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ORIGINAL ARTICLE

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Increased arterial stiffness and reduced left ventricular long-axis function in patients recovered from peripartum cardiomyopathy

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Abstract

Background: Peripartum cardiomyopathy (PPCM) is idiopathic pregnancy-associated heart failure (HF) with reduced left ventricular ejection fraction (LVEF). We aimed to assess arterial stiffness and left ventricular (LV) function in women recovered from PPCM compared with controls.

Methods: Twenty-two PPCM patients were compared with 15 age-matched controls with previous uncomplicated pregnancies. Eleven of the patients were at inclusion in the study recovered and off medication since at least 6 months and still free from cardiovascular symptoms with normal LVEF and normal NT-proBNP. All underwent echocardiography, including LV strain, left atrial (LA) reservoir strain and tissue Doppler early diastolic velocity (e´) and non-invasive assessment for arterial stiffness and central aortic systolic blood pressure (AoBP) at rest and immediately postexercise.

Results: The patients off medication showed alterations compared with controls. AoBP was higher (120 ± 9 mm Hg vs. 104 ± 13 mm Hg; $p = .001$), a difference which persisted postexercise. The arterial elastance was higher (1.9 ± 0.4 mm Hg/ml vs. 1.3 ± 0.2 mm Hg/ml; $p < .001$), while there were lower e´ septal (8.9 ± 1.7 cm/s vs. 11.0 ± 1.1 cm/s; $p = 0.002$), LV global strain (18.7 ± 3.9% vs. 23.1 ± 1.6%; $p = .004$) and LA reservoir strain (24.8 ± 9.1% vs. 37.7 ± 6.3%; $p = .002$).

Conclusions: Compared with healthy controls, PPCM patients considered recovered and off medication had increased arterial stiffness, decreased LV longitudinal function and reduced LA function.

KEYWORDS
arterial function, echocardiography, heart failure, preeclampsia, pregnancy

1 | INTRODUCTION

Peripartum cardiomyopathy (PPCM) is idiopathic, pregnancy-associated heart failure with left ventricular ejection fraction (LVEF) ≤45%, presenting towards the end of pregnancy, or in the months following delivery (Bauersachs et al., 2019). The exact causes are still unknown, but multifactorial mechanisms are likely at play where angiogenic imbalance may play an important part due to late gestational hormonal

changes, with increased oxidative stress and faulty splitting of prolactin (Goland et al., 2016).

Peripartum cardiomyopathy is potentially life-threatening and devastating for the affected patient and her family. With treatment, the majority of patients recover within twelve months (Sliwa et al., 2018), and treatment usually continues for about a year after resolution of symptoms and normalization of LVEF (Hilfiker-Kleiner et al., 2015). Left ventricular (LV) recovery in PPCM has mostly been examined with respect to LVEF, but cardiovascular abnormalities may persist even when LVEF is normalized. Reduced LV longitudinal function, reduced left atrial (LA) function and signs of impaired endothelial function have been found in recovered PPCM patients (Ersboll et al., 2018; Goland et al., 2016).

Peripartum cardiomyopathy is associated with hypertension, a condition often interlinked with increased arterial stiffness. Non-invasive devices can assess arterial stiffness with measures of pulse wave velocity (PWV), augmentation index (Aix) and central aortic systolic blood pressure (AoBP), the actual pressure the heart is exposed to. PWV increases with increasing arterial stiffness and the reflected pulse wave will arrive prematurely in the proximal aorta in mid-to late systole instead of in diastole creating increased systolic pressure and widened pulse pressure. The increased pulsatile afterload in late systole adversely affects the heart with impaired LV relaxation and LA dysfunction (Chirinos et al., 2019; Ochoa et al., 2018). In healthy persons, arterial stiffness decreases after exercise as a part of normal adaptation so alterations may be unmasked postexercise (Naka et al., 2003), and testing arterial stiffness also after exercise may shed further light on cardiovascular function. Changes in arterial stiffness thus seem to be reflected in LV longitudinal function which can be measured with tissue Doppler and LV strain and may also be reflected in LA strain. These issues are insufficiently described in patients recovering from PPCM and may be important as raised arterial stiffness predisposes to increased cardiovascular long-term risk (Chirinos et al., 2019). We therefore aimed to perform comprehensive testing of cardiovascular function in recovering PPCM patients, in order to deepen the knowledge and contribute to further understanding, beyond LVEF normalization, in recovering PPCM patients.

We assessed non-invasively arterial stiffness, AoBP, LV and LA function by echocardiography at rest and immediately postexercise. The study aimed to test the hypothesis that cardiovascular dysfunction is present also in the PPCM patients that are considered recovered and are weaned off medication, compared with healthy postpregnant women and with PPCM patients still on medication.

2 | METHODS

2.1 | Study population

The study population comprised patients with PPCM from a catchment area of 1.8 million people from five hospitals in Western Sweden. All cardiology and internal medicine departments in the region were contacted to identify women with suspected or confirmed PPCM over a 10-year period.

Consecutive patients were identified either through liaising with chief physicians from cardiology/internal medicine departments in order to identify patients with suspected PPCM, or through direct access to e-health records. International Classification of Diseases (ICD) codes and journals were reviewed to identify all hospital discharges in women of fertile age (15–54) with PPCM, HF or cardiomyopathy diagnoses codes (O90.3, I50, I42 and I43).

Inclusion criteria for the patients were as follows:

1. A PPCM diagnosis according to recommendations (Sliwa et al., 2010).
2. At least 24 weeks after initial presentation.
3. Clinically stable and outpatient.

Thirty-six patients were identified, of whom four moved out of the region, one underwent heart transplantation and one died during her first admission. Another five did not meet the PPCM criteria (Sliwa et al., 2010), and finally three declined to participate, leaving 22 included patients. According to clinical routine, patients were weaned off medication by their treating physician after symptom regression and normalization of LVEF and N-terminal prohormone brain natriuretic peptide (NT-proBNP). Eleven of the patients were at inclusion in the study off medication since at least 6 months and still free from cardiovascular symptoms with normal LVEF and normal NT-proBNP.

The presence of preeclampsia was identified as new-onset hypertension >20 weeks of gestation and proteinuria (Roberts, 2013).

Healthy age-matched controls were recruited through local advertisement. Inclusion criteria for the controls were as follows:

1. At least one complication free pregnancy and delivery.
2. Absence of any past or present cardiovascular disease.
3. Absence of any current health issue requiring medical attention, or which would interfere with data collection.

Seventeen healthy controls were examined of whom two were excluded, because of LV wall motion abnormalities and bicuspid aortic valve disease, respectively. Hence, 15 controls and 22 patients were included.

2.2 | Data collection

Examinations included clinical evaluation, echocardiography and non-invasive assessment of aortic BP and arterial stiffness, at rest and postexercise. They were carried out in room temperature within office hours. Subjects were asked to abstain from any intake of caffeinated or alcoholic beverages prior to the examination. A 12-lead electrocardiogram (ECG) and PWV assessment were done prior to blood sampling to avoid pain elicited vasoconstriction. Analyses of NT-proBNP, serum sodium, serum creatinine, haemoglobin,

high-sensitive C-reactive protein and glycated haemoglobin (HbA1c) were performed.

2.3 | Echocardiography

Images were registered using commercially available echo machines (Philips IE33, Amsterdam, The Netherlands or Vivid 7 General Electric, Fairfield, CT, USA). Measurements were performed off-line blinded to clinical data using EchoPAC (General Electric). In line with current recommendations (Lang et al., 2015), LV mass was calculated from linear measurements. LVEF was measured with biplane Simpson. Reduced LV longitudinal function, which can be measured with tissue Doppler and with two-dimensional strain, is associated with increased arterial stiffness (Weber et al., 2008). Left ventricular longitudinal tissue velocity in systole (s') and early diastolic (e') was measured at the septal and lateral border of the mitral plane, and for the right ventricle at the tricuspid annulus. Reduced e´ correlates with invasively assessed slower LV myocardial relaxation, and is a sign of reduced diastolic function. E/e'-ratio was calculated using the mean value of lateral and septal e´ and an increased value is considered a sign of increased LV filling pressure (Nagueh et al., 2016). Two-dimensional longitudinal strain was measured with Tomtec software (Unterschleissheim, Germany). LV strain was measured in apical long-axis, four-chamber and two-chamber views, and the absolute value of global longitudinal strain was registered. The LA reservoir strain (LA strain), also a measure of diastolic function, was measured with QRS as reference point in apical four-chamber view and presented as mean of two consecutive beats.

Time intervals were measured using tissue Doppler as isovolumic contraction time (ICT), isovolumic relaxation time (IRT) and ejection time (ET) at the septal mitral plane. LV myocardial performance index (MPI) was calculated as MPI = (ICT + IRT)/ET. Increased MPI is correlated with prolonged myocardial relaxation and is a sign of worsened LV diastolic function (Su et al., 2006). LV stroke volume (SV) was measured using the velocity time integral of the pulsed wave Doppler in left ventricular outflow tract and the diameter of the outflow tract.

2.4 | Stress echocardiography

Left ventricular contractility increases during exercise, and lack of cardiac reserve is a negative prognostic sign in heart failure. Semi-supine bicycle exercise stress (Sana Cardio Ergosana, Bitz, Germany) was performed with echocardiography images collected at rest, at peak stress and postexercise. The initial workload was arbitrarily set at 50 Watts with 10 Watts increments every two minutes until either—whichever occurred first—a heart rate ≥130 bpm, or cardio-respiratory exhaustion was achieved. Stress echo was analysed with corresponding baseline and stress/poststress images side by side. A visual estimate of the difference global wall motion between baseline and poststress was made, by two expert observers, separately and blinded to patient identification. Discrepancies were settled in consensus with a third observer. Contractile cardiac reserve was defined as a clearly distinguishable increase in LV global wall motion.

2.5 | Arterial stiffness

AoBP, PWV and AIx were measured at rest and postexercise with the patient recumbent, and no sleeping or talking was allowed during measurements. A non-invasive device, the Arteriograph© by Tensiomed™ version 3.0.0.4 (Budapest, Hungary), was used (Figure 1). Arteriograph only requires an upper-arm cuff and the jugular fossa-symphysis distance (an approximation of the length of the descending aorta; Figure 1). Based on sphygmomanometric measurements, it uses an algorithm to calculate AoBP, PWV and AIx. Mean values were calculated from three consecutive measurements made at rest and three postexercise. AIx was calculated as the difference between the reflected and direct systolic peak pressures, divided by the pulse pressure, mm Hg (PP); $(P_{reflected}-P_{direct})/PP \times 100$). Aortic diastolic BP was assumed to be the same as the brachial diastolic BP.

Arteriograph measurements correspond well with SphygmoCor (AtCor Medical, Itasca, IL, USA) and Complior (Alam Medical, Fallavier, France) outputs, and are strongly correlated with invasive recordings (Horvath et al., 2010; Rajzer et al., 2008; Ring et al., 2014). The time elapsed between the direct pressure wave (P_{direct}), and the reflected pressure wave ($P_{reflected}$) to reach the brachial cuff, allowed for determination of PWV (m/s), AIx aortic (%) and AIx brachial (%). $AIx_{brachial}$ was calculated directly from the pulse pressure wave at the brachial artery, whereas AIx_{aortic} was estimated from an empirically derived regression algorithm which estimates indirect central aortic pressure changes. Both AIx_{aortic} and $AIx_{brachial}$ were normalized to 80 beats per minute (bpm).

Arterial elastance, a measure of the pulsatile load on the LV, was calculated as AoBP/stroke volume.

2.6 | Statistical methods

Data are described as mean ± *SD* or median and range. Continuous data were analysed using one-way ANOVA. Bivariate correlation was analysed with Spearman's rho. Two-sided $p < .05$ was considered significant. We used the software R (R, 2019) with coin package (Bates, 2015) to perform exact permutation tests for group comparisons (Strasser & Weber, 1999).

3 | RESULTS

The clinical and biochemistry characteristics of the study population are shown in Table 1. The follow-up time from diagnosis to study

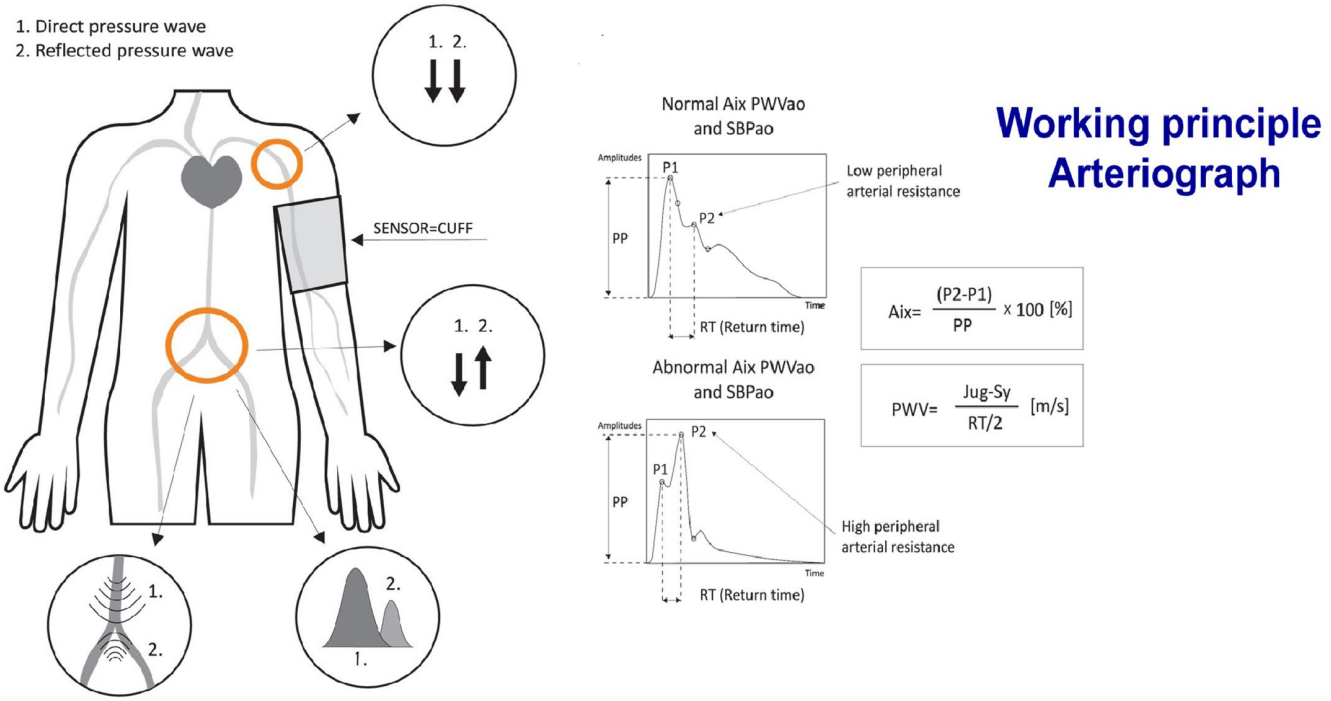

FIGURE 1 The principle of the Arteriograph©. A pressure sensor in the BP-cuff records the pressure fluctuations at 35 mm Hg above systolic pressure. Jug-Sy is the distance between jugulum and symphysis, an estimate of aortic length (Horvath et al., 2010). By courtesy of Arteriograph/Tensiomed.com (Tensiomed, 2019)

TABLE 1 Clinical and biochemistry characteristics of controls, patients off medication and patients on medication

	Controls, $n = 15$	$p^{(1)}$	Patients off medication, $n = 11$	$p^{(2)}$	Patients on medication, $n = 11$	$p^{(3)}$
Mean FU, years after diagnosis	5.3 ± 4.0[a]	>.2	4.5 ± 1.8	.002	1.8 ± 1.5	.002
Diagnosis, days after delivery			4 (0–79)	>.2	3 (0–167)	>.2
NYHA I, *n* (%)	15 (100)		11 (100)	>.2	9 (82)	.165
NYHA II, *n*(%)	0		0		2 (18)	
Maternal age, years	32.8 ± 3.7	.134	35.3 ± 3.8	>.2	32.8 ± 5.1	>.2
Preeclampsia, *n* (%)	0		8 (73)	>.2	6 (54)	.000
BMI, kg/m^2	24.0 ± 4.3	>.2	24.8 ± 3.3	.091	29.0 ± 5.4	.065
Biochemistry						
s-Na, mmol/L	138 ± 1.1	>.2	138 ± 1.5	>.2	139 ± 1.3	>.2
s-Creatinine, µmol/L	58 ± 7.1	.184	62 ± 8.4	.084	68 ± 8.1	.012
Haemoglobin, g/L	127 ± 9.1	>.2	128 ± 6.7	>.2	131 ± 8.0	>.2
NT-proBNP, ng/L	<125[b]		64 ± 40	.098	106 (23–1,060)	.098

Note: Continuous data are mean ± *SD* or median (range).

Abbreviations: BMI, body mass index; FU, follow-up; NT-proBNP, N-terminal pro-brain natriuretic peptide; serum sodium; s-Na.

p values given unless over 0.2.

$p^{(1)}$ test for equality of controls versus patients off medication.

$p^{(2)}$ test for equality for patients on versus off medication.

$p^{(3)}$ test for equality for all 3 groups: patients on medication, patients off medication and controls.

[a]Years after last delivery; †no data available—normal range given.

[b]Controls not tested; normal reference value given.

TABLE 2 Echocardiography data in controls, patients off medication and patients on medication

	Controls, $n = 15$	$p^{(1)}$	Patients off medication, $n = 11$	$p^{(2)}$	Patients on medication, $n = 11$	$p^{(3)}$
LVEF	56.1 ± 4.6	.181	53.9 ± 4.5	.102	48.1 ± 8.3	.014
LVEF < 50%, *n* (%)	0		0	.035	6 (54)	.002
LVEDVI, ml/m2	67 ± 11.8	>.2	70 ± 19.1	.488	75 ± 15.9	>.2
LVMI, g/m^2	63 ± 14	.112	72 ± 12	.3	82 ± 21	.053
LAVI, ml/m^2	28.0 ± 4.2	>.2	28.0 ± 6.3	.176	35.6 ± 19.4	>.2
E, cm/s	84 ± 10	.019	74 ± 12	.509	77 ± 13	.064
s' septal, cm/s	7.5 ± 0.6	.002	6.5 ± 0.8	.508	6.6 ± 1.4	.013
e' septal, cm/s	11.0 ± 1.1	.002	8.9 ± 1.7	.565	8.3 ± 1.9	.000
e' lateral, cm/s	13.9 ± 1.6	.002	11.3 ± 2.0	.163	13.0 ± 3.5	.027
E/e' mean	6.8 ± 1.2	>.2	7.5 ± 1.7	.918	7.3 ± 1.6	>.2
s' RV, cm/s	12.6 ± 1.2	>.2	12.3 ± 2.0	.488	13.3 ± 3.0	>.2
e' RV, cm/s	13.6 ± 2.1	.137	12.4 ± 2.5	.356	11.3 ± 1.3	.022
RV MPI %	0.35 ± 0.07	>.2	0.40 ± 0.16	.374	0.42 ± 0.11	>.2
LV ET ms	319 ± 26	.004	291 ± 26	.986	288 ± 19	.001
LV ICT, ms	60 ± 14	.109	69 ± 13	.25	79 ± 15	.013
LV IRT, ms	63 ± 12	.155	75 ± 21	.112	82 ± 18	.027
LV MPI	0.39 ± 0.05	.005	0.50 ± 0.12	.27	0.56 ± 0.07	.000
GLS %	23.1 ± 1.6	.004	18.7 ± 3.9	.314	16.4 ± 3.9	.000
LA strain %	37.7 ± 6.3	.001	24.8 ± 9.1	.024	19.8 ± 8.1	.000
Art elastance mmHg/ml	1.3 ± 0.2	.000	1.9 ± 0.4	.102	1.5 ± 0.3	.000

Note: All values are mean ± *SD* unless otherwise stated.

Abbreviations: Art, arterial; E, mitral early inflow velocity; E/e´, mean septal and lateral; e', early diastolic tissue velocity; ET, ejection time; GLS, global longitudinal strain; ICT, isovolumic contraction time; IRT, isovolumic relaxation time,, all measured with tissue Doppler; LA strain = left atrial reservoir strain; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction using Simpson biplane; LVMI, left ventricular mass index; MPI, myocardial performance index; RV, right ventricle; s', systolic tissue velocity.

p values given unless over 0.2.

$p^{(1)}$ controls versus off medication.

$p^{(2)}$ test for equality for patients on versus off medication.

$p^{(3)}$ test for equality for all 3 groups: controls, patients off medication and patients on medication.

examination was shorter in patients still on medication compared to patients off medication. The LVEF at diagnosis did not differ significantly in patients off medication compared to patients still on medication (37 ± 7% vs. 31 ± 10% $p = .09$).

3.1 | Echocardiography

Recovered patients off medication displayed several alterations compared to controls, such as lower e´, s´, LV and LA strain and increased arterial elastance (Table 2). Contractile reserve was present in 19 of the 22 patients and in all controls with no statistical significance between groups. The reproducibility of septal e´ measurements was tested in a random sample of 40% of the study population. The interobserver and intra-observer variation coefficients were 8.8% and 6.4%, respectively.

3.2 | Arterial stiffness in rest and post exercise

The recovered patients off medication had higher arterial stiffness compared to controls with higher PWV and higher central aortic systolic BP as shown in Table 3. There were correlations between AoBP and echocardiography data with the strongest correlation for e´ sept ($r = -.55$, $p < .001$), and otherwise moderate correlations ($r = .35–.40$) for e´ lat, LA strain, LV strain and LVMPI, but no correlation with E/e´.

4 | DISCUSSION

At 5 years after diagnosis, recovered PPCM patients off medication displayed altered cardiovascular function including increased arterial stiffness, higher AoBP, impaired LV longitudinal function with reduced LV

TABLE 3 Arterial stiffness data in controls, patients off medication and patients on medication

	REST					POSTEXERCISE				
	Controls, $n = 15$	p	Off medication, $n = 11$	On medication $n = 11$	p^*	Controls, $n = 15$	p	Off medication $n = 11$	On medication $n = 11$	p^*
HR, bpm	65 ±9	.168	73 ± 11	67 ± 9	.165	88 ± 11	.162	86 ± 13	77 ± 8	.054
SBP, mm Hg	111 ± 14	.007	123 ± 9	120 ± 9	.545	115 ± 16	.016	130 ± 14	127 ± 21	.455
DBP, mm Hg	69 ± 8	.006	80 ± 7	73 ± 10	.095	67 ± 8	.011	79 ± 9	74 ± 14	.191
AoBP, mm Hg	104 ± 13	.001	120 ± 9	118 ± 12	.756	100 ± 12	.001	119 ± 9	119 ± 24	.314
PWV, m/s	7.5 ± 1.4	.032	8.7 ± 1.4	9.3 ± 3.6	.641	7.5 ± 1.0	.095	8.8 ± 1.7	7.5 ± 0.5	.099
AIx aortic, %	19.6 ± 10.1	.125	29.4 ± 13.0	24.3 ± 17.0	.197	4.9 ± 4.7	.001	18.0 ± 9.6	14.2 ± 13.7	.248
AIx brachial, %	−43 (−63– 7)	.041	−31 (−41 – 32)	−31 (−61– 52)	.605	−65 (−84– −33)	.001	−40 (−70– 61)	−47 (−71 – 135)	.859
PP Ao mm Hg	35.6 ± 6.6	.004	40.4 ± 6.6	44.7 ± 6.1	.069	33.5 ± 4.9	.001	39.7 ± 6.5	45.2 ± 12.3	.349

Note: Values are mean ± *SD* or median and range (in brackets).

Abbreviations: AIx, augmentation index; AoBP, central aortic blood pressure; DBP, diastolic brachial blood pressure; HR, heart rate; PP Ao, pulse pressure central aorta; PWV, pulse wave velocity; SBP, systolic brachial blood pressure.

p is value for controls versus off medication-patients in rest/postexercise.

p^* is value for on medication-patients versus off medication-patients in rest/postexercise.

strain and reduced septal velocities in both systole and diastole, a pattern often seen in hypertensive heart disease (Solomon et al., 2010). The time sequence of contraction and relaxation within the LV was also impaired as recovered patients had increased MPI, a marker of systolic and diastolic dysfunction. Reduced long-axis function and increased MPI are both known to be negative prognostic signs (Nagueh et al., 2016). The reduced LV longitudinal function is in alignment with the study by Okada and coworkers which showed a similar pattern in patients with recovered LVEF after dilated cardiomyopathy (Okada et al., 2012). The increased systolic load, especially in late systole, due to increased PWV, may lead to fibrosis, impairs LV relaxation and reduces diastolic function and LV strain (Chirinos et al., 2019; Kim et al., 2015). A novelty in this study is the assessment of arterial stiffness both at rest and after physical exercise. PPCM is a disease thought to recover in up to 50% of patients, compared with dilated cardiomyopathy where medication is needed to avoid relapse also in asymptomatic patients with recovered EF (Haghikia et al., 2013; Halliday et al., 2019). To our knowledge, no study has examined arterial stiffness in PPCM, but series on other dilated cardiomyopathies indicated an inverse relation between arterial compliance versus LV stiffness, adverse LV remodelling and myocardial fibrosis (Puntmann et al., 2014)—a finding fully consistent with these study findings.

The prevalence of preeclampsia was high 64%, but similar to other studies with PPCM patients (Barasa et al., 2017). The conditions seem to share an anti-vascular pathobiology. A mechanism found in both PPCM and preeclampsia is endothelial dysfunction with reduced vascular endothelial growth factor (VEGF; Gennari-Moser et al., 2013; Goland et al., 2016). Hypertensive pregnancies may result in increased aortic stiffness and microvascular rarefaction persisting 5–10 years after (Boardman et al., 2020).

Patients on medication were examined earlier after diagnosis than those off medication, and maybe many of them will recover. Besides more frequently reduced LVEF, there were however no significant differences compared with the patients off medication in this small group of patients. The arterial stiffness was similar both in rest and post exercise, indicating vascular structural alterations that not are modified by foundational heart failure therapy, in line with current knowledge (Chirinos et al., 2019).

4.1 | Clinical implications

Our findings stress the need for continued long-term follow-up of women with PPCM, including assessment of diastolic function and potentially also aortic BP. The changes found in those who were clinically recovered and off medication may support the notion of a lifelong heart failure therapy as recently suggested by some members in the ESC PPCM working group (Sliwa et al., 2018).

4.2 | Strengths and limitations

This case–control study has several strengths such as novel data on arterial stiffness, LV and LA strain in women recovering from PPCM.

The patient population was small, and statistically non-significant differences may therefore be due to type II errors. For example, we found no significant differences regarding BMI, while a large registry study actually revealed prepregnancy obesity to be a risk factor for PPCM (Cho et al., 2020).

5 | CONCLUSIONS

Cardiovascular dysfunction was present in recovered PPCM patient weaned off medication, almost five years after diagnosis, compared with healthy postpregnant women. Arterial stiffness was more pronounced, AoBP was higher, and LV long-axis function and LA strain were reduced. Except for LVEF, the findings were similar in patients on medication.

This suggests long-term detrimental effects on cardiovascular compliance, despite clinical recovery, in individuals with a history of PPCM, and may indicate that prolonged pharmacological treatment is warranted, but this requires further studies.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

ETHICAL APPROVAL

The protocol was approved by the local ethical committee of the University of Gothenburg and conforms to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

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