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Research Paper

CMR and adverse clinical outcomes in peripartum cardiomyopathy

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ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) is associated with significant morbidity and mortality. Recent studies show recovery of left ventricular ejection fraction (LVEF) can still be associated with longitudinal adverse clinical outcomes. Cardiac MRI (CMR) may yield additional prognostic parameters of serious adverse outcomes (SAE) beyond LVEF.

Methods: Individuals with PPCM and CMR within 3 months of diagnosis were analyzed from the Investigations in Pregnancy Associated Cardiomyopathy (IPAC) trial and our institution from 2010-present. Indexed left ventricular (LV) mass, ventricular volumes, cardiac output, global longitudinal strain (GLS), extracellular cellular volume (ECV) as well as epicardial fat volume (EFV) were analyzed. SAEs included left ventricular assist device (LVAD), heart transplant and death. CMR parameters were compared between SAE and no SAEs groups by non-parametric techniques.

Results: Among 51 individuals with mean age of 31 years at diagnosis, 6/51 (12 %) experienced 11 adverse outcomes. EF at time of CMR (15.0 vs 37.3 %, $p < 0.001$), peak LV GLS (−4.1 % vs −10.0, $p = 0.002$) ECV (43.6 vs 28.2, $p = 0.02$) and stroke volume differed significantly among groups. In univariate regression analysis, worse LVEF, lower peak GLS and greater LVESVi were predictive of adverse outcomes.

Conclusion: Prior studies found baseline LVEF by echo is a predictor of serious adverse outcomes. CMR identified significantly different baseline LVESVi peak LV GLS and ECV among PPCM with SAEs vs no SAEs. If confirmed in larger studies, diffuse myocardial fibrosis may represent a therapeutic target in PPCM.

1. Introduction

Peripartum cardiomyopathy (PPCM) is a serious sequela of pregnancy for which predictors of long-term morbidity and mortality are not well defined. The largest US-based multicenter registry, the Investigations in Pregnancy Associated Cardiomyopathy (IPAC), examined 100 PPCM individuals over one year postpartum. This study found baseline left ventricular ejection fraction (LVEF) was a predictor of both cardiac recovery and clinical serious adverse outcomes (SAE), defined by need for left ventricular assist device (LVAD), heart transplant, and/or death [1]. Further, obesity was also correlated with worse cardiac recovery [2]. Cardiac indices predictive of clinical SAE beyond echo measures (LVEF) are lacking and a focus of this study.

Multiparametric cardiac MRI (CMR) allows unique assessment of myocardial characteristics including diffuse interstitial cardiac fibrosis by extracellular volume (ECV). Prior studies in dilated cardiomyopathy (DCM) have shown ECV holds prognostic value for long-term outcomes [3]. This was particularly true in DCM without late gadolinium enhancement (LGE), which is characteristic of PPCM [4]. No prior studies have examined whether CMR indices, including ECV, associate with clinical adverse events in PPCM, and is a focus on this study.

2. Methods

Individuals with PPCM and CMR within 3 months of diagnosis were analyzed from Investigations in Pregnancy Associated Cardiomyopathy (IPAC) trial sites and our healthcare system (University of Pittsburgh Medical Center) from 2009 to 2023 [1]. Baseline demographic

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information was collected on all subjects at the time of diagnosis for UPMC participants or at time of enrollment to IPAC for the remaining sites. This included age, self-designated race, body mass index (BMI), history of smoking and substance use disorders. Obstetric variables were collected from index pregnancy right prior to diagnosis with PPCM including singleton or multiparous pregnancy, multifetal gestation, and delivery methods. Serious adverse events were defined as a composite of need for left ventricular assist device (LVAD), heart transplant, and/or death.

Several CMR parameters including indexed LV mass (LVMI) and volumes (LVESVi, LVEDVi) were measured using the short axis cine images. LV stroke volume and index (SV and SVi), cardiac output (CO) from short axis volume measurements and average heart rate during short axis image acquisition. Concentricity (LVM/LVEDV) was also calculated. Right ventricular size and function were qualitatively assessed. Parametric mapping, including mean T1 and T2 times, were reported for CMRs performed at UPMC ($n = 16$). Post-processing ECV, LV global longitudinal strain (GLS) and epicardial fat volume (EFV) were measured by pre-published protocols [5,6]. Mitral regurgitation, given known prognostic significance in dilated cardiomyopathies, was also qualitatively assessed. Images were processed using cvi42 (Circle Cardiovascular Imaging, Inc.; Calgary, AB, Canada).

Clinical variables and CMR indices were compared between patients who experienced SAEs and individuals without SAEs. Categorical variables were analyzed using Fisher exact tests (due to small numbers) and reported as frequencies. Non-parametric Wilcoxon rank sum (Mann Whitney) was utilized to compare continuous variables between the SAE and non-SAE comparator groups given small numbers. Univariate logistic regression analysis was performed to assess for predictors of SAEs. Due to small sample size, multivariable logistic regression analysis was not performed. All analyses were done in Stata 18 (Stata Statistical Software: Release 18. College Station, TX: StataCorp LP).

3. Results

3.1. Baseline demographics

51 PPCM individuals were identified with CMR within 3 months of diagnosis, 35 from IPAC study sites and 16 from our center. There were no significant differences in median age, self-identified race, BMI, prevalence of hypertension (composite of chronic hypertension and/or hypertensive disorders of pregnancy) or obesity (BMI > 30) comparing subgroups with and without SAEs. **(**Table 1**).**

Table 1
Baseline demographics comparing individuals with and without serious adverse outcomes. Clinical variables, including obstetrics variables, were collected at time of diagnosis of PPCM (UPMC) or enrollment in IPAC. Categorical variables are presented as n(%).Continues variables are presented as median (IQR) BMI: body mass index, C-section: cesarian section.

Demographics	No adverse outcomes ($n = 45$)	Adverse outcomes ($n = 6$)	*P*-value
Age	31 (26, 34)	30 (24, 32)	0.64
Self-identified race			1.0
Non-Black	30/45 (67 %)	4/6 (67 %)	
Black	15/45 (33 %)	2/6 (33 %)	
BMI (kg/m^2)	28.0 (24.0, 34.0)	28.3 (26.1, 29.4)	0.92
Hypertension	23/45 (51 %)	2/6 (33 %)	0.67
Obesity (BMI > 30 kg/m^2)	20/45 (44 %)	1/6 (17 %)	0.38
Obstetrics variables			
Days postpartum	25 (10, 51)	15 (5, 64)	0.57
Primiparous	29/45 (64 %)	3/6 (50 %)	0.66
Multiparous	16/45 (36 %)	3/6 (50 %)	
Vaginal delivery	26/45 (58 %)	3/6 (50 %)	1.0
C-section	19/45 (42 %)	3/6 (50 %)	
Smoking	13/45 (29 %)	3/6 (50 %)	0.58
Substance Use	3/45 (7 %)	1/6 (17 %)	0.40

3.2. Serious adverse events

A total of 6/51 (12 %) participants experienced 11 serious adverse events, including 5 LVADs, 3 heart transplants, and 3 deaths. Participants were a median of 25 days (IQR: 20, 163 days) postpartum at time of index event.

3.3. CMR variables comparing SAE vs non-SAE subgroups

Regarding left ventricular indices, there were no significant differences in indexed left ventricular end-diastolic or end-systolic volumes as well as left ventricular mass between SAE and no SAE groups. Stroke volume, both absolute and indexed, was significantly lower among individuals who experienced SAEs while cardiac output did not. Notably, heart rate at time of CMR was higher among those with SAEs. Regarding parametric mapping variables, there were no differences between subgroups with respect to mean T1 and T2 times. (Table 2**).**

Among individuals that experienced adverse outcomes, a

Table 2
Baseline (within 3 months) CMR and clinical variables comparing individuals with and without serious adverse outcomes. Variables presented as median (IQR). LVESVi: indexed left ventricular end-systolic volume, LVEDVi: indexed left ventricular end-diastolic volume, LVSVi: left ventricular stroke volume index, LVMI: left ventricular mass index, ECV: extracellular volume, LV GLS: left ventricular global longitudinal strain, BMI: body mass index. *Mean T1 and T2 times only reported for UPMC participants (T1 normative range: 960-1080 msec, T2 normative range < 45 msec).

CMR variables	No adverse outcomes (n = 45)	Adverse outcomes (n = 6)	P-value
Left ventricular variables			
LVESVi (ml/m^2)	67.4 (49.5, 99.4)	145.0 (44.4, 162.0)	0.07
LVEDVi (ml/m^2)	101.6 (81.3, 122.7)	164.2 (59.4, 191.0)	0.22
LVMI (g/m^2)	62.0 (49.0, 72.0)	68.5 (54.0, 70.0)	0.51
Concentricity (g/ml)	0.57 (0.48, 0.65)	0.49 (0.42, 0.59)	0.34
LV stroke volume (ml)	58.4 (39.4, 74.6)	32.1 (29.2, 34.2)	**0.005**
LV SVi (ml/m^2)	33.3 (20.9, 42.0)	17.5 (15.0, 20.2)	**0.007**
Heart rate (bpm)	79 (67, 96)	110 (98, 122)	**0.001**
Cardiac output (L/min)	4.6 (3.2, 5.4)	3.6 (3.4, 4.3)	0.32
LVEF (%) (by CMR)	37.3 (25.6, 49.1)	15.0 (15.0,17.0)	**0.001**
Valvular abnormalities			
Mitral regurgitation			
Mild/moderate/severe	12/4/4 (27/9/9 %)	1/1/0 (25/25/0 %)	0.69
Right ventricular variables			
Systolic function			
Mild/moderate/severe	2/2/5 (4/4/11 %)	2/2/1 (33/33/17 %)	**0.002**
Dilation			
Mild/moderate/severe	4/1/1 (9/2/2 %)	3/1/0 (60/20/0 %)	**0.005**
Parametric mapping			
Mean T1 time (msec)*	1116.8 (1053.5, 1151,0) (n = 14)	1108 (994.5, 1223.0) (n = 2)	1.0
Mean T2 time (msec)*	55.1 (52.9, 60.2) (n = 14)	60.3 (50.9, 82.0) (n = 2)	0.55
Post-processing			
Mean ECV (%)	28.2 (24.7, 33.8) (n = 13)	43.6 (42.4,44.8) (n = 2)	**0.02**
Peak LV GLS (%)	−10.0 (−12.6, −6.9)	−4.1 (−5.9, −3.9)	**0.002**
Obesity markers			
Epicardial fat volume (ml)	61.2 (45.3, 72.8)	64.2 (62.1, 66.2)	0.64

significantly lower LVEF at time of CMR (15.0 vs 37.3 %, $p < 0.001$), a worse peak GLS (−4.1 vs −10.0 %, $p = 0.002$) and greater calculated ECV (43.6 vs 28.2 %, $p < 0.01$) was observed. Additionally, greater severity of right ventricular dilatation and systolic dysfunction were noted among PPCM individuals with SAEs. **(**Table 2**).**

3.4. Univariate logistic regression analysis

In univariate logistic regression analysis, lower LVEF at CMR (OR 0.80 (95 % CI 0.65–0.97), $p = 0.02$), greater LVESVi (OR 1.03 (95 % CI 1.00–1.06), $p = 0.01$), lower stroke volume (OR 0.93 (95 % CI 0.87–0.99), $p = 0.03$), lower stroke volume index (OR 0.87 (95 % CI 0.77–0.99), p = 0.03) and worse peak GLS (OR 1.64 (95 % CI 1.07–2.50), p = 0.02) were predictive of adverse events.

4. Discussion

Our study identified worse peak GLS and higher ECV among those who experienced serious adverse clinical events. Additionally, LVESVi, stroke volume and stroke volume index were predictive of SAEs in univariate regression analysis. In qualitative analysis, right ventricular dilatation and systolic dysfunction were also significantly worse in the SAE subgroup.

Prior studies using primarily echo found LVEF and LVEDD at diagnosis of PPCM were predictors of short-term adverse outcomes and cardiac recovery, respectively [1]. While LVESVi by CMR was a significant predictor of adverse outcomes, LVEDD on diagnosing echo in this study was not (OR: 1.06 (95 % CI 0.94–1.19, $p = 0.37$). This may be reflective of more accurate volumetric assessment by CMR as compared to echo. Prior longitudinal follow-up studies have shown that individuals even with initially recovered LVEF may continue on to experience adverse events [7]. This underscores the importance of a more comprehensive approach using CMR to identify cardiac volumetric and myocardial parameters which may predict long-term adverse outcomes.

In addition to LV and RV function, our study identified peak GLS and ECV as significantly different in those who experienced adverse outcomes compared to those who did not. While stroke volumes were lower at diagnosis in those who experienced SAE, cardiac output was not significantly different among groups. This is likely due to compensatory higher heart rates among those with lower stroke volumes. (Table 2) While ECV has previously been shown to have prognostic value in DCM, this study is the first to show ECV was greater in PPCM individuals who experienced clinical adverse outcomes [3].

There are several limitations to this study, including a small sample size which is not surprising for a study focused on an uncommon type of cardiomyopathy with known low rates of serious adverse outcomes. Further, given that T1 mapping was not undertaken at all sites, we have a limited number of participants with quantifiable ECV. However, this represents one of the largest CMR studies of PPCM patients based on our review of the literature [8]. As data from the IPAC study was only collected to one year postpartum, we could not assess whether CMR indices continued to be predictors in longer term follow-up. CMR studies need be undertaken among larger PPCM cohorts as well as those with detailed longitudinal follow-up to further understand how volumetric and myocardial characteristics at time of PPCM diagnosis could predict long-term clinical outcomes.

5. Conclusion

This study noted ECV was greater in PPCM individuals who experienced clinical adverse outcomes beyond cardiac recovery by echo LVEF [8]. This is particularly notable given prior evidence that late gadolinium enhancement is seldom found in PPCM, and diffuse myocardial fibrosis is targetable with current therapeutics [4,9]. Future studies should focus on examining whether certain cardiac phenotypes at diagnosis change with cardiac recovery and whether these impact clinical outcomes over long-term follow-up. This information will be imperative to better inform patients about prognosis and aid in decision making for future pregnancy.

CRediT authorship contribution statement

Agnes Koczo: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Deeksha Acharya:** Writing – review & editing, Writing – original draft, Data curation. **Benay Ozbay:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Rami Alharethi:** Writing – review & editing, Project administration, Investigation, Data curation. **Michael M. Givertz:** Writing – review & editing, Investigation, Data curation. **Uri Elkayam:** Writing – review & editing, Investigation, Data curation. **Erik B. Schelbert:** Writing – review & editing, Project administration, Investigation, Formal analysis. **Dennis M. McNamara:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation. **Timothy C. Wong:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Ethical statement

This study was approved by our Institutional Review Board (STUDY23050037). All authors have read and approved the edits to the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. No relationships with industry exist for any of the authors that pertain to the contents of this paper. The corresponding author for this paper is Agnes Koczo.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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