardiac dysfunction might persist or relapse late after peripartum cardiomyopathy.
- Whether this is useful to predict the risk of subsequent recurrence of heart failure remains unknown and should be explored in future studies of long-term outcome.

better 6- to 12-month outcome associated with concomitant HDP,[5,6,13] but the clinical and prognostic implications of concomitant HDP are not clear: In the multicenter IPAC (Investigations in Pregnancy-Associated Cardiomyopathy) cohort, hypertension did not predict LVEF at 12-month follow-up,[4] whereas Lindley et al recently noted increased morbidity and mortality among PPCM women with concomitant preeclampsia compared with PPCM women without preeclampsia.[7] The impact of concomitant HDP on long-term outcome is unknown.

We hypothesized that women with previous PPCM and women with previous severe preeclampsia have graded degrees of cardiovascular dysfunction at long-term follow-up compared with women with uncomplicated pregnancies. We aimed to invite all women diagnosed with PPCM in Denmark from 2005 to 2014 to a clinical follow-up study in order to measure (1) systolic and diastolic cardiac function using cardiac magnetic resonance imaging (CMR) and (2) exercise capacity defined as peak oxygen consumption (peak VO_2) during maximal exercise testing, and compare the findings with 2 age-matched groups of women with either previous severe preeclampsia or previous uncomplicated pregnancies.

Methods

Study Population

Three groups of age-matched women were invited by letter to participate:

1. Women with previous PPCM (PPCM group).
2. Women with a history of severe preeclampsia without cardiac complications (PE group).
3. Women with a history of uncomplicated pregnancies (UCP group).

The PPCM group was recruited from a nationwide Danish cohort of 61 women with a validated PPCM diagnosis during 2005–2014, as previously described.[6] Women in the PE group and the UCP group were identified in an obstetric database that covers deliveries in the Capital Region of Denmark and accounts for approximately one third of all deliveries in Denmark.[14] These women either had an *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis of severe preeclampsia (O14.1) or no diagnoses that indicated complications during their past pregnancy.

For women in the PE group who agreed to participate, we reviewed charts to preclude heart failure or other cardiac complications and validate the diagnosis according to the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy.[3] Women in the UCP group verbally confirmed the database information.

The study complies with the Declaration of Helsinki, and the protocol was approved by the Danish Data Protection Agency (RH-2016-174, I-Suite 04729) and the Capital Region's Committee on Biomedical Research Ethics (H-1-2014-131). All participants provided written informed consent.

The data, analytical methods, and study materials will not be made publicly available to other researchers for purposes of reproducing the results or replicating the procedure.

Experimental Design and Procedures

All measurements were performed during 1 visit 2 to 11 years after the index delivery. In sequential order, urine and nonfasting venous blood samples were collected and height, weight, and blood pressure were measured. An ECG, exercise testing, and CMR were then performed. After exercise testing, the participating women were offered a meal and at least 2 hours of rest before CMR.

Exercise Testing

Maximal cardiopulmonary exercise test, using an upright exercise bicycle (Ergoselect; Ergoline, Windhagen, Germany), was performed. After a period of unloaded cycling, the workload, starting at 50 W, was sequentially increased by 50 W every 2 minutes at speeds of 60 to 80 revolutions per minute. During the exercise test, women were monitored with 12-lead ECG. The anaerobic threshold was defined as the time at which the respiratory exchange ratio exceeded 1 without dropping to levels below 1 during the remaining time of

exercise, and respiratory exchange ratio >1 was used as an indicator of an adequately performed test. Respiratory gas analysis was performed using the breath-by-breath technique (CS-200 Ergospiro, Schiller AG, Baar, Switzerland). At exhaustion, women rated the perceived exertion on the Borg scale,[15] maximal workload was noted, and peak oxygen consumption (peak VO_2) was calculated as mL/kg/min (Standard Pressure Temperature Dry).

Cardiac Magnetic Resonance Imaging

CMR was performed using a 1.5 Tesla magnetic resonance scanner (GE Optima MR450; GE Healthcare, Waukesha, WI). Steady-state free precession, end-tidal breath-hold images were obtained in the 2-, 3-, and 4-chamber views as well as a transaxial and a short-axis cine stack covering the whole heart with no gaps (slice thickness 8 mm, echo time 1.6 ms, field of view 320 to 370 mm, resolution matrix 256 × 256 mm, and 25 phases per cardiac cycle). Ten minutes after an intravenous bolus of gadobutrol (0.15 mmol/kg body weight, Gadovist; Bayer HealthCare AG, Leverkusen, Germany), the short- and long-axis views were repeated using a T_1-weighted inversion recovery gradient echo sequence to demonstrate late gadolinium enhancement (slice thickness 8 mm, echo time 2.9 ms, inversion time 300–375 ms, field of view 320–400 mm, and resolution matrix 256×256 mm). Inversion time was continuously adjusted to null the myocardial signal.

Offline image analysis was performed using semiautomated CMR software (cvi42; Circle Cardiovascular Imaging, Calgary, AB, Canada) for manual tracing of the epi- and endocardial borders. For segmentation of the left ventricle (LV), papillary muscles were excluded from LV mass and LV blood pool.[16] LV end-systolic volume, LV end-diastolic volume (LVEDV), LV peak filling rate (LVPFR), LV stroke volume, and LVEF were read from the LV volume-time curve.

Manual tracing of the right ventricle endocardial borders on the transaxial cine stack in end-systole and end-diastole were used for determination of right ventricular end-systolic volume, right ventricular end-diastolic volume, and right ventricular ejection fraction.

In the segmentation of the left atrium (LA), the left atrial appendage was included, the pulmonary veins were excluded,[17] and the mitral valve annulus was defined as the inferior LA border.[18] From the transaxial cine stack, the LA volume-time curve was constructed to asses LV diastolic function. This enabled determination of LA passive emptying volume (LAPEV), LA active emptying volume, LA passive emptying fraction (LAPEF), and LA active emptying fraction[19] (Figure S1).

All volumes and LV mass were indexed to body surface area according to the Mosteller method.

Focal late gadolinium enhancement (LGE) was considered as myocardial areas of high signal intensity (>5 SDs) and required confirmation in 2 orthogonal planes.[20]

LVEF estimated by echocardiography ≈12 months after diagnosis was available from chart reviews that were part of the parent cohort study,[6] where complete recovery was defined as LVEF ≥55% 12 months after the initial diagnosis. Improvement in LVEF from 12 months after diagnosis to participation was defined as ≥10% increase in LVEF. Correspondingly, deterioration was defined as ≥10% decrease in LVEF at participation.

Statistical Analyses

Data are presented as numbers and proportions for categorical data, as means and SDs for normally distributed continuous data, and as medians and ranges for non-normally distributed continuous data. Categorical data were compared between groups using chi-square test or Fisher's exact test, as appropriate. Continuous characteristics and outcome were compared between the 3 study groups using the ANOVA test in the case of normal distribution and the Kruskal–Wallis test in the case of non-normal distribution. Continuous data were compared between 2 groups (all women with PPCM included in the main cohort by participation in the follow-up study or not, and participating women in the PPCM group by concomitant HDP or not) by *t* test or Mann–Whitney U test, as appropriate. $P<0.05$ was considered statistically significant.

Some post-hoc analyses were made: First, we performed multiple comparisons of outcome variables that were significant in the global ANOVA or Kruskal–Wallis tests using chi-square test, Fisher's exact test, Student *t* test, or Mann–Whitney U test, as appropriate. To correct for multiple comparisons, the Bonferroni method was applied and level of significance in these post-hoc analyses was defined as 0.05 divided by the number of comparisons per outcome (3) as we compared the PPCM group with the PE group and the UCP group, respectively, as well as the PE group with the UCP group, and by the number of dependent outcome variables examined (20). Thus, level of significance was defined as $0.05/(3\times20)=0.0008$. Second, analysis of covariance of key outcome variables was performed in order to report differences in means between the 3 study groups, adjusted for body mass index (BMI) and age. Furthermore, a multiple linear regression analysis was performed to assess the effect of selected candidate variables of clinical importance with a likely impact on peak VO_2 among all women, who completed the exercise test. The variables chosen were: time to follow-up, BMI at follow-up, age at follow-up, current use of beta-blockers, time spent on exercise weekly, LVEF at follow-up, and, as a marker of diastolic function, LVPFR/LVEDV ratio.

We included only 1 marker of diastolic function to avoid colinearity, and we chose LVPFR/LVEDV ratio, because it is more easily obtained and clinically accessible than markers such as LAPEV and LAPEF that both require recordings and analysis of LA images.

Author A.S.E. had full access to all data and takes responsibility for its integrity and the data analysis. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the authors at the Center for Pregnancy and Heart Disease, Copenhagen University Hospital Rigshospitalet (Copenhagen, Denmark) at ajoe0026@regionh.dk or nvej0001@regionh.dk.

All statistical analyses were performed using SAS Enterprise Guide software (version 7.1; SAS Institute Inc, Cary, NC).

Results

Of 61 women in the parent PPCM cohort, 2 had died, both within a year after the diagnosis, and another was lost to follow-up because of emigration. Of the remaining 58 women, 28 agreed to participate (48%). Among eligible women with PPCM, more participating women were of white race, whereas disease severity and incidence of major adverse events did not differ significantly between participants and decliners (Table S1). A total of 94 women with previous preeclampsia were invited by letter in order to recruit 28 participants in this PE group (30%), and 129 women with a previous uncomplicated pregnancy were invited in order to recruit 28 women in this UCP group (22%). The 3 groups of participants did not differ significantly from one another in terms of age, race, smoking habits, comorbidities, self-reported exercise routines, or time from index delivery to follow-up (Table 1 and

Table 1. Distribution of Baseline Characteristics Among All Participants in the Index Pregnancy and at Study Participation

	Peripartum Cardiomyopathy, n=28	Preeclampsia, n=28	Controls, n=28	*P* Value*
Index pregnancy characteristics				
Age at delivery, y	30.7 (6.0)	30.5 (5.0)	31.0 (5.2)	0.73
Race, n (%)				
White	28 (100)	28 (100)	27 (96)	0.364
Black	0	0	1 (4)	
Body mass index, kg/m^2	28.3 (6.4)	22.8 (3.2)	21.3 (1.8)	<0.0001
Concomitant HDP, n (%)				
Gestational hypertension	2 (7)	0	0	
Preeclampsia	11 (39)	28 (100)	0	
HELLP	2 (7)	0	0	
Follow-up characteristics				
Age, y	38.0 (6.9)	39.1 (5.3)	38.8 (5.6)	0.754
Median time from index delivery to follow-up (range), mo	91 (227–137)	95 (26–143)	101 (25–146)	0.603
Engaged in exercise, n (%)	20 (71)	26 (93)	25 (89)	0.060
Median weekly exercise (range), h	2 (0–14)	5.5 (0–20)	4 (0–8)	0.031
NYHA class, n (%)				
I	24 (86)	28 (100)	28 (100)	
II	3 (11)	0	0	0.078
III	1 (3)	0	0	
Current antihypertensive/heart failure medication†, n (%)	13 (46)	3 (11)	0	<0.0001
Body mass index, kg/m^2	30.0 (8.4)	23.3 (4.1)	22.6 (3.0)	<0.001

Data are presented as means±SDs, unless otherwise stated. HDP indicates hypertensive disorders of pregnancy; HELLP, hemolysis elevated liver enzymes low platelets syndrome; NYHA, New York Heart Association.

*Global analyses of difference between means, medians, and proportions across the 3 groups were performed by ANOVA, Kruskal–Wallis, or chi-square test, respectively.

†Daily antihypertensive/heart failure medications: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium antagonists, and diuretics.

Table 2. Exercise Testing and Cardiac Magnetic Imaging Findings at Study Participation

	Peripartum Cardiomyopathy	Preeclampsia	Controls	*P* Value*
Exercise testing	n=24	n=28	n=27	
Peak VO_2, mL/kg/min	29.6 (7.2)†‡	43.2 (11.1)	45.4 (10.2)	<0.0001
Heart rate at rest, bpm	72 (17)	68 (7)	69 (10)	0.418
Heart rate at peak, bpm	168 (19)	167 (19)	176 (16)	0.185
Systolic BP at rest, mm Hg	129 (16)	129 (16)	119 (11)	0.019
Diastolic BP at rest, mm Hg	83 (14)	82 (10)	73 (9)	0.007
Systolic BP at peak, mm Hg	185 (38)	182 (30)	179 (21)	0.759
Diastolic BP at peak, mm Hg	92 (27)	94 (18)	99 (23)	0.571
Perceived exertion, Borg scale	18 (1)	18 (1)	17 (1)	0.752
Respiratory exchange ratio	1.04 (0.14)	1.03 (0.11)	1.00 (0.11)	0.496
Peak workload, W	179 (30)	208 (34)	207 (37)	0.004
Cardiac magnetic resonance imaging	n=25	n=27	n=27	
Left ventricular parameters				
Left ventricular ejection fraction, %	62 (6)†‡	69 (4)	67 (5)	<0.0001
LVEDV, mL/m^2	84 (14)	78 (10)	80 (10)	0.233
Left ventricular end-systolic volume, mL/m^2	31 (7)	25 (8)	27 (6)	0.008
Median left ventricular mass (range), g/m^2	62 (43–143)	60 (48–86)	57 (44–74)	0.205
LVPFR, mL/s per m^2	229 (49)	276 (57)	265 (45)	0.005
Left atrial volumes				
Left atrial passive emptying volume, mL/m^2	13 (5)†‡	19 (4)	20 (3)	<0.0001
Left atrial active emptying volume, mL/m^2	11 (4)	9 (2)	9 (2)	0.129
LVPFR/LVEDV ratio	2.8 (0.6)†	3.5 (0.6)	3.2 (0.6)	<0.0001
Left atrial passive emptying fraction, %	34 (10)	40 (8)	42 (8)	0.002
Left atrial active emptying fraction, %	38 (9)	35 (9)	35 (8)	0.359

Data are presented as means±SDs, unless otherwise stated. BP indicates blood pressure; LVEDV, left ventricular end-diastolic volume indexed to body surface area; LVPFR, left ventricular peak filling rate indexed to body surface area.

*Global analyses of difference between means, medians, and proportions across the 3 groups were performed by ANOVA, Kruskal–Wallis, or chi-square test, respectively. $P<0.05$ was considered statistically significant.

†PPCM group significantly different compared with the preeclampsia group. Post-hoc analyses were performed by Student *t* test, Mann–Whitney U test, or chi-square test, as appropriate. $P<0.05/(3\times20)=0.0008$ was considered statistically significant.

‡PPCM group significantly different compared with the uncomplicated control group. Post-hoc analyses were performed by Student *t* test, Mann–Whitney U test, or chi-square test, as appropriate. $P<0.05/(3\times20)=0.0008$ was considered statistically significant.

Table S2). Median time to follow-up from index delivery was 91 months for the PPCM group, 95 months for the PE group, and 101 months for the UCP-group. There were more nulliparous women, more caesarean deliveries, and earlier mean gestational age at time of delivery in the PE group, whereas fewer women in the PPCM group started breastfeeding and breastfed for a shorter period of time. Women in the PPCM group had higher BMI and reported less time spent on exercise at follow-up compared with the other 2 groups. They also used more antihypertensive/heart failure medications: 11 women (43%) were still on daily medication at study participation. No women in the PPCM group received bromocriptine therapy as previously reported.

Eight women in the PPCM group (29%) had ECG abnormalities at follow-up (Table S3). A normal ECG did not exclude the cardiac functional abnormalities described below.

Exercise Testing

Four women in the PPCM-group did not participate in exercise testing because of extreme obesity (BMI >60 kg/m^2), physical inability caused by concomitant multiple sclerosis

Table 3. Difference in Means (95% Confidence Interval) of Key Outcome Variables in the 3 Study Groups Adjusted for Body Mass Index and Age at Follow-up

	UCP Group (Reference)	PE Group	PPCM Group	*P* Value
Peak VO_2, mL/kg/min	…	−0.34 (−4.92 to 4.23)	−6.17 (−11.87 to −0.47)	0.071
Left ventricular ejection fraction, %	…	2.11 (−0.41 to 4.63)	−7.31 (−10.51 to −4.11)	<0.0001
Left ventricular peak filling rate, mL/s/m^2	…	23.83 (−3.52 to 51.18)	−14.33 (−49.03 to 20.36)	0.053
LVPFR/LVEDV ratio	…	0.31 (−0.01 to 0.62)	−0.56 (−0.95 to −0.17)	<0.0001
Left atrial passive emptying volume, mL/m^2	…	−1.13 (−3.43 to 1.18)	−4.92 (−7.82 to −2.02)	0.004
Left atrial passive emptying fraction, mL/m^2	…	−1.66 (−6.33 to 3.01)	−6.79 (−12.66 to −0.91)	0.074
Systolic blood pressure at rest, mm Hg	…	9.87 (2.48–17.3)	5.75 (−3.47 to 15.0)	0.034
Diastolic blood pressure at rest, mm Hg	…	8.36 (2.47–14.24)	7.22 (−0.12 to 14.55)	0.017

LVEDV indicates left ventricular end-diastolic volume; LVPFR, left ventricular peak filling rate; PE, preeclampsia; PPCM, peripartum cardiomyopathy; UCP, uncomplicated pregnancy.

developed after PPCM onset, white coat hypertension with in-hospital resting systolic blood pressure >200 mm Hg, and technical problems with the equipment. Also, 1 woman in the UCP group did not complete the exercise test because of technical problems. The 2 women who experienced technical problems were offered new appointments to redo the test, but were both unable to attend a new appointment within the study period. Overall, women in the PPCM group had significantly lower peak VO_2 compared with women in the PE group and the UCP group (Table 2). Mean peak VO_2 was 29.6, 43.2, and 45.4 mL/kg/min, respectively (P<0.0001). Despite an overall high perceived exertion on the Borg scale, not all women reached the anaerobic threshold. Among women who reached the anaerobic threshold, peak VO_2 was still significantly lower in the PPCM group: Mean peak VO_2 was 29.1, 43.5, and 46.0 mL/kg/min, respectively (P<0.0001). After adjusting for BMI and age, this difference was attenuated (P=0.071; Table 3). Additional adjustment for amount of time spent on exercise weekly did not change the result (analysis not shown).

Cardiac Magnetic Resonance Imaging

Three women in the PPCM group did not undergo CMR: 2 had implantable cardioverter defibrillator units incompatible with magnetic resonance imaging and 1 because of claustrophobia. Both in the PE group and in the UCP group 1 participant also could not complete the CMR protocol because of claustrophobia. The 25 women in the PPCM group, who underwent CMR, had lower mean LVEF compared with the other 2 study groups: Mean LVEF was 62% in the PPCM group, 69% in the PE group, and 67% in the UCP group (P<0.0001; Table 2).

Out of the 25 women in the PPCM group who underwent CMR, 9 (36%) had further improved their LVEF after 12 months, 16 women (64%) had a stable LVEF, and no one deteriorated. The 3 women in the PPCM group, who did not undergo CMR, all had an available echocardiographic LVEF assessment within 6 months from their study participation: The 2 women with implantable cardioverter defibrillator units both had a reduced LVEF of 45% and 20%, respectively, whereas the third woman had an LVEF of 55%.

Mean LVEF at baseline, after 12 months and at last follow-up (study CMR or echocardiography within 6 months before study enrollment), was 27±9%, 52±9%, and 60±10%, respectively (Figure).

Diastolic left ventricular function was affected in women in the PPCM group because both mean LVPFR and mean LAPEV were lower in this group. Mean LVPFR was 229 mL/s/m^2 in the PPCM group, 276 mL/s/m^2 in the PE group, and 265 mL/s/m^2 in the UCP group (P=0.005). Mean LAPEV was 13, 19, and 20 mL/m^2, respectively (P<0.0001). Also, LVPFR/LVEDV ratio was significantly lower in the PPCM group (Table 2). After adjusting for BMI and age, differences in mean systolic (LVEF) and some diastolic functional parameters (LVPFR/LVEDV ratio and LAPEV) remained significantly different between the 3 groups (Table 3).

In a multiple linear regression analysis of peak VO_2 among all 79 women who completed the maximal exercise test, BMI, PPCM, and LVEF all independently predicted peak VO_2 after adjusting for time to follow-up, age, current use of beta-blockers, amount of time spent on exercise weekly, and LVPFR/LVEDV ratio (Table 4).

Only 1 woman with PPCM (4%) and no women in the other 2 groups had LGE. The woman who had LGE had concomitant preterm preeclampsia and a baseline LVEF of 35%, improving to 45% after 7 months and 73% after 42 months. LGE pattern was multifocal with both midwall, transmural, and epicardial foci. The left ventricle was moderately dilated (LVEDV index 119 mL/m^2), and left myocardial mass was hypertrophic

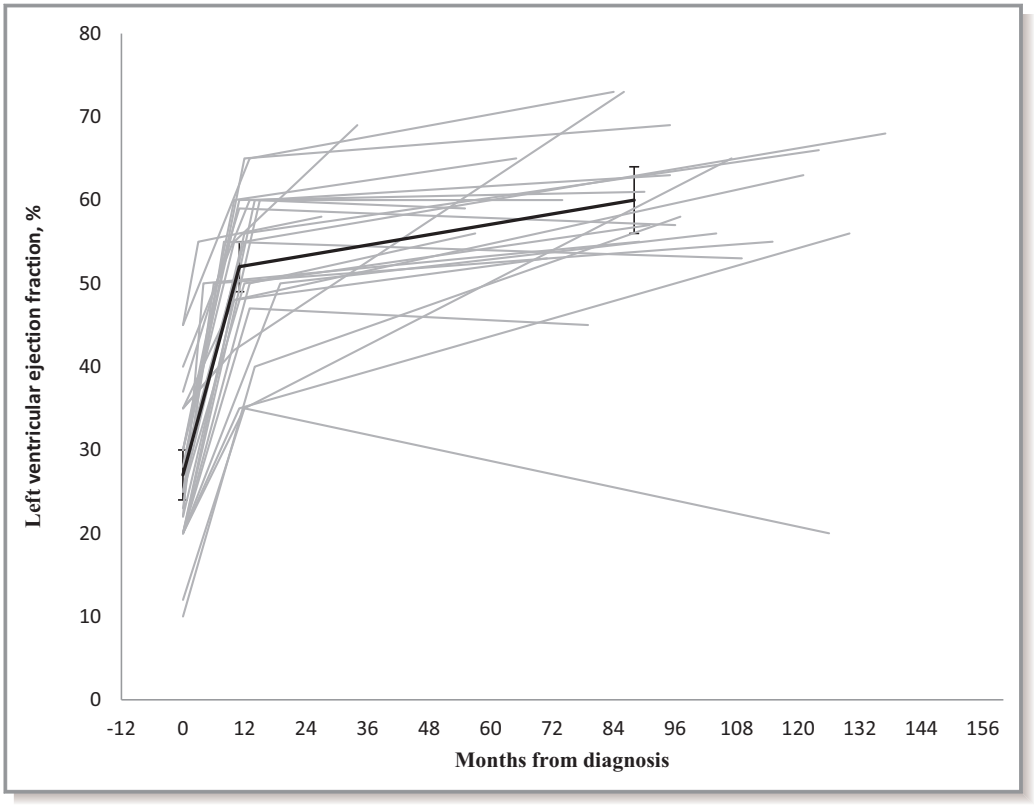

Figure. Changes in left ventricular ejection fraction. Left ventricular ejection fraction at diagnosis, at ≈12 months and at study visit among 28 women with peripartum cardiomyopathy. Mean with 95% confidence interval in bold.

(mass index of 143 g/m^2), but wall thickness was nowhere ≥15 mm, and the woman did not meet the criteria for hypertrophic cardiomyopathy. She had no family history of cardiomyopathy and no initial major adverse events in terms of need of inotropic therapy, mechanical circulatory support, or prolonged need for intensive care, but had a stroke 2 years after the PPCM diagnosis.

Right ventricular volumes and systolic function did not differ between the 3 groups (Table S3).

There were 15 participants in the PPCM group who had concomitant HDP (54%) and 13 who did not (46%). Of the 15 women with concomitant HDP, 12 had preeclampsia and 3 had gestational hypertension. Women who had concomitant HDP had significantly higher systolic and diastolic blood pressure at rest. They also had significantly higher LA active emptying fraction, and LAPEF was correspondingly lower, but this did not reach statistical significance (Table 5).

In a subanalysis, we compared peak VO_2 and diastolic and systolic functional parameters among those women diagnosed with PPCM who reported to be free from heart failure symptoms at study participation (New York Heart Association class I, n=24) with the 2 other groups. Differences in peak VO_2, LVEF, LVPFR, LAPEV, and LAPEF persisted, whereas LVEDV did not differ between the 3 groups in this analysis (not shown).

Discussion

In this Danish nationwide study of the long-term effect of PPCM on cardiac structure and function, we observed a high rate of recovery of LV systolic function with a mean LVEF of 62% and the majority of patients (85%) reporting to be free from heart failure symptoms. Women in the PPCM group, however, had evidence of left ventricular diastolic dysfunction and much lower exercise capacity compared with those in the PE group and in the UCP group. PPCM, high BMI, and low LVEF were independent predictors of reduced peak VO_2 overall. LGE was uncommon in this cohort of women with PPCM and only noted in 1 of 25.

The notion of delayed recovery beyond the early phase is in accord with other studies, showing further increased recovery rates after 12 compared with 6 months[4,13] and, in 1 study, an average time to recovery of 19 months.[21] Barasa et al recently reported on 24 Swedish women with PPCM and a mean follow-up time for echocardiography of 2.1 years, and found that the majority recovered with 54% early recovery

Table 4. Multiple Linear Regression Analysis of Predictors of Maximal Exercise Capacity (Peak VO_2) Among All Women Who Completed the Maximal Exercise Test at Study Participation (N=79)

	β-Value*	95% Confidence Interval	*P* Value
Time to follow-up, mo	0.010	−0.056 to 0.077	0.754
Age at follow-up, y	−0.330	−0.745 to 0.085	0.117
Body mass index at follow-up, kg/m^2	−1.228	−1.742 to −0.7114	<0.0001
Study group			
PPCM group	−11.269	−18.257 to −4.282	0.008
PE group	−0.999	−5.835 to 3.838	
UCP group	Reference		
Current use of beta-blockers	4.455	−3.817 to 12.728	0.286
Time spent weekly on exercise, h	0.264	−0.283 to 0.881	0.339
Left ventricular ejection fraction, %	−0.517	−1.003 to −0.032	0.037
LVPFR/LVEDV ratio	0.990	−2.926 to 4.905	0.615

LVEDV indicates left ventricular end-diastolic volume; LVPFR, left ventricular peak filling rate; PE, preeclampsia; PPCM, peripartum cardiomyopathy; UCP, uncomplicated pregnancy.
*The β-value represents the slope of the linear regression or the number of units the outcome variable (peak VO_2) change with a 1-unit change in the predictor variable.

before 100 days after diagnosis and further 21% late recovery.[22]

In a study of 71 Chinese PPCM women with a mean time to follow-up of 43±33 months, 44% had persistently left ventricular systolic dysfunction at follow-up.[23] In our study, we noted a higher recovery rate with only 2 of 28 women (7%) having LVEF <50% after a median of 91 months, but similar to Li et al, we did not observe any differences in long-term LV systolic function between women with and without concomitant HDP. In an American cohort of 39 predominantly black women with PPCM, concomitant preeclampsia was identified in 44% and was associated with higher 1-year mortality and more hospital readmissions.[7] This contrasts with the findings in our primarily white parent PPCM cohort, where all major adverse events occurred in women without HDP.[6] Despite the higher early mortality and morbidity observed by Lindley et al, they found a higher mean LVEF at 1-year follow-up in the group with concomitant preeclampsia whereas persistent diastolic dysfunction was common in both groups, similar to our findings.

In order to explain these conflicting reports on the effect of concomitant preeclampsia on PPCM, race and genetics must be taken into account. It has previously been shown that race affects outcome and severity of both preeclampsia and PPCM, with black women experiencing more-severe disease.[4,24,25] Mutations in the *TTN* gene, encoding the cardiac sarcomere protein, titin, have been found in a subgroup of 15% of women with PPCM, predominantly in black women who did not have concomitant HDP. Black women with *TTN* mutations had a lower LVEF after 12 months compared with black women without *TTN* mutations, whereas this difference was not observed among women of white descent.[25] The different impact of concomitant HDP observed in the 2 studies of primarily black and white women thus could reflect different genetic susceptibilities to, for example, sFlt-1–mediated endothelial injury.[8]

In our study, subtle diastolic dysfunction was present in the setting of LVEF recovery. Residual myocardial injury correlating modestly with sFlt-1 levels have been described previously.[26] Whether persistent diastolic dysfunction as assessed by CMR is related to sFlt-1 and other biomarkers associated with PPCM and HDP is currently unknown.

Exercise capacity was significantly reduced in women in the PPCM group, who largely reported to be free from heart failure symptoms. Also, physical activity was lower and BMI higher in the PPCM group compared with women in the PE group and in the UCP group. This may reflect exercise intolerance attributed to diastolic dysfunction, which may again precede symptomatic heart failure with preserved ejection fraction. Heart failure with preserved ejection fraction occurs more often in women and is thought to be the result of a systemic proinflammatory state with microvascular endothelial inflammation similar to that of preeclampsia.[9,27] Diastolic dysfunction expressed as reduced LAPEF has previously been noted in heart failure with preserved ejection fraction patients,[28] and diastolic dysfunction further correlates with exercise capacity.[29] This supports the hypothesis that the observed reduced exercise capacity in PPCM women could be related to the diastolic dysfunction observed.

BMI, a well-known predictor of exercise capacity, also in our study proved to be an independent predictor of exercise capacity and was significantly increased in the PPCM group, both at the beginning of the index pregnancy and at study follow-up. We were unable to match the control groups with the PPCM group on BMI, but in a recent study from Finland, previously sedentary women with a mean BMI of 26 kg/m^2 underwent exercise testing after a 9-week exercise intervention.[30] In terms of BMI, this study population may be a better comparator to our PPCM group, who reported a median of 2 hours of weekly exercise. Mean peak VO_2 was ≈38 mL/kg/min in the Finnish group, which is less than our UCP group but still 25% higher than the PPCM group.

Overweight has not traditionally been listed as a risk factor for PPCM,[1,2] but in a nationwide Swedish study, BMI was higher in women with PPCM compared with controls,[5] and mean BMI was also above the normal range (26.4 kg/m^2) in

Table 5. Characteristics and Clinical Findings in Women With Peripartum Cardiomyopathy by HDP in the Index Pregnancy

	HDP	No HDP	*P* Value
Characteristics	n=15	n=13	
LVEF at diagnosis, %	29 (7)	24 (0)	0.113
Median time from index delivery to follow-up (range), mo	90 (26–143)	104 (25–156)	0.083
Age at follow-up, y	37 (7)	39 (7)	0.470
Median weekly exercise (range), h	3 (1–14)	1 (0–10)	0.410
NYHA functional class at follow-up, n (%)			
I	13 (87)	11 (84)	
II	2 (13)	1 (8)	0.506
III	0	1 (8)	
Current antihypertensive/heart failure medication, n (%)	5 (33)	7 (54)	0.274
Body mass index at follow-up, kg/m^2	28.3 (1.2)	30.1 (1.3)	0.483
Exercise testing	n=13	n=11	
Peak VO_2, mL/kg/min	29 (7)	31 (8)	0.456
Systolic BP at rest, mm Hg	135 (16)	121 (14)	0.019
Diastolic BP at rest, mm Hg	90 (13)	74 (10)	0.0008
Cardiac magnetic resonance imaging	n=14	n=11	
LVEF, %	63 (6)	61 (6)	0.460
LVEDV, mL/m^2	82 (15)	86 (12)	0.538
Left ventricular end-systolic volume, mL/m^2	29 (6)	34 (8)	0.153
Median left ventricular mass (range), g/m^2	62 (43–143)	62 (47–75)	0.784
LVPFR, mL/min/m^2	224 (48)	236 (51)	0.535
Left passive atrial emptying volume, mL/m^2	11.8 (5)	15.6 (5)	0.083
Left atrial active emptying volume, mL/m^2	12 (4)	10 (3)	0.238
LVPFR/LVEDV ratio	2.8 (0.6)	2.8 (0.7)	0.909
Left atrial passive emptying fraction, %	32 (10)	36 (8)	0.334
Left atrial active emptying fraction, %	42 (8)	34 (9)	0.043

Data are presented as means±SDs, unless otherwise stated. BP indicates blood pressure; HDP, hypertensive disorders of pregnancy; LVEDV, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVPFR, left ventricular peak filling rate indexed to body surface area; NYHA, New York Heart Association; RER, respiratory exchange ratio.

women from the worldwide EURObservational Research Programmes's PPCM registry.[31]

Echocardiography studies have repeatedly demonstrated diastolic, and, to some extent, systolic dysfunction in preeclamptic women and this cardiac impairment may persist or relapse several years postpartum.[12,32] This is the first study to incorporate CMR in this patient group. CMR is more accurate in terms of volumetric measurements compared with echocardiography,[33] but even with CMR we were unable to detect any statistically significant differences in neither systolic nor diastolic function between the PE group and the UCP group after a mean follow-up time of 95 months.

Similar to findings in the IPAC cohort,[34] focal myocardial fibrosis assessed as LGE was rare and LVEF recovery was high in our PPCM group. This is in contrast to a German cohort of 34 PPCM women who underwent CMR at the time of diagnosis and after 5 months, where 71% had LGE.[35] In a smaller study, LGE was found in 4 of 10 women and was associated with a worse prognosis.[36] LGE is associated with a poorer prognosis in nonischemic cardiomyopathies,[37] and its absence in our study population is reassuring in order to predict prognosis. But the observed difference in LGE prevalence after PPCM is still unexplained and should be explored in future studies that may also include measurement of diffuse myocardial fibrosis, which is associated with heart failure with preserved ejection fraction.[38]

Some limitations of our study must be considered. Selection bias could have been introduced given that PPCM

nonparticipants could have been more affected by the disease. However, participants and nonparticipants did not differ significantly on baseline characteristics, including major adverse events. Nine of the 61 women in the parent cohort suffered a major adverse outcome, as previously reported.[6] All these events occurred within 12 months after diagnosis, but upon review of charts for validation of the PPCM diagnosis and additional data collection, we screened all available chart notes up to 2016 for any major adverse events and did not find any beyond 12 months. Also, no additional deaths were noted in the Causes of Death Register beyond 12 months. The study design of a nationwide population-based PPCM cohort reduces the risk of selection bias that is more significant in, for example, tertiary, single-center cohorts. Our study reports on a white cohort, and the results may potentially not be extrapolated to women of black descent. Finally, complete blinding of CMR analyses was not possible in our study setting, which may be a source of bias.

Conclusion

In this nationwide long-term follow-up of Danish PPCM patients, the majority experienced recovery of LV systolic function. However, subtle diastolic dysfunction on CMR imaging and markedly reduced peak VO_2 were common in PPCM patients and uncommon in women with previous severe preeclampsia. Improvement in LV systolic function can be expected for several years after PPCM. Focal myocardial fibrosis assessed with LGE was uncommon in this cohort.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of women with peripartum cardiomyopathy by participation in the clinical follow-up study.

	Participated in study follow-up, n=28	Did not participate in study follow-up, n=33	P value
Age at index delivery, years	30.7 (6.0)	32.4 (6.5)	0.294
Race, n (%):			
Caucasian	28 (100)	27 (82)	0.018
Other (black, Asian or Inuit)	0	6 (18)	
Body mass index at the beginning of index pregnancy, kg/m^2	28.3 (6.4)	25.3 (6.1)	0.063
Year of PPCM diagnosis, n (%):			
2005	2 (7)	5 (15)	
2006	2 (7)	3 (9)	
2007	4 (13)	2 (6)	
2008	5 (18)	5 (15)	
2009	5 (18)	3 (9)	0.741
2010	3 (11)	2 (6)	
2011	1 (4)	3 (9)	
2012	3 (11)	4 (13)	
2013	1 (4)	1 (3)	
2014	2 (7)	5 (15)	
Any diabetes, n (%)	3 (11)	3 (9)	0.832

Hypertensive disorder of pregnancy, n (%)	15 (54)	18 (55)	0.939
Timing of PPCM diagnosis, days from delivery	28 (43)	23 (46)	0.962
LVEF at diagnosis, %	26.7 (8.8)	26.7 (9.3)	0.983
Major adverse event*, n (%)	4 (14)	5 (15)	0.924
Complete recovery of LVEF after 12 months†, n (%)	19 (68)	22 (67)	0.921

Data are presented as means ± standard deviations unless otherwise stated.

PPCM, peripartum cardiomyopathy; LVEF, left ventricular ejection fraction

*Major adverse events included death, heart transplantation, mechanical circulatory assist device or persistent heart failure with LVEF < 35 % after 12 months.

†Complete recovery of LVEF after 12 months was defined as LVEF ≥ 55 %

Table S2. Distribution of additional baseline characteristics among all participants in the index pregnancy and at study participation.

	Peripartum cardiomyopathy, n=28	Preeclampsia, n=28	Controls, n=28	P value*
Index pregnancy characteristics				
Early HDP[†], n (%)	3 (20)	13 (46)	0	0.231
Any diabetes, n (%)	3 (11)	0	0	0.045
Other comorbidities[‡], n (%)	8 (29)	4 (14)	8 (29)	0.350
Parity, n (%):				
0	12 (43)	24 (86)	12 (43)	
1	11 (39)	3 (11)	10 (36)	0.007
≥ 2	5 (18)	1 (3)	4 (21)	
Twin pregnancies, n (%)	1 (4)	6 (22)	2 (7)	0.063
Median gestational age at delivery (range), days	274 (181-294)	256 (168-287)	280 (215-291)	< 0.0001
Delivery mode,				

n (%):				
Vaginal delivery	12 (43)	8 (29)	25 (89)	< 0.0001
Caesarean section	16 (57)	20 (71)	3 (11)	< 0.0001
Started breastfeeding, n (%)	17 (61)	24 (86)	28 (100)	0.0005
Median duration of any breastfeeding (range), days	60 (3-300)	158 (30-540)	300 (30-450)	< 0.0001
Follow-up characteristics				
Smoking, n (%)	5 (18)	7 (25)	6 (21)	0.685
Any comorbidities[§], n (%)	14 (50)	9 (32)	8 (29)	0.205
Subsequent child birth after index pregnancy, n (%)	3 (11)	13 (46)	12 (43)	0.008
Change in body mass index since index pregnancy, kg/m^2	1.7 (1.0)	0.5 (0.5)	1.2 (0.5)	0.471

Data are presented as means ± standard deviations unless otherwise stated.

* Global analyses of difference between means, medians and proportions across the three groups were performed by ANOVA, Kruskal-Wallis or chi-square test, respectively.

‡ Other comorbidities in the index pregnancy: asthma (n=7), thyroid diseases (n=4), migraine (n=3), multiple sclerosis (n=1), psoriasis (n=2), SLE (n=1), thrombophilia (n=1), depression (n=1).

§ Any comorbidities at follow-up: hypertension (n=7), asthma (n=6), migraine (n=5), thyroid diseases (n=2), thrombophilia (n=3), multiple sclerosis (n=2), psoriasis (n=2), paroxysmal atrial fibrillation (n=1), SLE (n=1), bipolar disorder (n=1), depression (n=1).

‖ Daily antihypertensive / heart failure medications: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium antagonists and diuretics.

Table S3. Clinical laboratory, electrocardiogram, additional exercise testing and cardiac magnetic imaging findings at study participation.

	Peripartum cardiomyopathy	Pre-eclampsia	Controls	P value*
Laboratory blood and urine tests	n=28	n=28	n=28	
Hemoglobin, mmol/L	8.7 (0.8)‡	8.3 (0.5)	8.3 (0.5)	0.022
Hemoglobin 1Ac, mmol/mol	33.9 (4.0)	34.2 (2.7)	34.2 (2.7)	0.926
Cholesterol, mmol/L	4.8 (1.3)	4.8 (0.7)	4.6 (0.8)	0.665
HDL-Cholesterol, mmol/L	1.4 (0.6)†	1.8 (0.4)	1.7 (0.5)	0.013
LDL-Cholesterol, mmol/L	3.1 (1.2)	2.8 (0.6)	2.7 (0.7)	0.204
Triglyceride, mmol/L	1.4 (0.7)†	1.0 (0.5)	1.1 (0.7)	0.009
Creatinine, µmol/L	71.6 (16.1)	69.0 (10.0)	68.7 (9.3)	0.616
Median NT-ProBNP (range), pmol/L	13.8 (5-188.0)†‡	6.8 (5-19.9)	6.9 (5-91.8)	0.015
Urine albumin /				

creatinine ratio, mg/g	11.4 (21.2)	9.9 (19.0)	6.4 (23.4)	0.593
Electrocardiogram at rest	n=28	n=28	n=28	
Any ECG abnormality	8 (29)‡	2 (7)§	0	0.003
Sinus rhythm	28 (100)	28 (100)	28 (100)	
PQ interval, ms	161 (25)	155 (19)	158 (26)	0.582
QRS interval, ms	91 (11)	89 (7)	86 (6)	0.120
Left ventricular hypertrophy	5 (18)	2 (7)	0	0.052
Strain	1 (4)	0	0	0.364
Negative T	2 (7)	0	0	0.129
Exercise testing	n=24	n=28	n=27	
Ventilatory efficiency, VE/VCO_2	23.2 (2.6)	22.9 (3.4)	23.6 (2.3)	0.631
Cardiac magnetic resonance imaging	n=25	n=27	n=27	
Left ventricular parameters				
Cardiac index, $l/min/m^2$	3.5 (0.6)	3.8 (0.5)	3.5 (0.5)	0.054
Stroke volume, ml/m^2	52 (11)	54 (7)	53 (7)	0.591

Left atrial volumes				
Left atrial minimal volume, ml/m^2	18 (9)	18 (6)	17 (6)	0.902
Left atrial maximal volume, ml/m^2	43 (14)	46 (8)	46 (7)	0.691
Left atrial mid-diastolic volume, ml/m^2	30 (14)	27 (6)	26 (7)	0.258
Left atrial conduit volume, ml/m^2	27 (8)	26 (6)	24 (4)	0.243
Right ventricular parameters				
Right ventricular ejection fraction, %	59 (7)	61 (4)	59 (4)	0.425
Right ventricular end-systolic volume, ml/m^2	33 (8)	34 (1)	36 (1)	0.296
Right ventricular end-diastolic volume, ml/m^2	82 (18)	85 (12)	88 (12)	0.359

Data are presented as means ± standard deviations unless otherwise stated.

ECG, electrocardiogram.

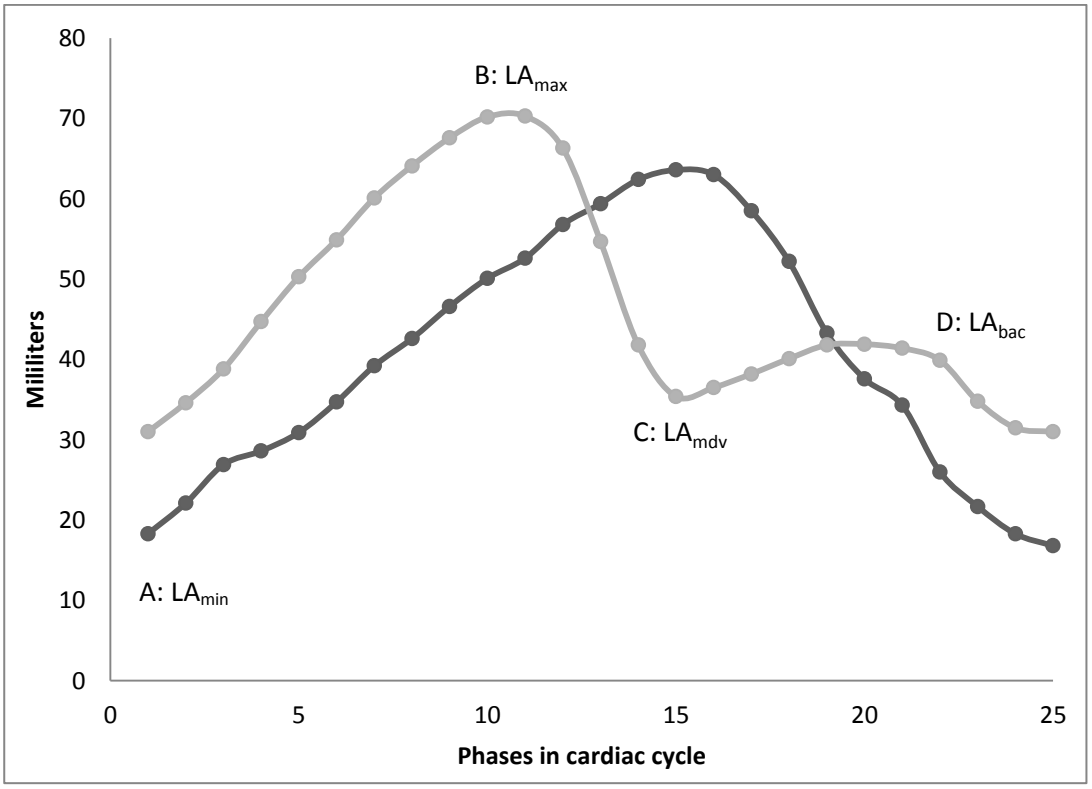
* Global analyses of difference between means, medians and proportions across the three groups were performed by ANOVA, Kruskal-Wallis or chi-square test, respectively. A p value < 0.05 was considered statistical significant.

† PPCM group significantly different compared with preeclampsia group. Post hoc analyses were performed by Student's t test, Mann-Whitney test or chi-square test as appropriate. A p value < 0.05/3 = 0.0167 was considered statistical significant.

‡ PPCM group significantly different compared with uncomplicated control group. Post hoc analyses were performed by Student's t test, Mann-Whitney test or chi-square test as appropriate. A p value < 0.05/3 = 0.0167 was considered statistical significant.

§ Preeclampsia group significantly different compared with uncomplicated control group . Post hoc analyses were performed by Student's t test, Mann-Whitney test or chi-square test as appropriate. A p value < 0.05/3 = 0.0167 was considered statistical significant.

Figure S1. Example of time-volume curves constructed from the 25 left atrial (LA) volumes during one cardiac cycle with determination of specific volumes.



A = minimal LA volume at the end of ventricular diastole (LA_{min}); B = maximal LA volume at the end of ventricular systole (LA_{max}); C = mid-diastolic LA volume after passive emptying of LA (LA_{mdv}); D = LA volume immediately before LA contraction and active emptying (LA_{bac}). The brighter curve illustrates a normal time-volume curve, and the darker curve is an example of diastolic dysfunction. LA emptying volumes that contributing to total LV filling were calculated as:

LA passive emptying volume (LAPEV) = LA_{max} - LA_{mdv} ;

LA active emptying volume (LAAEV) = LA_{bac} - LA_{min}; and

LA conduit volume = LVSV – (LAPEV + LAAEV)

LA passive emptying fraction (LAPEF) was calculated as:

$LAPEF = 100 \times (LA_{max} - LA_{bac})/LA_{max}$

LA active emptying fraction (LAAEF) was calculated as

$LAAEF = 100 \times (LA_{bac} - LA_{min})/LA_{bac}$.