OBSTETRICS

Cardiac magnetic resonance imaging in preeclampsia complicated by pulmonary edema shows myocardial edema with normal left ventricular systolic function

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BACKGROUND: Preeclampsia complicates approximately 5% of all pregnancies. When pulmonary edema occurs, it accounts for 50% of preeclampsia-related mortality. Currently, there is no consensus on the degree to which left ventricular systolic dysfunction contributes to the development of pulmonary edema.

OBJECTIVE: This study aimed to use cardiac magnetic resonance imaging to detect subtle changes in left ventricular systolic function and evidence of acute left ventricular dysfunction (through tissue characterization) in women with preeclampsia complicated by pulmonary edema compared with both preeclamptic and normotensive controls.

STUDY DESIGN: Cases were postpartum women aged ≥18 years presenting with preeclampsia complicated by pulmonary edema. Of note, 2 control groups were recruited: women with preeclampsia without pulmonary edema and women with normotensive pregnancies. All women underwent echocardiography and 1.5T cardiac magnetic resonance imaging with native T1 and T2 mapping. Gadolinium contrast was administered to cases only. Because of small sample sizes, a nonparametric test (Kruskal-Wallis) with pairwise posthoc analysis using Bonferroni correction was used to compare the differences between the groups. Cardiac magnetic resonance images were interpreted by 2 independent reporters. The intraclass correlation coefficient was calculated to assess interobserver reliability.

RESULTS: Here, 20 women with preeclampsia complicated by pulmonary edema, 13 women with preeclampsia (5 with severe features and 8 without severe features), and 6 normotensive controls were recruited. There was no difference in the baseline characteristics between groups apart from the expected differences in blood pressure. Left atrial sizes were similar across all groups. Women with preeclampsia complicated by pulmonary edema had increased left ventricular mass (P=.01) but had normal systolic function compared with the normotensive controls. Furthermore, they had elevated native T1 values (P=.025) and a trend toward elevated T2 values (P=.07) in the absence of late gadolinium enhancement consistent with myocardial edema. Moreover, myocardial edema was present in all women with eclampsia or hemolysis, elevated liver enzymes, and low platelet count. Women with preeclampsia without severe features had similar findings to the normotensive controls. All cardiac magnetic resonance imaging measurements showed a very high level of interobserver correlation.

CONCLUSION: This study focused on cardiac magnetic resonance imaging in women with preeclampsia complicated by pulmonary edema, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count. We have demonstrated normal systolic function with myocardial edema in women with preeclampsia with these severe features. These findings implicate an acute myocardial process as part of this clinical syndrome. The pathogenesis of myocardial edema and its relationship to pulmonary edema require further elucidation. With normal left atrial sizes, any hemodynamic component must be acute.

Key words: cardiac magnetic resonance imaging, eclampsia, hemolysis, elevated liver enzymes, and low platelet count, preeclampsia, pulmonary edema, ventricular edema

Introduction

Preeclampsia complicates 3% to 5% of all pregnancies.[1] Pulmonary edema is a defining feature of preeclampsia with severe features and accounts for up to 50% of preeclampsia-related deaths.[2,3] In nonpregnant patients with hypertension, diastolic dysfunction has been identified as the usual cause of acute pulmonary edema.[4] Similarly, in women with preeclampsia, the prevailing opinion seems to favor a composite of diastolic dysfunction, increased afterload (because of endothelial dysfunction and vasoconstriction), and capillary leak with interstitial edema.[3,5–7]

In studies of women with preeclampsia who have undergone echocardiography, some have reported normal systolic function accompanied by diastolic dysfunction,[8–12] whereas others have shown systolic dysfunction to a greater or lesser degree.[13–17] Most studies did not assess women with pulmonary edema as a distinct group. There are limited data on the echocardiographic findings in women with preeclampsia complicated by pulmonary edema.

Cardiac magnetic resonance imaging (MRI) has become the reference standard for quantifying chamber size and ejection fraction.[18] Despite the favorable risk-benefit ratio of cardiac MRI in pregnancy, it remains an underutilized tool.[19] Of note, 2 small studies have

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AJOG at a Glance

Why was this study conducted?

The mechanisms underlying the development of pulmonary edema in preeclampsia are not well understood, and the literature is conflicting. We evaluated left ventricular (LV) function and tissue characterization in women with preeclampsia with severe features and controls using cardiac magnetic resonance imaging (MRI).

Key findings

LV systolic dysfunction did not play a role in the development of pulmonary edema. Evidence of myocardial edema was found in women with preeclampsia complicated by pulmonary edema; hemolysis, elevated liver enzymes, and low platelet count; and eclampsia.

What does this add to what is known?

Systolic dysfunction was not the mechanism underlying pulmonary edema in preeclampsia. The presence of myocardial edema in preeclampsia with severe features without pulmonary edema suggested more widespread subclinical myocardial involvement than previously suspected. The absence of left atrial enlargement suggested that any hemodynamic cause for pulmonary edema is acute.

reported cardiac MRI findings in women with preeclampsia, and no woman with preeclampsia complicated by pulmonary edema was included.[20,21] Both studies primarily reported left ventricular (LV) volumes and masses, and 1 study reported on short-tau inversion recovery (STIR) imaging findings.[20] With its ability to characterize myocardial pathology, for instance, through edema imaging (STIR, native T1 and T2 mapping), cardiac MRI offers the opportunity to determine the pathophysiological basis for the anatomic abnormalities detected. There is no report detailing native (pregadolinium contrast) tissue mapping.

Considering the paucity of data and the overall poor understanding of the mechanisms and pathophysiology underlying pulmonary edema in women with preeclampsia, we set out to use cardiac MRI to assess for subtle changes in LV systolic function in women with preeclampsia complicated by pulmonary edema. Furthermore, we utilized tissue characterization to assess for evidence of acute myocardial edema and altered gadolinium kinetics as markers of acute ventricular pathology leading to dysfunction. By comparing these findings in women with preeclampsia complicated by pulmonary edema with those in women with preeclampsia without pulmonary edema and normotensive controls, we aimed to advance the understanding of the pathologic mechanisms underlying pulmonary edema in preeclampsia.

Materials and Methods

This prospective observational study (S17/10/260) was approved by the human research ethics committee of the University of Stellenbosch, Cape Town, South Africa. Furthermore, these women were included in the Preeclampsia Obstetric Adverse Event biobank.[22]

Study population

We included postpartum women who delivered at Tygerberg Hospital in Cape Town, South Africa. Cases were women with preeclampsia complicated by pulmonary edema. These cases were compared with cases of women with preeclampsia without pulmonary edema and normotensive controls. Women with other target organ dysfunction, such as eclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), were eligible for inclusion in the preeclampsia control group.

We included women aged $\geq$18 years without secondary hypertension. The exclusion criteria included non–preeclamptic-related pulmonary edema, an alternative cause for respiratory failure, and claustrophobia.

Pulmonary edema was diagnosed in the presence of respiratory failure necessitating respiratory support not because of infective or embolic causes, the presence of bibasal fine inspiratory crackles on auscultation, which responded to diuresis or positive pressure ventilation and/or compatible radiologic features on chest x-ray or computed tomography scanning.

Women were classified using the International Society for the Study of Hypertension in Pregnancy definition of preeclampsia.[23] Moreover, significant proteinuria was defined as a urine protein-to-creatinine ratio (PCR) of $\geq$30 mg/mmol (0.3 mg/mg). A 24-hour urine PCR of $\geq$0.3 g or urine dipstick >1+ (if a PCR was not available) was required to make the diagnosis. Women with only hypertension and proteinuria were classified as having preeclampsia without severe features. We did not include severe hypertension as a feature of severe disease. Women with acute renal injury, liver dysfunction, neurologic features (including eclampsia), hemolysis, or thrombocytopenia were classified as having preeclampsia with severe features. A woman was considered normotensive if she had no documented systolic blood pressure (BP) of >139 mm Hg or diastolic BP of >89 mm Hg during her pregnancy until discharge after birth. Body surface area (BSA) and body mass index (BMI) were calculated using postpartum weight and height. BSA was calculated using the DuBois formula ($0.0247 \times \text{height [m]}^{0.725} \times \text{weight [kg]}^{0.425}$). Medical therapy was at the discretion of the treating physician.

Women were identified in the high care unit, labor ward, and postpartum ward by the investigators and research nurses. Folders were reviewed to find the most appropriate candidates. Cases and controls were concurrently recruited,

TABLE 1
Baseline characteristics and cardiac magnetic resonance imaging findings in women with preeclampsia with pulmonary edema and women with preeclampsia without pulmonary edema and normotensive controls

Characteristic	Preeclampsia with pulmonary edema (n=20)	SD or %	Preeclampsia without pulmonary edema(n=13)	SD or %	Normotensive controls (n=6)	SD or %	*P* value
Demographics							
Age	28.3	5.9	27.6	6.0	28.0	5.8	.96
Gravidity	2.5	1.3	2.4	1.5	2.2	1.2	.87
Parity	1.2	1.1	1.2	1.5	1.5	0.8	.83
Gestation (wk)	32.2	5.5	34.8	5.0	35.2	6.1	.243
CD	16	80%	10	77%	2	33%	<.001
BMI (kg/m^2)	34.1	12.7	35.9	7.9	34.4	9.6	.58
BSA (m^2)	1.9	0.4	2.1	0.2	1.9	0.2	.269
Heart rate (bpm)	95.0	11.0	95.5	16.0	86.8	18.5	.475
Systolic BP (mm Hg)	189.4	24.9	163.9	18.1	116.0	8.7	<.001
Diastolic BP (mm Hg)	110.6	15.5	103.6	20.6	62.3	5.2	<.001
Imaging findings							
LVEF (%)	62.8	10.9	68.5	4.4	58.2	7.7	.027
LVEDV (mL)	149.6	34.7	145.1	29.3	141.3	18.3	.942
LVESV (mL)	55.3	22.2	45.3	9.1	58.9	13.6	.194
LVMI (g/m^2)	77.4	19.9	67.3	15.0	56.0	7.6	.01
LA area	22.8	4.3	21.4	3.2	22.3	4.1	.625
LAVI (mL/m^2)	38.9	9.2	32.7	6.9	34.8	7.3	.207
Basal STIR	1.1	0.6	0.9	0.4	1.2	0.4	.377
Middle STIR	1.2	0.5	1.1	0.2	1.4	0.2	.02
Apical STIR	1.1	0.3	1.1	0.3	1.4	0.2	.05
Global T1 (ms)	1082.4	52.7	1032.3	52.5	1037.3	19.8	.025
Global T2 (ms)	55.5	7.0	53.5	5.1	49.2	1.7	.07
Time to MRI (d)	5.4	3.0	1.5	1.1	1.7	0.8	<.001

Time to MRI is defined as time from delivery to cardiac MRI in days.

BMI, body mass index; *BP*, blood pressure; *BSA*, body surface area; *CD*, cesarean delivery; *LA*, left atrial; *LAVI*, left atrial volume indexed to BSA; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV*, left ventricular end-systolic volume; *LVMI*, left ventricular mass indexed to BSA; *MRI*, magnetic resonance imaging; *SD*, standard deviation; *STIR*, short-tau inversion recovery.

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but women with preeclampsia with pulmonary edema were prioritized for inclusion. After signing the informed consent, all women underwent cardiac MRI. Baseline data were obtained by interview and extraction from medical records and entered and stored using Research Electronic Data Capture tools (Siemens AG Munich, Germany) hosted at the University of Stellenbosch.[24,25] Electronic data were double-checked for accuracy and cross-referenced with original data collection forms collected by research midwives.

Magnetic resonance imaging assessment

Cardiac MRI was performed following current guideline recommendations.[26–28] A 1.5T cardiac MRI (Siemens Aera, REDcap Nashville,TN) was performed as soon as cardiac MRI could be tolerated. All cases with pulmonary edema had gadolinium contrast (Gadavist Bayer Healthcare Pharmaceuticals Inc. Leverkeusen, Germany) administered at the standard recommended dosage (0.2 mL/kg). Controls had a cardiac MRI without gadolinium. The analysis of the cardiac MRI data was performed using CVI 42 (Circle Cardiovascular Imaging Inc, Calgary, Canada). We determined LV

TABLE 2
Baseline characteristics and imaging findings in women with preeclampsia with pulmonary edema, women with eclampsia or HELLP syndrome, and women with preeclampsia without severe features and normotensive controls

Characteristic	Preeclampsia with pulmonary edema (n=20)	SD or %	Eclampsia or HELLP syndrome (n=5)	SD or %	Preeclampsia without severe features (n=8)	SD or %	Normotensive controls (n=6)	SD	*P* value
Demographics									
Age (y)	28.3	5.9	26.0	7.0	28.6	5.5	28	5.8	.93
Gravidity	2.5	1.3	3.0	1.9	2.0	1.2	2.2	1.2	.583
Parity	1.2	1.1	1.8	1.8	0.8	1.2	1.5	0.8	.435
Gestation (wk)	32.2	5.5	34.3	5.7	35.2	4.9	35.2	6.1	.401
CD	16	80%	4	80%	6	75%	2	33%	.006
BMI (kg/m^2)	34.1	12.7	38.1	11.1	34.5	5.6	34.4	9.6	.747
BSA (m^2)	1.9	0.4	2.1	0.3	2.0	0.1	1.9	0.2	.453
Heart rate (bpm)	94.6	10.9	93.0	16.5	97.0	16.6	86.8	18.5	.545
Systolic BP (mm Hg)	189.4	24.9	172.4	16.2	158.6	18.1	116.0	8.7	<.001
Diastolic BP (mm Hg)	110.6	15.5	122.0	14.8	92.1	14.5	62.3	5.2	<.001
Imaging findings									
LVEDV (mL)	149.6	34.7	170.1	26.1	129.5	18.7	141.3	18.3	.123
LVESV (mL)	55.3	22.2	47.9	9.7	43.7	8.9	58.9	13.6	.303
LVEF (%)	62.8	10.9	71.8	4.1	66.4	3.4	58.2	7.7	.02
LVMI (g/m^2)	77.4	19.9	79.4	12.0	59.7	11.4	56.0	7.6	.002
LA area	22.8	4.3	23.5	3.1	20.0	2.5	22.3	4.1	.274
LAVI (mL/m^2)	38.9	9.2	34.7	3.7	31.5	8.3	34.8	7.3	.322
Basal STIR	1.1	0.6	0.8	0.5	1.0	0.3	1.2	0.4	.372
Middle STIR	1.2	0.5	1.1	0.3	1.1	0.2	1.4	0.2	.049
Apical STIR	1.1	0.3	1.0	0.3	1.2	0.3	1.4	0.2	.094
Global T1 (ms)	1082.4	52.7	1081.8	43.6	1001.4	28.3	1037.3	19.8	.002
Global T2 (ms)	55.5	7.0	55.4	6.8	52.4	3.9	49.2	1.7	.114
Time to MRI (d)	5.4	3.0	2.2	1.6	1.1	0.4	1.7	0.8	<.001

Time to MRI is defined as time from delivery to cardiac MRI in days.

BMI, body mass index; *BP*, blood pressure; *BSA*, body surface area; *CD*, cesarean delivery; *HELLP*, *hemolysis, elevated liver enzymes, and low platelet count*; *LA*, left atrial; *LAVI*, left atrial volume indexed to BSA; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV*, left ventricular end-systolic volume; *LVMI*, left ventricular mass indexed to BSA; *MRI, magnetic resonance imaging; SD*, standard deviation; *STIR*, short-tau inversion recovery.

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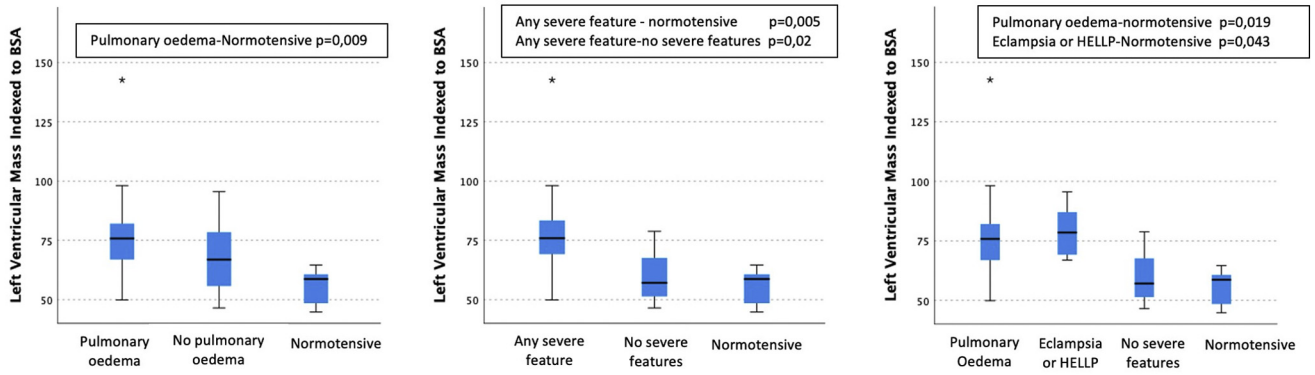
volumes, mass, and functional parameters. We assessed edema using STIR sequences. Furthermore, native T1 and T2 tissue characterizations were performed. Further detail on the methodology can be found in the Supplemental Material section. All cardiac MRIs were read by a single reporter (L.H.J.) who was not blinded to the participant group. To reduce observer bias, the first 27 of 39 MRIs were independently reported by a second reporter (A.S.H.), who was blinded to the participant group.

Statistical methods

Data were analyzed using the SPSS Statistics software (version 27; IBM SPSS Statistics, IBM Corporation 2020, Chicago, IL). Participant characteristics and cardiac MRI variables were expressed as means with standard deviations, medians with interquartile ranges, and numbers with percentages, according to order of the variables and distribution of data. Categorical variables were compared using cross-tabulation and the chi-square test. Because of small sample sizes, a nonparametric test (independent-samples Kruskal-Wallis test) with pairwise post hoc analysis using Bonferroni correction was used to compare the differences between the groups with normal distribution. The

FIGURE 1
Box and whisker plot comparing indexed left ventricular mass



Inset text boxes show *P* values for significant pairwise comparisons using the Bonferroni correction.

BSA, body surface area; *HELLP syndrome*, hemolysis, elevated liver enzymes, and low platelet count.

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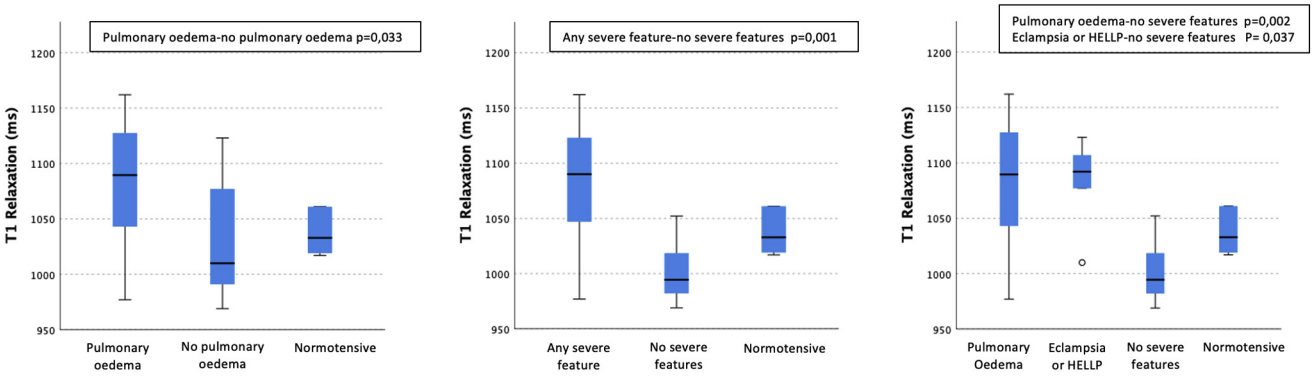
Mann-Whitney *U* test was used to compare the means of groups without normal distribution. Correlation between continuous variables was evaluated using the Pearson correlation coefficient. A *P* value of $<.05$ was used to ascribe statistical significance. The intraclass correlation coefficient was calculated to assess interobserver reliability for the cardiac MRI reports for each of the measured variables.

Results

A total of 42 postpartum women underwent cardiac MRI. Of note, 3 women were excluded from the final analysis. Moreover, 1 woman with pulmonary edema was excluded because of mapping-related artifact, which precluded accurate assessment of the T1 and T2 sequences. Furthermore, 2 normotensive postpartum controls were excluded. Of the 2 women, one had absent native T2 mapping data, and the other had non—preeclampsia-related myocardial abnormalities on MRI. Overall, 39 women were included in the final analysis. Of those women, 20 had preeclampsia complicated by pulmonary edema, and 13 women had preeclampsia without pulmonary edema, 5 of whom had preeclampsia with severe features (4 with eclampsia and 1 with HELLP syndrome). Moreover, 6 normotensive postpartum women were included. Of the 4 women with chronic hypertension were included in the study. Of the 4 women, 3 were in the pulmonary edema group, and 1 was included in the preeclampsia without severe features group.

There was no significant difference between women with preeclampsia complicated by pulmonary edema and controls in terms of mean age, gestation, gravidity and parity, BSA, BMI, and

FIGURE 2
Box and whisker plot comparing native T1 relaxation time



Inset text boxes show *P* values for significant pairwise comparisons using the Bonferroni correction.

HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count.

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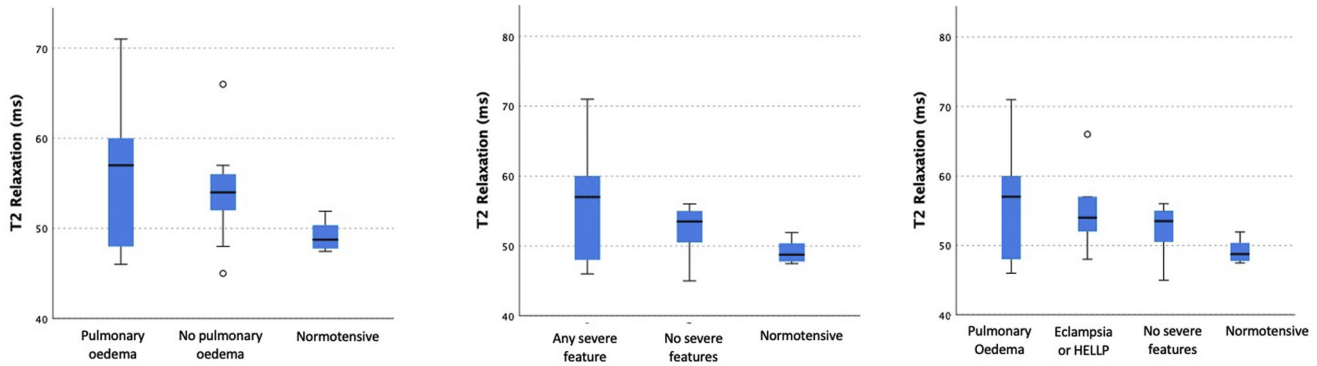
FIGURE 3
Box and whisker plot comparing native T2 relaxation time



HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count.

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heart rate at the time of inclusion (Table 1). As expected, there was a statistically significant difference in systolic and diastolic BPs between the groups. Patients with preeclampsia complicated by pulmonary edema had significantly higher BPs than both preeclamptic and nonpreeclamptic controls. When the control cases with preeclampsia were divided into those with and without severe features, the difference in BP persisted compared with normotensive controls, but there was no other significant difference in the baseline characteristics (Table 2). The use of antihypertensive medication, namely, nifedipine, methyldopa, and intravenous labetalol, was similar for all women with preeclampsia. Women with pulmonary edema were more likely to receive intravenous furosemide. Women with any form of preeclampsia were more likely to deliver via cesarean delivery, whereas normotensive controls were more likely to deliver vaginally (X^2 [9, n=39] = 23.18; P=.006)

LV end-diastolic volumes and LV end-systolic volumes were similar for all participants (Tables 1 and 2). Of note, 3 women with pulmonary edema had LV ejection fractions (LVEFs) of <50% (44%–47%), but the mean LVEF in the pulmonary edema group was similar to the normotensive controls (Table 1). Women with preeclampsia with severe features without pulmonary edema had a higher mean ejection fraction than normotensive controls (Bonferroni correction, P=.023) (Table 2).

LV mass indexed to BSA (LVMI) was increased in women with preeclampsia complicated by pulmonary edema compared with normotensive women (Table 1; Figure 1). Women with preeclampsia with severe features but without pulmonary edema had the highest mean LVMI, whereas those with preeclampsia without severe features had similar LVMI to normotensive controls (Table 2; Figure 1). There was no difference in LVMI between women with chronic hypertension and those without (Mann-Whitney U, P=.876). Furthermore, there was no association between chronic hypertension and the presence of preeclampsia with severe features (X^2 [2, n=39] = 0.81; P=.62). These results were unchanged when LV mass was indexed to height. There was no between-group difference in the left atrial (LA) area, LA volume indexed to BSA, and LA volume indexed to height.

Edema imaging (STIR) demonstrated an elevated myocardial muscle–to–skeletal muscle signal intensity ratio of greater than 2:1 (indicative of myocardial edema) in 2 women with preeclampsia complicated by pulmonary edema. Overall, the average STIR ratios were not elevated. The midventricular STIR ratios were higher in the normotensive women than in women with preeclampsia. Furthermore, this nonstatistically significant trend was present in the basal and apical segments. There was no evidence of abnormal early or late myocardial gadolinium enhancement in women with preeclampsia complicated by pulmonary edema.

The average native T1 values were increased in women with preeclampsia complicated by pulmonary edema compared with women with preeclampsia without pulmonary edema and normotensive women (Table 1; Figure 2). Moreover, this increase in the T1 value was present in women with preeclampsia with severe features without pulmonary edema (Table 2; Figure 2). Women with preeclampsia and pulmonary edema showed a trend toward elevated T2 values. These values decreased in a stepwise fashion in women with preeclampsia complicated by pulmonary edema compared with women with preeclampsia without pulmonary edema and normotensive controls (P=.07). A similar trend in T2 values was seen in women with preeclampsia with severe features compared with those without severe features and normotensive controls (P=.051) (Figure 3; Table 3).

Women with preeclampsia complicated by pulmonary edema and women with HELLP syndrome or eclampsia did not differ in terms of LVMI and T1 and T2 values (Figures 1–3). There was a positive correlation between LVMI and

TABLE 3
Women with preeclampsia with severe features (including pulmonary edema, eclampsia and HELLP syndrome) compared with women with preeclampsia without severe features and normotensive controls

Parameter	Any severe feature (n=25)	SD	No severe features (n=8)	SD	Normotensive control (n=6)	SD	*P* value
Demographics							
Age (y)	27.8	6.1	28.6	5.5	28.0	5.8	.924
Gravidity	2.6	1.4	2.0	1.2	2.2	1.2	.492
Parity	1.3	1.3	0.8	1.2	1.5	0.8	.421
Gestation (wk)	32.7	5.5	35.2	4.9	35.2	6.1	.313
CD	20	80%	6	75%	2	33%	.002
BMI (kg/m^2)	34.9	12.3	34.5	5.6	34.4	9.6	.894
BSA (m^2)	2.0	0.4	2.0	0.1	1.9	0.2	.444
Heart rate (bpm)	94.6	11.9	97.0	16.6	86.8	18.5	.437
Systolic BP (mm Hg)	186.0	24.2	158.6	18.1	116.0	8.7	<.001
Diastolic BP (mm Hg)	112.8	15.7	92.1	14.5	62.3	5.2	<.001
Imaging findings							
LVEF (%)	64.6	10.5	66.4	3.4	58.2	7.7	.143
LVEDV (mL)	153.7	33.8	129.45	18.7	141.27	18.3	.117
LVESV (mL)	53.8	20.4	43.7	8.9	58.9	13.6	.178
LVMI (g/m^2)	77.8	18.4	59.7	11.4	56.0	7.6	<.001
LA area	22.9	4.1	20.0	2.5	22.3	4.1	.164
LAVI (mL/m^2)	38.1	8.5	31.5	8.3	34.8	7.3	.234
Basal STIR	1.0	0.6	1.0	0.3	1.2	0.4	.385
Middle STIR	1.2	0.4	1.1	0.2	1.4	0.2	.02
Apical STIR	1.1	0.3	1.2	0.3	1.4	0.2	.042
Global T1 (ms)	1082.2	50.1	1001.4	28.3	1037.3	19.8	<.001
Global T2 (ms)	55.5	6.8	52.4	3.9	49.2	1.7	.051
Time to MRI (d)	4.7	3.0	1.1	0.4	1.7	0.8	.001

Time to MRI is defined as time from delivery to cardiac MRI in days.

BMI, body mass index; *BP*, blood pressure; *BSA*, body surface area; *CD*, cesarean delivery; *HELLP syndrome*, hemolysis, elevated liver enzymes, and low platelet count; *LA*, left atrial; *LAVI*, left atrial volume indexed to BSA; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV*, left ventricular end-systolic volume; *LVMI*, left ventricular mass indexed to BSA; *MRI*, magnetic resonance imaging; *SD*, standard deviation; *STIR*, short-tau inversion recovery.

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both T1 value (Pearson correlation, 0.361; *P*=.02) and T2 value (Pearson correlation, 0.371; *P*=.02).

Interobserver correlation of findings was assessed using the intraclass correlation coefficient. All cardiac MRI measurements showed a high level of interobserver correlation (Supplemental Table).

Comment

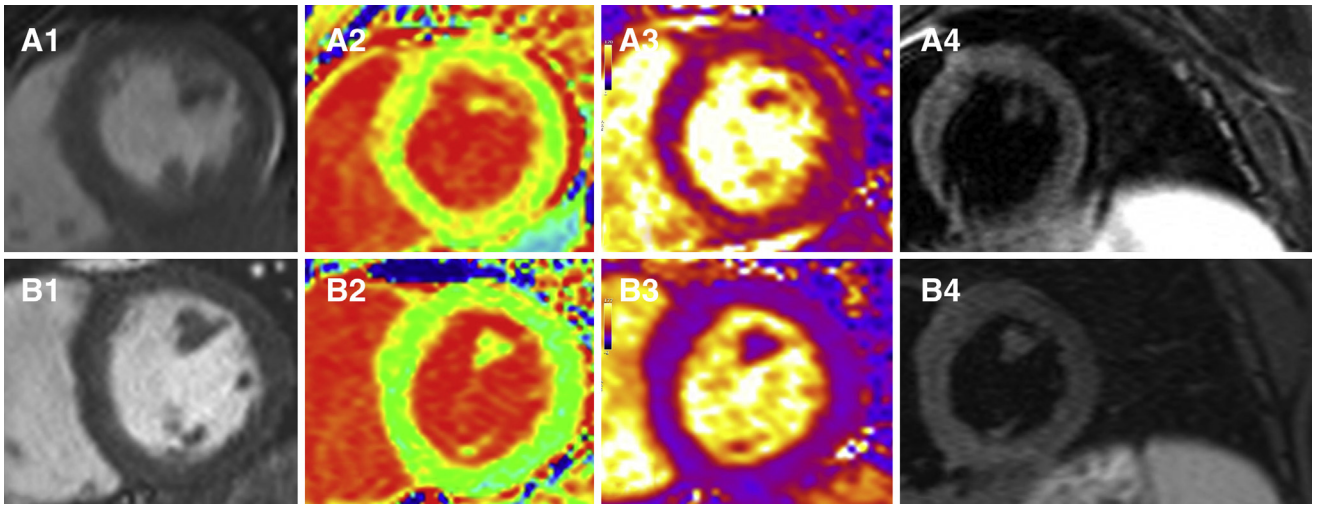
Principal findings

This study demonstrated that systolic function is not altered in women with preeclampsia complicated by pulmonary edema compared with normotensive controls, supporting the concept that systolic dysfunction does not underlie the mechanism of pulmonary edema in preeclampsia. A further novel finding from this study was that preeclampsia complicated pulmonary edema and eclampsia and HELLP syndrome (without pulmonary edema) were all characterized by the presence of acute LV myocardial edema. This was an important finding, implicating local pathology at a cardiac level in preeclampsia with severe features, even without pulmonary edema.

Results in the context of what is known

Women with preeclampsia complicated by pulmonary edema had significantly increased LVMI compared with normotensive controls. This increase in LVMI in women with preeclampsia on cardiac MRI has previously been shown.[20,21] Interestingly, in our population, women with preeclampsia with severe features of eclampsia and HELLP

FIGURE 4
Cardiac magnetic resonance imaging findings



Series A, Typical findings in a woman with preeclampsia complicated by pulmonary edema. **A1,** Steady-state free precession short-axis midventricular level in diastole. **A2,** Native T1 relaxation demonstrating diffuse prolongation of T1 relaxation. **A3,** Native T2 relaxation demonstrating diffuse T2 prolongation. **A4,** In STIR imaging without convincing edema, the average myocardial muscle—to—skeletal muscle STIR ratio for this woman was 1:1.1. **Series B,** Corresponding typical findings in a normotensive postpartum control.

STIR, short-tau inversion recovery.

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syndrome had increased LVMI compared with women with preeclampsia without severe features and normotensive controls. Moreover, the groups with higher LVMI had higher systolic and diastolic BPs. This could be interpreted as a correlation between pressure load on the left ventricle, more severe in the women with preeclampsia with severe features, and subsequent LV hypertrophy, leading to diastolic dysfunction and pulmonary edema. However, the process of hypertrophy takes time. Given that chronic hypertension was not associated with increased LVMI in our population, it is unlikely that there is a chronic preexisting component to this increased LV mass. Furthermore, LA areas and volumes were similar across all groups, arguing strongly against long-standing elevated LV end-diastolic pressures (LVEDPs) and LV diastolic dysfunction. A more acute process must underly the increased LVMI. The presence of acute myocardial edema is a well-described cause of transiently increased myocardial mass, which may better explain these findings. Furthermore, the tissue characterization abnormalities suggestive of myocardial edema are not present in patients with LV hypertrophy because of increased LV pressure load.[29]

There was a correlation between elevated myocardial mass and elevated native T1 and T2 values. With the absence of late gadolinium enhancement, this is consistent with myocardial edema. Moreover, the signal for myocardial edema was seen in women with preeclampsia complicated by pulmonary edema and those who had eclampsia and HELLP syndrome. Myocardial edema was not present in women with preeclampsia without severe features.

Given the trend in the native T1 and T2 values, we would have expected to see more positive edema imaging (STIR) (Figure 4). In our cohort, STIR imaging only reached the prespecified cutoff for diagnosing myocardial edema (myocardial muscle—to—skeletal muscle signal intensity ratio of >2) in 2 women, both of whom had pulmonary edema. Women with preeclampsia with severe features tended to have lower STIR ratios than the normotensive controls. In the study by Chen et al,[20] native mapping data were not available, but 2 of 5 women with preeclampsia (both classified as severe) demonstrated elevated STIR ratios in keeping with edema. Our population had significantly higher heart rates with a mean heart rate of 95 beats per minute, whereas Chen et al[20] reported a mean heart rate of 73 beats per minute. Because of the nature of the STIR imaging sequence, the diagnostic utility is significantly impacted by increased heart rates. This may explain the low level of edema observed in our cohort compared with other data. However, the between-group difference in our cohort was unexplained with heart rates being similar. It is accepted that preeclampsia causes generalized edema. Skeletal muscle edema, leading to increased skeletal muscle signal intensity, would falsely lower the signal intensity ratio. This may explain why women with myocardial edema on native mapping had lower STIR ratios than the normotensive controls. This finding should be explored in subsequent studies. In this group of critically unwell women with generalized edema and tachycardia, native mapping

may have greater utility than STIR imaging for detecting myocardial edema.

Clinical implications

Cardiac MRI in this cohort of critically ill women demonstrated cardiac abnormalities beyond the capacity of echocardiography, despite a delay in time to cardiac MRI in patients with preeclampsia complicated by pulmonary edema. Preeclampsia with severe features of pulmonary edema, eclampsia, or HELLP syndrome results in a degree of cardiac involvement no matter the presenting feature.

Research implications

Although the increase in LV mass likely represents myocardial edema, the cause of the myocardial edema is unclear. Similarly, the mechanism leading to pulmonary edema is unclear. Is preeclampsia just a diffusely edematous state with capillary leak? Our findings would suggest that not all forms of preeclampsia result in myocardial edema. This seems to be specific to preeclampsia with eclampsia and HELLP syndrome and not just limited to preeclampsia complicated by pulmonary edema. Does this merely reflect the degree of endothelial dysfunction or is the myocardial edema in preeclampsia with severe features an active process? Is the pulmonary edema just an extension of capillary leak or is there a hemodynamic basis for this complication? Without hemodynamic data detailing the LV afterload and the LVEDP, the answers remain uncertain.

Strengths and limitations

Our study focused on cardiac MRI in women with preeclampsia and we describe the native mapping findings, but there is no reference standard for this group. Moreover, this cardiac MRI study included women with severe features of preeclampsia, including eclampsia, HELLP syndrome, and pulmonary edema. With no follow-up cardiac MRI, the extent of resolution of the myocardial abnormalities was not known. Gadolinium contrast was only given to women with preeclampsia complicated by pulmonary edema, and therefore, characterization of the myocardium was incomplete in the control cohort. There is no robust hemodynamic data available in these women enabling afterload estimation. Similarly, LVEDP has not been measured directly, and the extent of diastolic pressure load and its effect on pulmonary edema were not evaluated. Finally, there is no published data detailing cardiac histologic findings in women with preeclampsia complicated by pulmonary edema. Cardiac MRI findings, which correlate well with histologic findings in other pathologies, could be extrapolated to our cohort.[30] However, this study did highlight a significant deficiency in our basic knowledge of the cardiac pathology associated with preeclampsia.

Conclusions

We have found normal systolic function, increased LV mass, and elevated native T1 and T2 values not only in women with preeclampsia complicated by pulmonary edema but also in women with eclampsia and preeclampsia with HELLP syndrome. Our data were in keeping with the hypothesis that this finding represents myocardial edema.[20,21] What remains to be answered is the exact nature of the pathologic process responsible for the development of the myocardial edema and whether a hemodynamic cause underlies the pulmonary edema rather than a similar pathologic process active in the lungs. ■

References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol 2013;170:1–7.
2. Olson-chen C, Seligman NS. Hypertensive emergencies in pregnancy. Crit Care Clin 2016;32:29–41.
3. Anthony J, Damasceno A, Ojji D. Hypertensive disorders of pregnancy: what the physician needs to know. Cardiovasc J Afr 2016;27:104–10.
4. Little WC. Hypertensive pulmonary oedema is due to diastolic dysfunction. Eur Heart J 2001;22:1961–4.
5. Guirguis GF, Aziz MM, Boccia Liang C, et al. Is preeclampsia an independent predictor of diastolic dysfunction? A retrospective cohort study. Pregnancy Hypertens 2015;5:359–61.
6. Gandhi S, Sun D, Park AL, Hladunewich M, Silversides CK, Ray JG. The Pulmonary Edema Preeclampsia Evaluation (PEPE) Study. J Obstet Gynaecol Can 2017;36:1065–70.
7. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. Lancet 2021;398:341–54.
8. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. Hypertension 2011;57:85–93.
9. Dennis AT, Castro J, Carr C, Simmons S, Permezel M, Royse C. Haemodynamics in women with untreated pre-eclampsia. Anaesthesia 2012;67:1105–18.
10. Fayers S, Moodley J, Naidoo DP. Cardiovascular haemodynamics in pre-eclampsia using brain naturetic peptide and tissue Doppler studies. Cardiovasc J Afr 2013;24:130–6.
11. Bamfo JE, Kametas NA, Chambers JB, Nicolaides KH. Maternal cardiac function in normotensive and pre-eclamptic intrauterine growth restriction. Ultrasound Obstet Gynecol 2008;32:682–6.
12. Dennis AT, Dyer RA, Gibbs M, Nel L, Castro JM, Swanevelder JL. Transthoracic echocardiographic assessment of haemodynamics in severe pre-eclampsia and HIV in South Africa. Anaesthesia 2015;70:1028–38.
13. Shahul S, Rhee J, Hacker MR, et al. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. Circ Cardiovasc Imaging 2012;5:734–9.
14. Melchiorre K, Sutherland GR, Watt-coote I, Liberati M, Thilaganathan B. Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. Hypertens Pregnancy 2012;31:454–71.
15. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens 2009;27:2257–64.
16. Tyldum EV, Backe B, Støylen A, Slørdahl SA. Maternal left ventricular and endothelial functions in preeclampsia. Acta Obstet Gynecol Scand 2012;91:566–73.
17. Borghi C, Esposti DD, Immordino V, et al. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. Am J Obstet Gynecol 2000;183:140–7.
18. Patel AR, Kramer CM. Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy. JACC Cardiovasc Imaging 2017;10:1180–93.
19. Committee Opinion No. 723: guidelines for diagnostic imaging during pregnancy and lactation. Obstet Gynecol 2017;130:e210–6.
20. Chen SSM, Leeton L, Castro JM, Dennis AT. Myocardial tissue characterisation and detection of myocardial oedema by cardiovascular magnetic resonance in women with pre-eclampsia: a pilot study. Int J Obstet Anesth 2018;36:56–65.
21. Kalapotharakos G, Salehi D, Steding-Ehrenborg K, et al. Cardiovascular effects of severe late-onset preeclampsia are reversed

within six months postpartum. Pregnancy Hypertens 2020;19:18–24.

22. Bergman L, Bergman K, Langenegger E, et al. PROVE-pre-eclampsia obstetric adverse events: establishment of a biobank and database for pre-eclampsia. Cells 2021;10:959.

23. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2018;13:291–310.

24. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

26. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J Am Coll Cardiol 2009;53:1475–87.

27. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158–76.

28. Moon JC, Messroghli DR, Kellman P, et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson 2013;15:92.

29. Burrage MK, Ferreira VM. Cardiovascular magnetic resonance for the differentiation of left ventricular hypertrophy. Curr Heart Fail Rep 2020;17:192–204.

30. Jan MF, Tajik AJ. Modern imaging techniques in cardiomyopathies. Circ Res 2017;121:874–91.

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Supplemental Material

Methods for performing cardiac magnetic resonance imaging

Of note, short axis cine images and 3 long axis cine images in the 2, 4 and 3 chamber orientations were acquired using a breath held retrospectively gated balanced steady-state free precession gradient-echo sequence. The slice thickness of the short-axis cines was 8 mm at 10 mm intervals (20% gap) from the left ventricle (LV) base to the apex. The endocardial and epicardial contours were traced in short axis at end diastole and end systole to determine LV volumes, mass, and functional parameters. Papillary muscles were excluded from the blood pool and contributed to myocardial mass. All volumes and masses were indexed to body surface area.

Edema imaging was performed using short-tau inversion recovery (STIR) sequences. A basal, middle, and apical short-axis image was acquired. During postprocessing, the LV was segmented into the 16-segment American Heart Association model.[1] A polar map of raw STIR values was generated using endo- and epicardial offset of 20% to ensure that only the myocardium was included. These were compared with the signal intensity value of the serratus anterior muscle on the same slice, and a polar map of cardiac muscle—to—skeletal muscle signal intensity ratios was extrapolated for each woman. This semiautomated method reduced operator bias and allowed for more detailed description of cardiac edema. T1 and T2 native imaging were acquired using the modified Look-Locker imaging (MOLLI) technique. Of note, 3 short-axis images were acquired at the level of the basal, middle, and apical LV and were used for quantification. Moreover, 4-, 2-, and 3-chamber images were acquired for cross-correlation. Polar maps of native T1 and T2 values were generated in a similar manner to the STIR images. This allowed for objective assessment of both segmental native T1 and T2 values and global, basal, middle, and apical LV T1 and T2 values.

Supplemental Reference

1. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. J Cardiovasc Magn Reson 2002;4:203–10.

SUPPLEMENTAL TABLE

Intraclass correlation coefficient for magnetic resonance imaging measurements

Parameter	ICC
Global T1	0.976
Global T2	0.965
LVESV	0.996
LVEDV	0.977
LVEF	0.911
LV mass	0.895
LA area	0.901

ICC of 0.75 to 0.90 indicates good interobserver reliability.

ICC, intraclass correlation coefficient; *LA*, left atrial; *LV*, left ventricular; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV*, left ventricular end-systolic volume.

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