ORIGINAL RESEARCH ARTICLE

Prognostic implication of right ventricular involvement in peripartum cardiomyopathy: a cardiovascular magnetic resonance study

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Abstract

Aims Peripartum cardiomyopathy (PPCM) is a major cause of acute heart failure in the peripartum period and considered potentially life threatening. While many aspects of its clinical profiles have been frequently reported, functional analysis, in particular of the right ventricle, and tissue characterization by cardiovascular magnetic resonance (CMR) imaging have been only sporadically described. The aim of the present study was to analyse pathological alterations and their prognostic relevance found in CMR imaging of patients newly diagnosed with PPCM.

Methods and results In this multicenter study 34 patients with confirmed PPCM underwent CMR imaging at the time of diagnosis and at 5 ± 1 months follow-up. Cine imaging of PPCM patients showed moderate to severe reduction of systolic left ventricular (LV) function (mean LVEF: $29.7 \pm 12.8\%$). In 35% of the patients right ventricular (RV) systolic function was also reduced with a mean RVEF of $42.9 \pm 13.9\%$. Dilatation of the LV was observed in 91% (mean LV-EDV/BSA 128.5 ± 32.1 mL/m^2), and dilatation of the RV was present in 24% (mean RV-EDV/BSA 87.4 ± 18.5 mL/m^2) of the patients. Focal non-ischemic late gadolinium enhancement (LGE) was visible in 71%, and regional wall motion abnormalities were evident in 88% of the patients. LGE and wall motion abnormalities were predominantly located in the anteroseptal and basal to midventricular segments. RV dysfunction at baseline was associated with reduced probability of full cardiac recovery at 5 ± 1 months follow-up.

Conclusions Besides LV systolic dysfunction, RV dysfunction and dilatation are observed in about one third of PPCM patients at the time of diagnosis. RV dysfunction is associated with unfavourable outcome. A distinct pattern of LV wall motion abnormalities and myocardial scar is evident in most PPCM patients. The present study may help to establish a set of CMR criteria suitable for diagnosis in patients with suspected PPCM and may add further knowledge to the pathology of the disease.

Introduction

Today 0.2 to 4% of all pregnancies are complicated by cardiovascular disease with increasing incidence.[1] Among them peripartum cardiomyopathy (PPCM) is a complication with high morbidity and mortality especially if untreated.[2,3] PPCM is an idiopathic heart disease with left ventricular (LV) systolic dysfunction that develops in the last month of pregnancy and the months following delivery with clinical signs of heart failure.[2,4,5] The disease is characterized by reduced LV ejection fraction (LVEF), typically below 45%. The diagnosis requires the exclusion of preexisting cardiomyopathies and other causes of heart failure.[4]

The aetiology is still unknown and risk factor profiles analysis in a more prospective way are currently performed for example in the worldwide registry on PPCM under the

EuroObservational Research Program of European society of cardiology (ESC).[6] Although the pathophysiology of PPCM is still not fully understood, advances have been achieved in understanding some underlying molecular circuits in PPCM that point to multiple causal factors. In particular, excessive oxidative stress and the subsequent cleavage of the nursing hormone prolactin into an anti-angiogenic 16 kDa subfragment have emerged as potential causal factors for PPCM.[7] Recent studies also demonstrated genetic factors contributing to increased susceptibility to PPCM in patients with positive family history for cardiomyopathies.[8]

The reported incidences of PPCM are regionally variable ranging from 1:299 live births in Haiti to about 1:1000 in South Africa and in the USA with different mortality rates.[2,9] Importantly, the clinical course also varies even between cases in one region from full recovery to partial improvement to rapid progression with end stage heart failure and even death.[10–12] The regional variance in incidence and mortality as well as the inhomogeneous morbidity within one region may reflect non-uniform etiologies, such as different genetic and environmental causes with diverse pathophysiologic components of PPCM.[10,11,13]

The diagnosis of PPCM remains challenging given the low prevalence, unspecific symptoms often difficult to be distinguished from normal pregnancy associated discomfort and the lack of clear-cut test results.[2,3] Cardiovascular magnetic resonance (CMR) has emerged as a powerful tool to analyse myocardial structure and function and is the modality of choice for the diagnosis of cardiomyopathies, in particular for non-ischemic heart diseases.[14,15] In addition, CMR imaging allows precise evaluation of the right ventricular (RV) function, which has not been precisely evaluated in PPCM so far.

In the present study we describe CMR analyses of 34 patients with newly diagnosed PPCM at the time of the acute event. The results of this study provide new insights into the cardiac phenotype of PPCM and may thereby provide valuable information to complement the clinical findings for establishing the diagnosis of PPCM.

Methods

Patients and inclusion criteria

This prospective observational multicenter study was conducted between 2010 and 2013. The study was approved by the local ethics committees, and all patients provided written informed consent to this study.

All patients underwent a diagnostic workup at acute presentation including clinical assessments, evaluation of symptoms, e.g. New York Heart Association (NYHA) functional class, electrocardiogram, echocardiographic analyses, blood tests, family history, and evaluation of diseases during pregnancy. If no contraindication was present, CMR imaging was conducted. All patients enrolled were diagnosed with PPCM according to the position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy.[4]

To analyse the prognostic value of specific CMR findings we classified the clinical outcome of the patients after a follow-up at 5 ± 1 months as either patients with or without full cardiac recovery as previously described.[11] In brief, patients were classified as improvers if they reached a LVEF of $\geq$ 55% and clinically improved to NYHA class I.

CMR imaging protocol

CMR imaging was performed as early as possible after initial stabilization using a scanner with a magnetic field strength of 1.5 T (Phlips Ingenia 1,5T, Philips Achieva 1,5T or Siemens Magnetom Avanto 1.5T at different study sites). Patients underwent a standardized CMR protocol in supine position and a dedicated eight channel cardiac coil placed around the patient's chest. Left and right ventricular mass and volumes, systolic function (ejection fraction, EF), the presence of myocardial oedema (T2-weighted imaging), and fibrosis/necrosis (focal or patchy late gadolinium enhancement, LGE) were investigated.

Myocardial tissue characterization and contractile performance were assessed by two-, three-, and four-chamber and short-axis slices (SAX). For investigation of cardiac volumes and ejection fraction, volumetric cavity assessment was obtained by whole-heart coverage of gapless SAX slices using a steady-state free precession (SSFP) sequence.

For investigation of myocardial oedema turbo inversion recovery magnitude (TIRM) was used in three contiguous SAX slices acquisitions as well as in two-, three-, and four-chamber views. LGE images were acquired approximately 15 min after intravenous administration of Gadobuterol (Gadovist®, Bayer HealthCare, Germany) at a dose of 0.15 mmol/kg body weight using a breath-hold two-dimensional phase-sensitive inversion recovery sequence (PSIR) with corresponding images in the short- and long-axis views. Lactation was stopped in all patients by treatment with bromocriptine prior to CMR scan based on our current treatment regime.[16] Thus, exposure of the newborns to gadolinium via breastfeeding could be ruled out. To optimize nulling of apparently normal myocardium, inversion times were individually adjusted.

Image analysis

Image analysis was performed offline using dedicated CMR evaluation software (cmr42, Circle CardiovascularIng, Calgary, Alberta, Canada) and evaluated by an experienced radiologist (with more than 10 year experience in CMR) and cardiologist (with more than 8 year experience in CMR) together in consensus. The Investigators were not aware of the clinical data

of the respective patient. Standard methods were used to calculate LV and RV end-diastolic and end-systolic volume, the resulting stroke volume and the ejection fraction from the cine SSFP images in the short-axis views images by manually tracing ventricular endocardial and epicardial contours in end-diastole and end-systole. The papillary muscles were excluded from the ventricular wall volume and included in the blood pool.[17] Dilatation of the left ventricle was defined as left ventricular end diastolic volume to body surface area (LV-EDV/BSA) above 90 mL/m^2 and dilatation of right ventricle defined as RV-EDV/BSA above 100 mL/m.[2,18]

The presence of myocardial oedema in TIRM-images and LGE was defined visually and only determined as positive if the enhanced signal intensity was visible in two different planes.

Echocardiographic examination

Echocardiographic examination was performed immediately after admission to hospital. The examination included parasternal long and short axis views as well as the apical four-, five-, two-, and three-chamber views with and without Doppler assessment. Global ventricular size and function and valvular function were evaluated including end-diastolic volume and diameter, end-systolic volume and diameter, left atrial size, and regurgitation severity of the mitral, aortic, and tricuspid valves. LV ejection fraction was assessed with the biplane Simpson's method. Image analysis was performed by an independent investigator of the core laboratory who was not aware of the patients' clinical data.

Statistical analysis

Database management and statistical analyses were performed using GraphPad Prism software version 5.0a and SPSS version 22. Continuous data were expressed as mean ± SD or median and range. Comparison of means and proportions between subgroups at baseline was performed by independent t test and Fisher exact test, respectively. Wilcoxon rank-sum test was used if data were not normally distributed. Multivariate logistic regression was used to analyse the predictive value of independent variables for a dichotomous outcome (cardiac recovery or no cardiac recovery). Significance was assumed at a two-sided value of $P < 0.05$.

Results

Clinical parameters, electrocardiographic findings, and laboratory test results

A total of 52 patients with PPCM matching the diagnostic criteria defined by Sliwa et al.[4] were screened for this study, of whom 18 patients were rejected either initially because of intolerance or unstable condition or they dropped out at

Table 1 Clinical parameters, electrocardiographic findings, and laboratory test results

Parameters	All patients (n = 34)	Patients with preserved RV-function (n = 22)	Patients with reduced RV-function (n = 12)	P-value PRVF vs. RRVF
Age (years) (mean ± SD)	34 ± 5	35 ± 5	32 ± 3	0.1422
Gravida median (range)	1 (1–5)	1 (1–5)	2 (1–5)	* **0.0488**
Parity median (range)	1 (1–4)	1 (1–3)	2 (1–4)	* **0.019**
BMI (mean ± SD)	27 ± 5	26 ± 5	29 ± 5	0.1720
NYHA: n, (%)				
II	9	10	8	1.0000
III	38	45	25	0.2919
IV	53	45	67	0.2966
Heart rate bpm (mean ± SD)	90 ± 17	88 ± 19	93 ± 12	0.4179
Systolic BP (mmHg) (mean ± SD)	114 ± 19	119 ± 19	104 ± 14	* **0.0307**
Diastolic BP (mmHg) (mean ± SD)	74 ± 12	76 ± 11	70 ± 13	0.1585
Left branch				
Bundle block (%)	9	8	9	1.0000
QRS-duration (ms) (mean ± SD)	94 ± 23	91 ± 22	100 ± 23	0.2942
Hb(g/dL) (mean ± SD)	11.5 ± 1.9	11.1 ± 1.9	12.1 ± 1.6	0.1260
Creatinine (μmol/L) (mean ± SD)	77 ± 15	73 ± 14	83 ± 15	0.0979
Total cholesterol (mg/dL) (mean ± SD)	218 ± 54	225 ± 55	206 ± 51	0.3938
ALT (U/L) median (range)	36 (13–432)	33 (13–296)	42 (15–432)	0.3500
AST (U/L) median (range)	34 (17–524)	36 (17–263)	32 (21–524)	0.9070
CRP (mg/L) median (range)	15 (1–76)	14 (1–53)	32 (1–76)	0.3765
hsTnT (pg/mL) median (range)	19 (1–313)	17 (1–170)	20 (11–313)	0.3396
Log NT-proBNP (pmol/mL) (mean ± SD)	8 ± 1	8 ± 1	8 ± 1	0.1595

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; Hb: haemoglobin; BP: blood pressure; CRP: C-reactive protein; hsTNT: high sensitive troponin T; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-brain natriuretic peptide; PRVF: preserved RV function; RRVF: reduced RV function.
Grade of significance was expressed as *P<0.05.

follow-up after implantation of an ICD or CRT/D in the meantime. In 34 patients CMR analyses were performed at the time of the initial diagnosis and at 5 ± 1 month follow-up. Clinical parameters, electrocardiographic findings, and laboratory test results of these patients are reported in *Table 1*. NT-proBNP was elevated in all patients and high sensitive troponin T (hsTnT) was elevated in 59% (20/34) patients (*Table 1*). Because coronary angiography and myocardial biopsy are not recommended for routine diagnosis in clinically suspected PPCM,[4,19] these procedures were only performed in patients with unclear abnormalities, e.g. pathologic ECG alterations or highly elevated cardiac serum markers (creatine kinase or troponin T). In two patients who presented normal coronary findings myocardial biopsies revealed a borderline inflammatory process without evidence of virus infection.

Myocardial tissue characterization by CMR

Focal non-ischemic (sub-epicardial or mid-wall) LGE was visible in 71% of PPCM patients. Myocardial oedema was detected in 26% of the patients (*Figure 1*). Regional wall motion abnormalities (RWMA) in terms of akinesia or hypokinesia were present in 88% of the patients (*Figure 1*). Interestingly, analysis of LGE (*Figure 2*) showed a similar pattern as observed for wall motion abnormalities (*Figure 3A*) with a predominant anteroseptal and basal to midventricular focus. This regional myocardial contractile dysfunction led to a ventricular dyssynchrony as characterized by abnormal septal motion and discoordinated LV and RV motion in these patients. However, this dyssynchrony was not based on relevant ventricular conduction disturbances as only 9% of patients (3/34) had a left branch bundle block with a wide QRS complex (*Table 1*). Twenty-four percent of the patients

demonstrated a hypertrabeculated myocardium of the dilated LV, but did not meet the diagnostic criteria for non-compaction cardiomyopathy (NCCM). For example, the segments of non-compacted myocardium in NCCM mainly involve the apex and the inferior and lateral midventricular regions of the LV, whereas in PPCM patients we observed a more global prominent trabeculation (*Figure 3B*). Also, the ratio of thickness of the hypertrabeculated (non-compacted) to compacted myocardium was not above 2.3 as described for NCCM.[20] Pleural and pericardial effusions were present in 45% and 65% of the patients, respectively. In one patient with an initial LVEF of 17%, a LV thrombus was detected in the apex.

CMR assessment of left and right ventricular function and volumes

All of the patients in this study were diagnosed with PPCM after delivery, and the CMR imaging was performed postpartum in all patients at a median of 14 days after delivery and a median of 3 days after admission with acute heart failure to hospital. Cine imaging displayed moderate to severe

Figure 2 (A) LGE was frequently detected in the anterior basal and midventricular segments (left upper short-axis view and right upper two-chamber view). Representative images of a PPCM patient with only LV heart failure (four-chamber view, left middle panel and short-axis view, right middle panel) and a patient with RV involvement (four-chamber view, left lower panel and short-axis view, right lower panel). Note the dilated RV in four-chamber and short axis view. Asterisk in left lower panel demonstrates pleural effusion in a patient with biventricular cardiac decompensation at acute presentation.
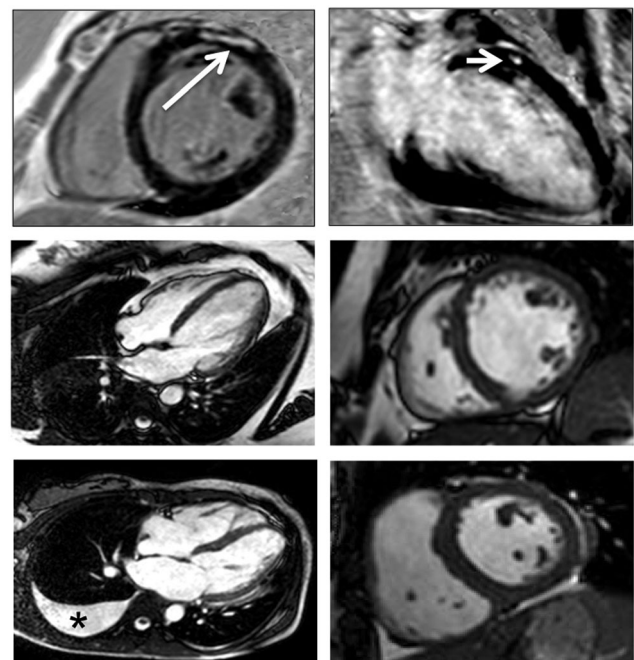

Figure 1 CMR characteristics of PPCM. Percentage of all PPCM patients with regional wall motion abnormalities (RWMA), myocardial oedema, late gadolinium enhancement (LGE), hypertrabeculation, pericardial effusion, LV thrombus, and pleural effusion.
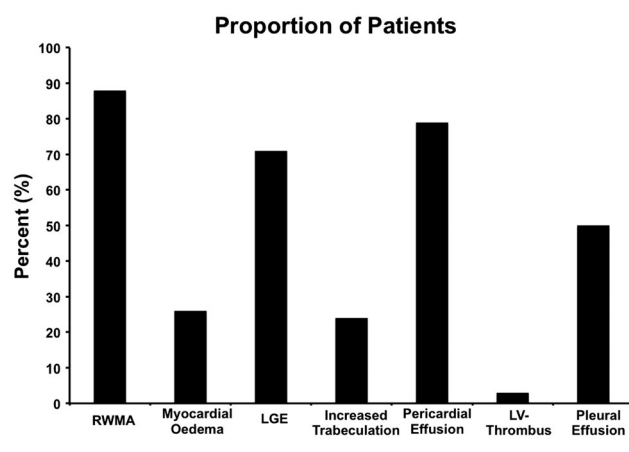
Figure 3 (A) LGE, myocardial oedema, and impaired regional myocardial contractility (akinesia, hypokinesia), in a 16-segment model of the left ventricle. The percentage of all PPCM patients is given for each myocardial segment. (B) Representative images of a PPCM patient with normal trabeculation of the left ventricle (upper panels) and with enhanced trabeculation (lower panels).
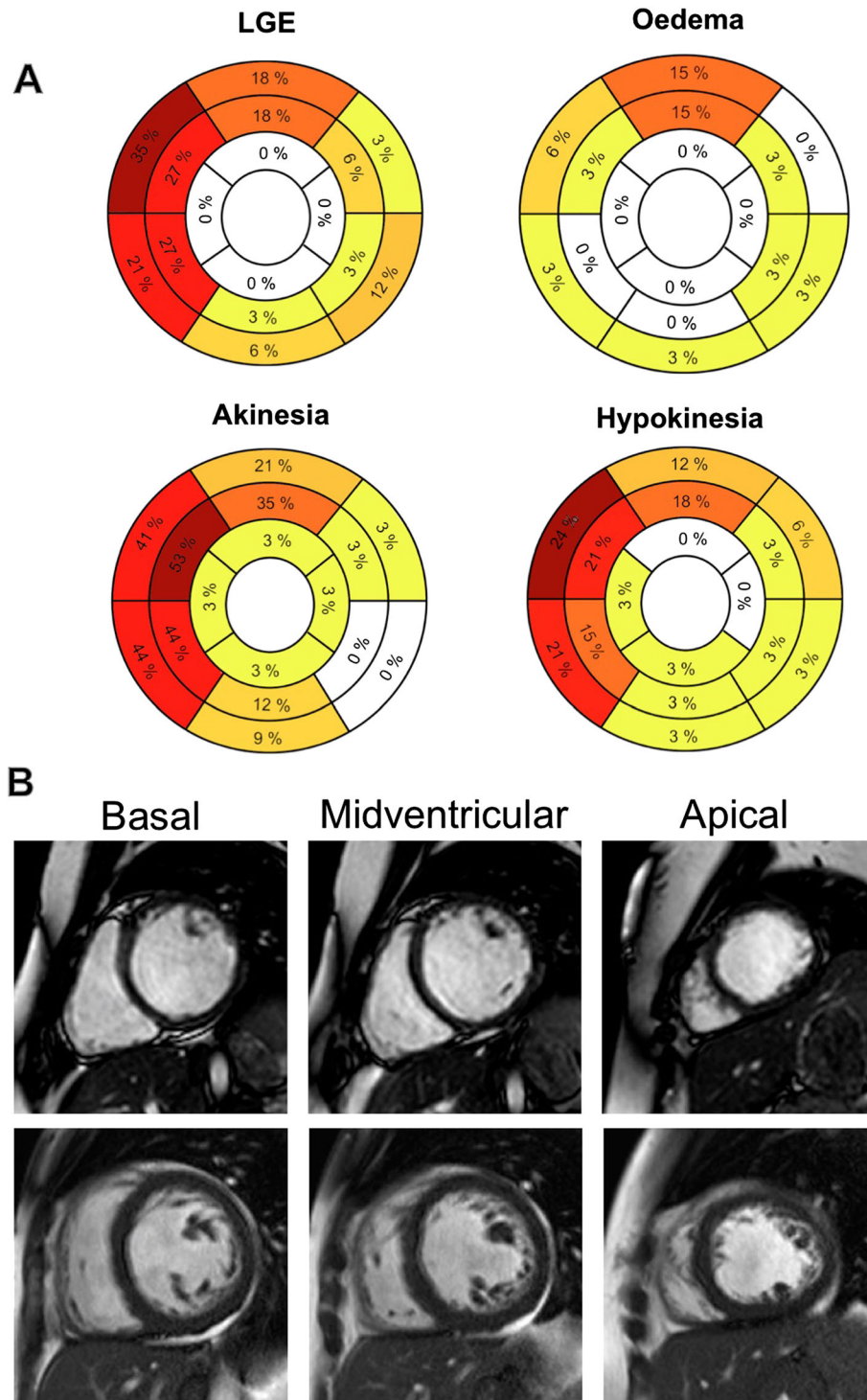
reduction of LV function in PPCM patients (mean 29.7 ± 12.8%). LVEF was less than 35% in 65% of the patients. Interestingly, 35% of the patients also showed reduction of RV systolic function with an RVEF of less than 40% at initial presentation. The mean RVEF of all patients was 42.9 ± 13.9%. Dilatation of the LV was observed in 91% of the patients

(mean LV-EDV/BSA 128.5 ± 32.1 mL/m^2). The RV was dilated in 24% with a mean RV-EDV/BSA of 87.4 ± 18.5 mL/m^2.

Outcome and predictive relevance of CMR findings

Clinical and CMR evaluation was performed after a follow-up period of 5 ± 1 months after PPCM was diagnosed. In seven patients CMR imaging was not possible because they had received an ICD or CRTD. According to the classification described above, 59% of all patients showed full cardiac recovery (16 of 27) (*Figure 4*). However, cardiac recovery was observed only in 25% of patients with initially reduced RV function (2 of 8). Moreover, 58% of patients with regional wall motion abnormality (14 of 24), 62% of patients with myocardial oedema (5 of 8), 60% of patients with late gadolinium enhancement (12 of 20), 59% of patients with pericardial effusion (13 of 22), and 57% of patients with pleural effusion (8 of 14) patients showed full cardiac recovery at follow-up (*Figure 4*).

Logistic regression analysis revealed a significant negative predictive value for only RV involvement (*P* = 0.019), whereas
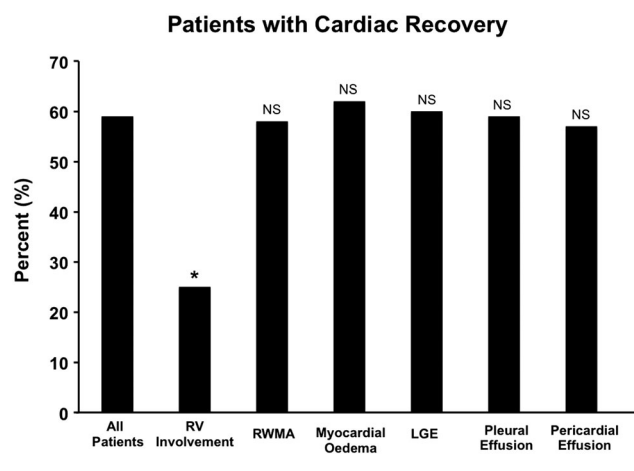
regional wall motion abnormality (*P* = 0.782), evidence of late gadolinium enhancement (*P* = 0.895), myocardial oedema (*P* = 0.824), pericardial effusion (*P* = 0.816), and pleural effusion (*P* = 0.0970) failed to show significant predictive relevance.

Clinical presentation, laboratory tests, risk factors, and co-morbidities in PPCM patients with and without right ventricular involvement

Information on clinical parameters, electrocardiography, and laboratory tests (*Table 1*) as well as assessment of risk factors and co-morbidities (*Table 2*) were compared between patients with RRVF and PRVF. Patients with RRVF revealed significantly higher gravidity and parity at the time when PPCM was diagnosed and had lower systolic blood pressure at the acute presentation indicative for more severe heart failure (*Table 1*). Evaluation of risk factors and co-morbidities, i.e. hyperlipidemia, family history of cardiovascular diseases and tobacco use, hypertension, gestation diabetes, pregnancy induced hypertension, and preeclampsia showed that none of these risk factors or conditions was distributed differently between PRVF and RRVF patients (*Table 2*).

CMR characteristics of PPCM patients with reduced vs. preserved right ventricular function

To better characterize patients with biventricular cardiac dysfunction at acute presentation we performed a dichotomous analysis of CMR findings in patients with reduced RV function (RRVF: RVEF <40%, n = 12) and patients with preserved RV function (PRVF: RVEF >40%, n = 22). A more pronounced dilatation was evident for the RV in patients with RRVF with enlargement of the RV end-diastolic volume to body surface area (RV-EDV/BSA) (RRVF: 100.6 ± 18.1 mL/m^2 vs. PRVF: 80.2 ± 14.4 mL/m^2, *P* = 0.001) and RV end-systolic volume/BSA (RRVF: 73.8 ± 18.1 mL/m^2 vs. PRVF: 39.3 ± 10.5 mL/m^2, *P* < 0.001, *Figure 5C,D*). Whereas the LV mass/BSA was not significantly different between patients with RRVF and PRVF (RRVF: 96.8 ± 16.1 g/m^2 vs. PRVF: 85.3 ± 28.8 g/m^2, *P* = 0.226, *Figure 5J*), RV mass was

Figure 4 Proportions of patients with distinct CMR findings at baseline who showed full cardiac recovery at follow-up. Note that only reduced right ventricular function at baseline had significant prognostic relevance.

Table 2 Patients' cardiovascular risk factors and complications in pregnancy

	All patients (n = 34)	Patients with PRVF (n = 22)	Patients with RRVF (n = 12)	*P*-value PRVF vs. RRVF
Hyperlipidemia (%)	12 (n = 4)	5 (n = 1)	25 (n = 3)	0.3636
Family's history of CVD (%)	21 (n = 7)	18 (n = 6)	25 (n = 3)	0.6769
Tobacco use (%)	53 (n = 18)	55 (n = 12)	50 (n = 11)	1.0000
Gestational diabetes (%)	3 (n = 1)	0	8 (n = 1)	0.3529
Hypertension (%)	26 (n = 9)	32 (n = 7)	17 (n = 2)	0.4385
Pre-eclampsia (%)	12 (n = 4)	18 (n = 4)	0	0.2728
Lung oedema (%)	15 (n = 5)	18 (n = 4)	8 (n = 1)	0.634

CVD: cardiovascular disease; PRVF: preserved RV function; RRVF: reduced RV function.

Figure 5 Bar graphs displaying differences between patients with preserved (PRVF) and reduced (RRVF) right ventricular function with regard to (A) right ventricular ejection fraction (RVEF), (B) right ventricular stroke volume to body surface area (RVSV/BSA), (C) right ventricular end-diastolic volume/BSA (RV-EDV/BSA), (D) right ventricular end-systolic volume/BSA (RV-ESV/BSA), (E) right ventricular mass/BSA (RV-Mass/BSA), (F) left ventricular ejection fraction (LVEF), (G) left ventricular stroke volume to BSA (LVSV/BSA), (H) left ventricular end-diastolic volume to BSA (LV-EDV/BSA), (I) left ventricular end-systolic volume to BSA (LV-ESV/BSA), and (J) left ventricular mass to BSA (LV-Mass/BSA). P-value compares PPCM patients with PRVF (white bar) vs. PPCM patients with RRVF (black bar), **$P < 0.01$.
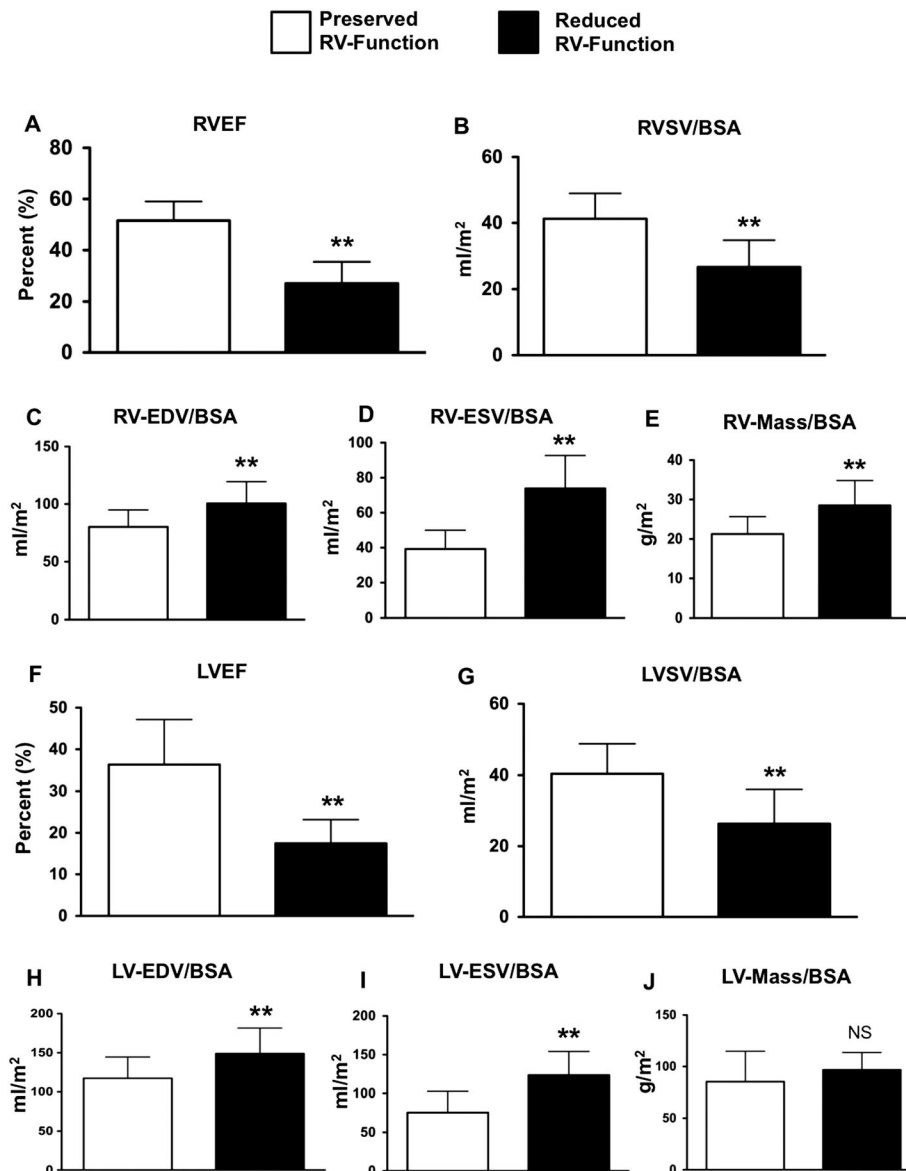
significantly increased in patients with RRVF (RRVF: 28.5 $\pm 6.1\,g/m^2$ vs. PRVF: $21.3 \pm 4.3\,g/m^2$, $P < 0.001$, *Figure 3E*). Patients with reduced RV function also had a more severe reduction of LV function (RRVF: $17.5 \pm 5.5\%$ vs. PRVF: $36.4 \pm 10.5\%$, $P < 0.001$) and LV stroke volume to body surface area (LV-SV/BSA) (RRVF: $26.3 \pm 9.3\,mL/m^2$ vs. PRVF: $40.4 \pm 8.2p\,mL/m^2$, $P < 0.001$, *Figure 5F,G*). Moreover, patients with RRVF demonstrated enhanced dilatation of the LV as

determined by LV end-diastolic volume/BSA (RRVF: 148.9 $\pm 31.3\,mL/m^2$ vs. PRVF: $117.4 \pm 26.6\,mL/m^2$, $P = 0.005$) and LV end-systolic volume/BSA (RRVF: $123.6 \pm 29.4\,mL/m^2$ vs. PRVF: $75.5.4 \pm 26.6\,mL/m^2$, $P < 0.001$, *Figure 5H,I*). Patients with RRVF and PRVF did not significantly differ with regard to the rate of RWMA, myocardial oedema, LGE, hypertrabeculation, pericardial, and pleural effusion (*Table 3*).

Table 3 CMR findings in PPCM patients with PRVF and RRVF

CMR findings	All patients (n = 34)	Patients with PRVF (n = 22)	Patients with RRVF (n = 12)	*P*-value PRVF vs. RRVF
RWMA (%)	88 (n = 30)	91 (n = 20)	83 (n = 10)	0.6015
Myocardial oedema (%)	26 (n = 9)	36 (n = 8)	8 (n = 1)	0.1135
LGE (%)	71 (n = 24)	68 (n = 15)	75 (n = 9)	1.0000
Hypertrabeculation (%)	24 (n = 8)	18 (n = 4)	33 (n = 4)	0.4097
Pericardial effusion (%)	79 (n = 27)	81 (n = 18)	75 (n = 9)	0.6769
LV-thrombus (%)	3 (n = 1)	0	8 (n = 1)	0.3529
Pleural effusion (%)	50 (n = 17)	55 (n = 12)	42 (n = 5)	0.7207

Percentage of PPCM patients with PRVF and RRVF with regard to regional wall motion abnormalities (RWMA), myocardial oedema, late gadolinium enhancement (LGE), hypertrabeculation, pericardial effusion, LV thrombus, and pleural effusion.

Comparison between patients with and without LGE

Patients who showed LGE in the LV also had significantly lower LVEF (LGE-positive vs. LGE-negative, $P = 0.035$). However, the occurrence of LGE was not associated with differences in RV function. Analysis of biomarkers for heart failure (NT-proBNP), myocardial injury (hsTnT), and inflammation (c-reactive protein, CRP) did not reveal significant differences between LGE-positive and LGE-negative patients (see Supporting Information *Figure S1*).

Comparison of echocardiographical findings in PPCM patients with and without right ventricular involvement

The more severe LV dysfunction (LVEF in RRVF: $19 \pm 7\%$ vs. PRVF: $26 \pm 9\%$, $P = 0.0309$) and LV enlargement (LVESD in RRVF: 49 ± 8 mm vs. 55 ± 6 mm, $p = 0.0327$) of patients with RV involvement were also observed in echocardiographic analyses (*Table S*1). However, no significant differences were found in left atrial size, LV wall thickness, or valve dysfunction of higher grade between patients with reduced and preserved RV function (*Table S*1).

Discussion

The present study is the first to present systematic CMR analyses in a collective of 34 patients with acute PPCM and provides several important observations: (i) A distinct pattern of regional wall motion abnormality and myocardial tissue injury with an anteroseptal basal to midventricular focus is evident in most PPCM patients; (ii) myocardial oedema and pericardial effusion suggesting (peri-)myocardial inflammation in acute PPCM; and (iii) involvement of RV in about one-third of the patients with a more severe LV dysfunction reflecting a biventricular and more severe subclass of PPCM.

To date, most studies on PPCM have been conducted with echocardiographic measurements. Although echocardiography provides profound estimation of LV size and function, its capability for assessment of RV function and evaluation of myocardial structure and injury is rather limited. Moreover, the image quality of echocardiography depends on the thoracic acoustic window and may be restricted in obesity, which is quite frequent among PPCM patients (mean body mass index of 27 in this study).

Multiparametric CMR may therefore be a more accurate imaging modality for the evaluation of patients with PPCM as it allows for precise quantification of LV and RV structure and function, the assessment of additional abnormalities (e.g. LGE, pericardial, and pleural effusion) and provides information regarding reversible (oedema) and irreversible injuries (necrosis/ fibrosis).

Focal non-ischemic (sub-epicardial or mid-wall) LGE was visible in the majority of patients and almost all patients demonstrated regional wall motion abnormalities in terms of akinesia or hypokinesia predominantly in the anteroseptal and basal to midventricular regions where also LGE and oedema were found in many cases. These observations suggest a distinct pattern of substantial myocardial injury in PPCM that appears like an 'inverted takotsubo-type cardiomyopathy' with contractile dysfunction particularly involving the basal and midventricular segments. This regional myocardial contractile dysfunction causes a global dyssynchronous LV motion, which is most likely based on primary myocardial injury rather than major impairment of ventricular conduction as most patients had a narrow QRS complex.

One of the most striking findings of this study was the reduction of RV systolic function in a considerable portion of the patients with one third of the patients presenting a RVEF less than 40% at the acute presentation. Because the RV stroke volume index was significantly reduced in patients with reduced RV function (see *Figure 5B*) we assume that the contractile function may be decreased as a primary result of the disease rather than a secondary reduction because of dilatation of the ventricle. Impairment of RV function has been previously observed in a Nigerian PPCM cohort based

on measurement of the tricuspid annular plane systolic excursion (TAPSE) by means of echocardiography.[21] Involvement of the right ventricle was observed in 54% of the Nigerian PPCM patients. A reason for the higher rate may be the more severe course of disease in Nigerian patients as compared to German or European patients. However, the diagnostic accuracy of the assessment of the RV function by echocardiography is limited and CMR imaging provides a more thorough tool to evaluate RV function as well as RV volume. In addition, our study identifies a prognostic relevance of RV impairment in PPCM in a prospective manner whereas the aforementioned study had a cross-sectional design.

Most of our patients with impaired RV function displayed also lower LV function and more pronounced enlargement of both ventricles indicative for an overall more severe cardiac pathology. Importantly, because RV dysfunction in PPCM emerged as a negative predictor for disease outcome, clinicians should focus also on RV dysfunction in PPCM patients at first diagnosis and in follow-up analyses as it might affect patient morbidity and may therefore have implications on therapy, risk stratification, and management. Whether specific pathomechanisms are responsible for RV disease involvement in PPCM require further investigation, i.e. in experimental PPCM models.

Severe RV dysfunction may also explain why implantation of a LV assist device fails to reach hemodynamic and clinical improvement in some PPCM patients. In addition, if patients present with symptoms of heart failure in the peripartum phase, attention should also be payed to the RV dimension and function as several PPCM patient report on initial peripheral oedema that had been misdiagnosed as normal pregnancy associated condition and PPCM was diagnosed in the later course of the disease.

About one fourth of the patients displayed a bilaminar ventricular myocardium with prominent trabeculation of the LV. However, the diagnostic criteria established for NCCM were not fulfilled. Interestingly, a very recent report screening over 100 primigravida women throughout the pregnancy and until two years postpartum demonstrated pregnancy induced de novo LV hypertrabeculations in about 25% of the women with 8% even fulfilling criteria for NCCM.[22] Almost all women demonstrated complete resolution or substantial reduction of trabeculation suggesting that LV hypertrabeculations occur within the physiological response to increased LV loading conditions during pregnancy. However, it remains to be evaluated whether pregnancy induced hypertrabeculation without complete resolution poses a risk for developing PPCM upon subsequent pregnancies.

The occurrence of myocardial oedema and high frequency of pericardial effusion suggests a considerable inflammatory component in acute PPCM. Indeed, myocarditis, caused by viral or bacteria infections, has long been proposed as a putative aetiology of PPCM based on histological analysis of endomyocardial biopsies.[23] However, subsequent biopsy studies found a high variability in the incidence of myocarditis in PPCM ranging between 9 and 62%.[24–27] Moreover, studies on viral infections in PPCM, as a major cause of myocarditis, showed a similar prevalence of cardiotropic virus genomes as compared to healthy postpartum women arguing against an infectious cause in PPCM.[28] Nevertheless, elevated levels of proinflammatory serum markers, such as c-reactive protein (CRP), interferon-γ and interleukin-6 have been found in PPCM[29] suggesting non-infectious inflammatory pathways of potential autoimmunological origin which are supported by investigations in experimental mouse models of PPCM.[30,31] Overall, varying CMR findings on myocardial tissue and structure add to the heterogeneity of this disease and may reflect diverse causes such as genetic or (auto-)immunologic etiologies.

In conclusion, the phenotypic profile of PPCM is considerably broader than reported so far. Multiparametric CMR imaging at the time of first presentation may provide relevant functional and tissue information that could contribute to the establishment of the diagnosis and aid to implement therapeutic strategies. In particular, patients with reduced RV function seem to have a poor prognosis in terms of cardiac recovery.

A limitation of this study is the lack of an external control group that ideally would consist of healthy early postpartum women. A longitudinal study on early postpartum women with serial CMR scans is planned to better characterize physiological alterations of the postpartum myocardium and to identify CMR patterns that are associated with increased risk of developing PPCM.

Supporting information

Supporting information may be found in the online version of this article.

Figure S1. Comparison of (A) LVEF, (B) RVEF, (C) serum levels of NT-proBNP, (D) high sensitive Troponin T (hsTnT), and (E) c-reactive protein (CRP) between patients with and without LGE in the myocardium of the LV. P-value compares PPCM patients with LGE and without LGE. $*P < 0.05$, NS = not significant.

Table S1. Echocardiograpic parameters.

Acknowledgements

(Rebirth). A.H. received a scholarship from the 'Junge Akademie' programme of Hannover Medical School.

Conflict of interest

All authors declare that they have no conflict of interest.

Author contribution

A.H., P.R., D.H.-K., and J.B. participated in research design; A.H., D.H.-K,. and J.B participated in the writing of the paper; A.H., P.R., J.S., R.W., P.E. D.B., and E.P. participated in the performance of the research; A.H., P.R., J.V-C., and D.B. participated in data analysis.

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