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ORIGINAL RESEARCH

Low Plasma Volume and Increased Pressure Load Relate to Concentric Left Ventricular Remodeling After Preeclampsia: A Longitudinal Study

Nicolette M. Breetveld, MD; Robert-Jan Alers, MD; Lauren Geerts, MD; Sander M. J. van Kuijk, PhD; Arie P. van Dijk, MD, PhD; Maureen J. van der Vlugt, MD, PhD; Wieteke M. Heidema, MD; Jolijn van Neer, MD; Vanessa P. M. van Empel, MD, PhD; Hans-Peter Brunner-La Rocca, MD, PhD; Ralph R. Scholten, MD, PhD; Chahinda Ghossein-Doha, MD, PhD; Marc E. A. Spaanderman, MD, PhD

BACKGROUND: During uncomplicated pregnancy, left ventricular remodeling occurs in an eccentric way. In contrast, during preeclamptic gestation, the left ventricle hypertrophies concentrically, concurrent with loss in circulatory volume and increased blood pressure. Concentric cardiac structure persists in a substantial proportion of women and may be associated with pressure and volume load after preeclampsia. We hypothesize that low volume load, as indicated by plasma volume (PV) after preeclampsia and increased pressure load, is associated with remote concentric remodeling.

METHODS AND RESULTS: In this longitudinal cohort study, we included 100 formerly preeclamptic women. Two visits were performed: at 0.8 years postpartum and at 4.8 years postpartum. During visit 1, we measured blood pressure and PV (I^{125} dilution technique, low PV ≤48 mL/kg lean body mass). During the second visit, we assessed cardiac geometry by cardiac ultrasound. Concentric remodeling was defined as relative wall thickness >0.42 and left ventricular mass index ≤95 g/m^2. We adjusted multivariable analysis for primiparity, systolic blood pressure, PV mL/kg lean body mass, and antihypertensive medication at visit 1. Low PV is associated with remote concentric remodeling (odds ratio [OR], 4.37; 95% CI, 1.06–17.40; and adjusted OR, 4.67; 95% CI, 1.02–21.42). Arterial pressure load (systolic, diastolic, and mean arterial pressure) is also associated with development of concentric remodeling (OR, 1.15 [95% CI, 0.99–1.35]; OR, 1.24 [95% CI, 0.98–1.58]; and OR, 1.20 [95% CI, 0.98–1.47], respectively).

CONCLUSIONS: In former preeclamptic women, development toward left ventricular concentric remodeling is associated with low volume load and increased pressure load.

Key Words: blood pressure ■ concentric remodeling ■ echocardiography ■ plasma volume ■ preeclampsia

Preeclampsia, a gestational hypertensive disease, is characterized by new-onset hypertension and proteinuria, and complicates 3% to 5% of all pregnancies.[1] Preeclampsia is associated with a 2- to 7-fold increased risk for cardiovascular disease (CVD) within 15 years after pregnancy and has been recognized as an important women-specific CVD risk factor.[2,3]

Preeclampsia and CVD share many classic risk factors, such as hypertension, hyperinsulinemia, obesity, and dyslipidemia.[4–6] The elevated risk for CVD after preeclampsia may in part relate to abnormal cardiovascular risk profiles in these women, but may also partly be contributed to differences in patterns of cardiac remodeling during pregnancy and incomplete cardiac recovery afterwards.[7–10] During normotensive

Correspondence to: Nicolette M. Breetveld, MD, Department of Obstetrics and Gynecology, P. Debyelaan 25, 6229 HX Maastricht, PO Box 5800, 6202 AZ Maastricht, the Netherlands. E-mail: n.breetveld@alumni.maastrichtuniversity.nl

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CLINICAL PERSPECTIVE

What Is New?

- In former preeclamptic women, concentric remodeling is associated with low volume load and increased pressure load.

What Are the Clinical Implications?

- Women with a preeclamptic pregnancy in their history and clinicians should be aware of the increased risk for cardiovascular disease, where a careful follow-up is important.
- Moreover, more attention is needed for the association between low plasma volume and increased pressure load on the one hand and on the other hand concentric remodeling.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
DBP	diastolic blood pressure
LBM	lean body mass
LV	left ventricle
LVEDd	left ventricular end-diastolic diameter
MAP	mean arterial pressure
OR	odds ratio
PV	plasma volume
SBP	systolic blood pressure
TPVR	total peripheral vascular resistance

pregnancies, the left ventricle (LV) remodels in an eccentric way, whereas during preeclampsia, the LV remodels in an aberrant concentric way, which remains present in 11% to 26% of affected women in the first decade after delivery.[11–13] Eccentric cardiac remodeling during normal pregnancy is viewed as a physiologically reversible phenomenon as a response to decreased gestational pressure load along with concomitant increased volume load.[12,14,15] Concentric remodeling during preeclamptic gestation may be the result of increased pressure load along with lower volume load.[16]

In hypertensive individuals, concentric remodeling, among other forms of remodeling, was significantly associated with more CVD and death.[17,18] Interestingly, compared with eccentric remodeling, concentric remodeling is associated with cardiac fibrosis and this stiffened cardiac concentric condition is associated with a 4-fold risk of subsequent cardiovascular events.[17,19] Concentric remodeling is thought to be an important step in the progression from asymptomatic heart disease to symptomatic heart failure, often in response to chronic pressure overload.[16]

After preeclamptic pregnancy, many women continue to have persistently higher blood pressure and decreased plasma volume (PV) compared with healthy parous women.[7–9,20,21] It is not known to what extent both pressure load and volume load shortly after delivery are associated with persistent or de novo concentric remodeling in the following decade. Cardiac remodeling is a dynamic and progressive process, susceptible to pressure and volume modulating medication.[22–26] Better insight in the system biology of concentric remodeling is of clinical value to predict the possible effect of modulating pressure and volume load, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, on reversibility of concentric remodeling in these women to decrease their cardiovascular risk.[24–26] This is of importance because the LV continues to remodel when the stressor persists.[27] Therefore, we performed, in former preeclamptic women, a longitudinal study to evaluate whether pressure and/or volume load, assessed shortly after delivery, is associated with concentric remodeling in the following decade. We hypothesize that low PV after preeclampsia and increased pressure load are associated with concentric remodeling in the subsequent years.

METHODS

The Medical Ethics Committee of the Radboud University Medical Center (NL32718.091.10) approved the protocol of this explorative longitudinal cohort study. Before participation, all subjects provided written informed consent. The followed procedures were in conformity with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulation, Part 46, Protection of Human Subjects, revised November 13, 2001, effective December 13, 2001. We invited women who previously had a clinical cardiovascular risk assessment following a pregnancy complicated by preeclampsia for a second follow-up screening between 2009 and 2011. While the data and materials have not been made publicly available, they are available from the authors upon reasonable request.

Study Population

Formerly preeclamptic women were recruited at their routine 6-week postpartum medical appointment and were asked to participate in the first cardiovascular screening assessment, at a median interval of 0.8 years postpartum. They underwent blood pressure measurements and PV measurements. A second visit was planned at 4.8 years postpartum.

During this second cardiovascular evaluation, we performed blood pressure measurements and cardiac ultrasound (Figure). Inclusion criteria were women with a history of preeclampsia, not pregnant, not breastfeeding, and not using oral contraceptives. Women who had become pregnant again after their index pregnancy had to be at least 6 months postpartum for their second measurement. Exclusion criterion was preexisting comorbidity (diabetes mellitus, autoimmune diseases, or preexisting hypertension) before their index pregnancy. Other exclusion criteria were an unsuccessful PV measurement at visit 1, inadequate cardiac ultrasound at visit 2, or both. All subjects were recruited from the eastern region of the Netherlands, a region with an average socioeconomic status. Preeclampsia was diagnosed according to the International Society of Hypertension in Pregnancy criteria as new-onset hypertension (systolic blood pressure [SBP] ≥140 mm Hg, diastolic blood pressure [DBP] ≥90 mm Hg, or both) after 20 weeks of gestation and proteinuria >0.3 g/d.[28] Early-onset preeclampsia was defined as preeclampsia developing at <34 weeks of gestation. Preterm preeclampsia was defined as preeclampsia requiring delivery before 37 weeks of gestation. Small-for-gestational age was defined as a birth weight ≤10th percentile, based on the Dutch reference curves.[29] Four women gave birth to twins. All birth weights were analyzed in our analysis.

First Visit: Cardiovascular Assessment

The first visit consisted of the standard cardiovascular assessment, which is embedded in standard clinical care. The examinations started at 8:00 AM in a temperature-controlled room (22°C) after an overnight fast. Body weight (kg; Seca 888, Hamburg, Germany) and height (m) were measured to calculate body mass index. Body mass index ≥30 kg/m^2 was defined as obesity. After at least 15 minutes of acclimatization, SBP, DBP, and mean arterial pressure (MAP) were measured for 30 minutes (at a 3-minute interval) in upright sitting position, using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL). The cuff size was appropriate for arm circumference. We used the median values for statistical analysis. During the 30-minute blood pressure measurement, participants were not allowed to talk and external disturbances were minimalized. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or the use of antihypertensive medication. Prehypertension was defined as SBP ranging from 120 to 139 mm Hg and/or DBP ranging from 80 to 89 mm Hg. Participants were asked to

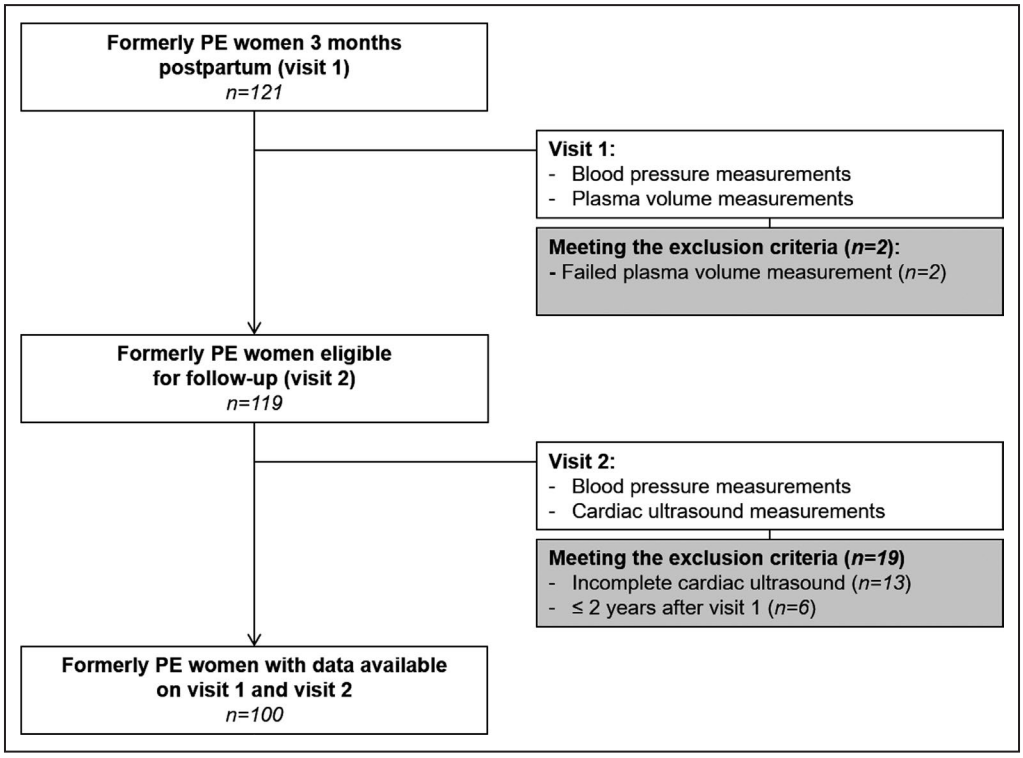

Figure. Flowchart of included formerly preeclamptic (PE) women in our explorative longitudinal cohort study.

complete a questionnaire at both visits consisting of general history, current medication intake, intoxications (smoking is defined as ≥1 cigarette a day), lifestyle factors, and family history for CVD (in first-line relatives aged <60 years).

During the first visit, PV was measured using the iodine^{125} albumin indicator dilution technique (iodine^{125} human serum albumin), as described elsewhere and indexed for body mass (lean body mass [LBM]).[30–32] LBM was calculated using the formula[32,33]:

$$\text{LBM} = \text{Body mass} - ((1.20 \times \text{BMI}) + (0.23 \times \text{age}) - 5.4) \times \text{body mass}/100.$$

Body mass index is calculated as weight (in kilograms) divided by height (in meters squared). Normal PV was defined as a PV index >48 mL/kg LBM, and we consider a low PV as a PV index ≤48 mL/kg LBM.[21,34]

Second Visit: Follow-Up Cardiovascular Assessment

At the second visit, we performed the same protocol to determine blood pressure and performed cardiac ultrasound to determine cardiac structure and function. Echocardiographic measurements were obtained using a phased array echocardiographic Doppler ultrasound system (ViVid 7; GE Vingmed Ultrasound, Horten, Norway). The assessments were performed offline using EchoPAC PC SW Vingmed Ultrasound, Version 6.1.2. We performed 2-dimensional, M-mode, and Doppler echocardiography according to the guidelines of the American Society of Echocardiography.[35] Using M mode in the parasternal long-axis view, we measured left ventricular end-diastolic diameter (LVEDd, in mm) and left ventricular end-systolic diameter (LVESd, in mm), as well as end-diastolic interventricular septal thickness (in mm) and posterior wall thickness (in mm). Left ventricular mass (in g) was calculated using the formula=0.8×(1.04 ((LVEDd+posterior wall thickness+interventricular septal thickness)^3–(LVEDd)^3))+0.6 and indexed for body surface area (left ventricular mass index), as recommended by the American Society of Echocardiography.[36] The relative wall thickness was calculated using the formula relative wall thickness=2×posterior wall thickness/LVEDd, as recommended by the American Society of Echocardiography.[36] Left ventricular end-diastolic volume (in mL) and end-systolic volume (in mL) were estimated using the Teichholz formula.[37] Left ventricular ejection fraction (%) was calculated by [(left ventricular end-diastolic volume–left ventricular end-systolic volume)/(left ventricular end-diastolic volume)]×100.

Heart rate (in beats per minute) was obtained by calculating the reciprocal of the mean of 5 consecutive RR intervals on the ECG multiplied by 60. We estimated the mean aortic velocity time integral by averaging the outer edge tracings of 5 consecutive continuous-wave Doppler recordings of the LV outflow tract velocity. By taking the product of velocity time integral and the midsystolic cross-sectional area at the level of the LV outflow tract in the parasternal long-axis view, we obtained stroke volume (in mL). Cardiac output (in L/min) was obtained by multiplying stroke volume by heart rate. Cardiac index was calculated as cardiac index=cardiac output/body surface area. Total peripheral vascular resistance (TPVR; in dyn·s·cm^{-5}) was obtained using the formula TPVR=80×MAP (in mm Hg)/cardiac output.[20] Total peripheral vascular resistance index, normalized for body surface area, was calculated as TPVR=80×MAP (in mm Hg)/cardiac index.[20]

Left ventricular hypertrophy was defined as left ventricular mass index >95 g/m^2, concentric remodeling was defined as relative wall thickness >0.42 and left ventricular mass index ≤95 g/m^2, and mildly impaired left ventricular ejection fraction was defined as left ventricular ejection fraction >40% and <55%.[36] We defined asymptomatic valvular disease as mild aortic valve insufficiency, mild thickening of mitral valve, or central aortic valve insufficiency.

Statistical Analysis

For all statistical analyses, we used SPSS version 21.0 (IBM SPSS Statistics, Armonk NY) and R version 3.6.1. Data are expressed as mean with SD for continuous variables and number with percentage for dichotomous variables. Postpartum intervals were reported as median with interquartile range. We used the independent *t* test to test for group differences of continuous variables. Differences in proportions between groups were tested using the χ^2 test if at least 5 cases were present in each category and the Fisher exact test if one of the categories contained <5 cases. Postpartum intervals were analyzed using the Mann-Whitney *U* test for intergroup differences. A logistic regression was performed to test the associations between both volume load and pressure load at the first visit with the presence of concentric remodeling at the second visit. We selected potential confounders based on clinical reasoning, as opposed to statistical significance. Using multivariable logistic regression, we adjusted the associations for primiparity, antihypertensive medication, and either SBP or PV mL/kg LBM, dependent on the variable to be tested. Logistic regression with the Firth correction was used as the number of events was limited. Results were reported as odds ratio (OR) and 95% CI, computed using the profile penalized log likelihood. *P*

Table 1. Patient Characteristics at Visits 1 and 2 in Former Preeclamptic Women With and Without Concentric Remodeling Defined at Visit 2

Characteristic	Concentric Remodeling (n=18)	No Concentric Remodeling (n=82)	*P* Value
Index pregnancy			
Early-onset preeclampsia, n (%)	11/15 (73)	50/80 (63)	0.42
Preterm preeclampsia, n (%)	13/18 (72)	62/82 (76)	0.77
Primiparous at 0.8 y, n (%)	8/18 (44)	67/82 (82)	<0.01
Primiparous at 4.8 y, n (%)	3/18 (17)	21/82 (26)	0.55
Parity at 0.8 y	1.7±0.7	1.2±0.6	<0.05
Parity at 4.8 y	2.2±0.7	1.9±0.7	0.16
GA at birth, wk	33±5	34±4	0.55
Birth weight, g	1717±1086	1868±942	0.55
SGA neonate, n (%)	10/18 (56)	31/82 (38)	0.17
IUFD, n (%)	4/18 (22)	6/81 (7)	0.08
Follow-up pregnancy, n (%)	11/18 (61)	57/82 (70)	0.49
Recurrent preeclampsia, n (%)	5/11 (45)	18/57 (32)	0.49
Patient characteristics at visit 1			
Postpartum, median (IQR), y	1.3 (0.5–2.6)	0.7 (0.5–1.9)	0.31
Age, y	32±5	33±4	0.34
Weight, kg	76±13	71±19	0.27
BMI, kg/m^2	26.5±3.2	24.8±6.4	0.28
Obesity, BMI ≥30 kg/m^2, n (%)	4/18 (22)	11/82 (13)	0.46
Smoking, n (%)	1/18 (6)	4/82 (5)	1.00
Alcohol, n (%)	2/18 (11)	13/82 (16)	1.00
Family history of CVD, n (%)	9/18 (50)	27/82 (33)	0.17
Antihypertensive treatment, n (%)	4/18 (22)	14/81 (17)	0.74
Patient characteristics at visit 2			
Postpartum, median (IQR), y	5.7 (4.3–6.9)	4.8 (4.1–6.1)	0.30
Age, y	35±5	36±4	0.36
Weight, kg	79±15	72±18	0.19
BMI, kg/m^2	27.2±3.8	25.3±6.3	0.21
Obesity, BMI ≥30 kg/m^2, n (%)	6/18 (33)	12/82 (15)	0.09
Smoking, n (%)	1/18 (6)	6/82 (7)	1.00
Alcohol, n (%)	2/18 (11)	22/82 (27)	0.23
Family history of CVD, n (%)	11/18 (61)	43/82 (52)	0.50
Antihypertensive treatment, n (%)	6/18 (33)	14/82 (17)	0.19

Data are presented as mean±SD or number/total (percentage). BMI indicates body mass index; CVD, cardiovascular disease; GA, gestational age; IQR, interquartile range; IUFD, intrauterine fetal death; and SGA, small-for-gestational age.

values were computed using the likelihood ratio test. A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

We included 121 formerly preeclamptic women in our longitudinal cohort study who had their first visit at a median interval of 0.8 years postpartum and their second visit at a median interval of 4.8 years postpartum. At visit 1, 2 women were excluded because of a failed PV measurement. At visit 2, when we examined blood pressure and cardiac ultrasound, 19 women were excluded: 13 because of an incomplete cardiac ultrasound evaluation and 6 because of a time interval of ≤2 years between both visits (Figure). Ultimately, 100 women met our criteria for both visits. The included patients (n=100) differed from the excluded patients (n=21) by having had more often a follow-up pregnancy (68% versus 38%; $P<0.05$) and a lower prevalence of smoking at visit 1 (5% versus 24%; $P<0.05$). All the included participants, except for 2, were White. One woman was of Turkish ancestry, and one woman was of Moroccan ancestry.

Of the 100 women eligible for our statistical analysis, 18 (18%) showed concentric remodeling at 4.8 years

Table 2. Hemodynamics and Volume Load at Visit 1 in Former Preeclamptic Women

Variable	Concentric Remodeling (n=18)	No Concentric Remodeling (n=82)	*P* Value
Hemodynamics			
SBP, mm Hg	126±17	119±15	0.06
DBP, mm Hg	74±12	69±10	0.07
MAP, mm Hg	92±13	86±12	0.08
HR, bpm	69±7	69±11	0.93
TPVR, $\times 10^3$ dyn·s·cm^{-5}	1.3±0.4	1.5±0.4	<0.05
TPVR index, $\times 10^3$ dyn·s·cm^{-5}	2.5±0.8	2.8±0.7	0.13
Prehypertension, n (%)	5/18 (28)	15/82 (18)	0.35
Hypertension, n (%)	6/18 (33)	20/82 (24)	0.55
Hypertension untreated, n (%)	2/18 (11)	6/82 (7)	0.63
PV			
PV mL/kg LBM	54±6	59±7	<0.05
Low PV, n (%)†	4/18 (22)	5/82 (6)	0.05

The group is subdivided in women with concentric remodeling and no concentric remodeling defined at visit 2 in formerly preeclamptic women. Data are presented as mean±SD or number/total (percentage). Bpm indicates beats per minute; DBP, diastolic blood pressure; HR, heart rate; LBM, lean body mass; MAP, mean arterial pressure; PV, plasma volume; SBP, systolic blood pressure; and TPVR, total peripheral vascular resistance.

†Low PV mL kg/LBM is defined as PV index ≤48 mL/kg LBM.

postpartum, whereas 82 (82%) had no concentric remodeling. Among the 18 women with concentric remodeling, 1 (6%) had asymptomatic valve disease (mild aortic valve regurgitation) and none had reduced left ventricular ejection fraction. In the no concentric remodeling group, 2 women (2%) had asymptomatic valve disease (1 woman with mild mitral valve regurgitations with mild thickening of mitral valve and 1 woman with mild aortic valve regurgitation) and 6 women (7%) had mildly impaired left ventricular ejection fraction.

Table 1 demonstrates the baseline characteristics of both groups. There were no statistically significant differences in obstetrical characteristics between both groups, except less women were primiparous at the first visit in the subsequently concentric remodeling group (44%) compared with the no concentric remodeling group at follow-up (82%). There were no statistically significant differences in age, weight, body mass index, obesity, smoking, alcohol consumption, family history of CVD, antihypertensive treatment, and postpartum interval between both groups at 0.8 and subsequent 4.8 years postpartum.

Concentric Remodeling Versus No Concentric Remodeling

Table 2 presents the hemodynamic indexes, measured at the first evaluation after index pregnancy (median, 0.8 years postpartum; interquartile range, 0.5–2.1 years postpartum). There were no statistically significant differences in SBP, DBP, and MAP between the groups. Heart rate did not differ between the concentric remodeling group and no concentric remodeling group. TPVR was significantly lower in the concentric remodeling group at follow-up compared with the no concentric remodeling group. TPVR index, prehypertension, hypertension, and untreated hypertension were comparable between both groups. PV was lower in the concentric remodeling group at follow-up compared with the no concentric remodeling group (54±6 versus 59±7 mL/kg LBM; $P<0.05$). Consequently, the concentric remodeling group seemed to have more often low PV (≤48 mL/kg LBM) compared with the no concentric remodeling group (22% versus 6%; $P=0.05$).

Table 3 demonstrates the ORs on concentric remodeling of volume and pressure load measured at visit 1. PV mL/kg LBM at the first evaluation associates inversely with remote concentric remodeling (OR, 0.91; 95% CI, 0.84–0.99), and remained so after adjustments for SBP, primiparity, and antihypertensive treatment measured at visit 1 (adjusted OR, 0.91; 95%

Table 3. Volume and Pressure Load at Visit 1 in Former Preeclamptic Women With the OR on Remote Concentric Remodeling Defined at Visit 2

Variable	Crude OR (95% CI)	*P* Value Crude OR	Adjusted OR (95% CI)	*P* Value Adjusted OR
PV				
PV mL/kg LBM	0.91 (0.84–0.99)	<0.05	0.91 (0.82–0.99)*	<0.05
Low PV†	4.37 (1.06–17.40)	<0.01	4.67 (1.02–21.42)*	<0.05
Pressure load				
SBP (per 5 mm Hg)	1.15 (0.99–1.35)	0.07	1.08 (0.90–1.29)‡	0.39
DBP (per 5 mm Hg)	1.24 (0.98–1.58)	0.08	1.12 (0.85–1.50)‡	0.41
MAP (per 5 mm Hg)	1.20 (0.98–1.47)	0.08	1.12 (0.89–1.42)‡	0.34

DBP indicates diastolic blood pressure; LBM, lean body mass; MAP, mean arterial pressure; OR, odds ratio; PV, plasma volume; and SBP, systolic blood pressure.

*Adjusted for SBP, primiparity, and antihypertensive treatment, measured at visit 1.

†Low PV mL/kg LBM is defined as PV ≤48 mL/kg LBM.

‡Adjusted for PV mL/kg LBM, primiparity, and antihypertensive treatment, measured at visit 1.

Table 4. Hemodynamic and Cardiac Indexes at Visit 2 in Former Preeclamptic Women With and Without Concentric Remodeling Defined at Visit 2

Variable	Concentric Remodeling (n=18)	No Concentric Remodeling (n=82)	*P* Value
Hemodynamics			
SBP, mm Hg	123±11	116±13	0.06
DBP, mm Hg	79±9	72±10	<0.05
MAP, mm Hg	91±10	86±11	0.08
HR, bpm	66±9	66±11	0.93
TPVR, $\times 10^3$ dyn·s·cm^{-5}	1.4±0.3	1.4±0.3	0.93
TPVR index, $\times 10^3$ dyn·s·cm^{-5}	2.6±0.5	2.5±0.6	0.50
Prehypertension, n (%)	7/18 (39)	13/82 (16)	<0.05
Hypertension, n (%)	6/18 (33)	19/82 (23)	0.38
Hypertension untreated, n (%)	0/18 (0)	5/82 (6)	0.58
Cardiac measurements			
RWT	0.46±0.03	0.32±0.05	<0.01
LVM, g	120±29	107±28	0.09
LVM index, g/m^2	63±12	58±13	0.16
SV, mL	82±17	80±18	0.65
CO, L/min	5.4±1.0	5.2±1.1	0.46
CI, L/min per m^2	2.8±0.4	2.8±0.6	0.99
LVEF, %	63±5	63±6	0.94
LVEDd, cm	4.1±0.3	4.6±0.4	<0.01
LVEDd index, cm/m^2	2.2±0.2	2.5±0.2	<0.01
LVESd, cm	2.6±0.4	2.9±0.4	<0.05
IVST, cm	0.87±0.12	0.73±0.16	<0.01
PWT, cm	0.95±0.09	0.74±0.12	<0.01
LAD, cm	3.6±0.5	3.5±0.5	0.60

Data are presented as mean±SD or number/total (percentage). Bpm indicates beats per minute; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; IVST, interventricular septal thickness; LAD, left atrium diameter; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; LVM, left ventricular mass; MAP, mean arterial pressure; PWT, posterior wall thickness; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; and TPVR, total peripheral vascular resistance.

CI, 0.82–0.99). Moreover, low PV was associated with concentric remodeling at follow-up (OR, 4.37; 95% CI, 1.06–17.40), also after adjustments (adjusted OR, 4.67; 95% CI, 1.02–21.42). Arterial pressure load is associated with the risk development of concentric remodeling at follow-up, but part of this effect seemed to originate from concurrent decrease in volume load, as after correction the effect of pressure load on the concentric cardiac phenotype was less.

Table 4 shows the hemodynamic and cardiac measurements at visit 2 (median, 4.8 years postpartum; interquartile range, 4.2–6.4 years postpartum) in both groups. The concentric remodeling group differed from the no concentric remodeling group by having a higher DBP. Moreover, SBP and MAP showed a trend toward significance, with a higher blood pressure in the concentric remodeling group compared with the no concentric remodeling group. Heart rate, TPVR, and TPVR index were comparable between the 2 groups. Prehypertension was more prevalent in the concentric remodeling group (39%) compared with the no concentric remodeling group (16%). The presence of hypertension and untreated hypertension did not differ between both groups. Of the cardiac measurements, relative wall thickness, interventricular septal thickness, and posterior wall thickness were higher in women with concentric remodeling, whereas LVEDd, LVEDd index, and LVESd were lower in the concentric remodeling group.

DISCUSSION

In this current explorative longitudinal cohort study, we observed that low volume load, as indicated by PV and increased pressure load in the first year after preeclamptic gestation, relates to an increased risk to develop later concentric cardiac remodeling.

Formerly preeclamptic women have an increased risk for CVD and share cardiovascular risk factors that may, at least in part, explain the relation between both diseases.[3–6,38] Besides the elevated prevalence of common CVD risk factors, which mostly predispose to macrovascular disease, the concentric cardiac adaptation to hypertensive complicated pregnancy may play an (additional) role in the associated elevated remote risk for CVD, especially when the additional increase in LV mass in women with preeclampsia does not resolve after delivery.[7–11] In the first decade after delivery, 25% of formerly preeclamptic women have structural or functional cardiac abnormalities, consistent with asymptomatic heart failure stage B, mostly along with a concentric phenotype.[11,13,39] This type of heart failure is thought to originate from a systemic proinflammatory state with the involvement of microvascular endothelial inflammation.[40] Both traditional cardiovascular risk factors and incomplete deconditioning from the vascular complicated pregnancy are thought to contribute to the increased risk of future heart failure.[41,42] It is believed that this increased risk is susceptible to preventive intervention while the disease is still in a preclinical stage.

Structural cardiac remodeling is an important compensatory mechanism to maintain the pumping capacity of the heart in response to alterations in either volume or pressure load.[16,43] Volume- and pressure load–induced stimuli induce various signaling pathways, leading to a hypertrophic response of the cardiomyocytes.[44,45] This induces eccentric cardiac hypertrophy with concomitant widening of the ventricle in uncomplicated normotensive pregnancies or concentric adjustments with relative loss of

ventricular volume when facing muscular hypertrophy in hypertensive pregnancies.[16,44,45] Cardiac myocyte hypertrophy is dose dependently associated with increased circulatory load. On the one hand, the difference in concentric or eccentric cardiac adaptation in our cohort is associated more to volume load than pressure load, in which each additional mL/kg LBM PV lowered the odds on concentric cardiac phenotype. On the other hand, the contribution of blood pressure should not be underestimated as we observed that blood pressure seems to be associated with the odds on concentric remodeling at follow-up. Nonetheless, when correcting for low volume load, part of the effect of pressure load on concentric remodeling at follow-up disappeared, suggesting that part of the effects that are associated with pressure load could originate from volume load. At any rate, both volume and pressure load affected the development toward concentric cardiac remodeling in a dose-dependent manner.

Given the large prevalence of persistent or de novo elevated blood pressure in formerly preeclamptic women, especially in women with low PV, low volume status may be an alarming characteristic, even in apparently healthy normotensive formerly preeclamptic women.[30,46]

Clinically, in normotensive formerly preeclamptic women, on the one hand, prepregnancy low PV is associated with recurrent hypertensive complicated pregnancy, growth restriction, and preterm birth and, on the other hand, low PV is associated with remote hypertension within the first decade after the hypertensive index pregnancy.[30,47] PV is considered to mirror cardiovascular reserve capacity in case of healthy cardiac functioning.[47] A total of 65% to 75% of the blood volume is localized in the venous system and can be mobilized in times of increased arterial demand, as in pregnancy or during exercise.[48–50] PV can be fundamentally diminished, either genetically or secondary to a structurally small venous compartment, in line with the fetal origin of adult disease complex (Barkers hypothesis).[47,51,52] Alternatively, low PV status may result from a functionally more constricted venous system diminishing venous dimensions and (resting) elastic properties of the venous wall and with it decreasing the venous capacitance as part of sympathetic overactivity, such as seen in obesity or the metabolic syndrome.[30,49,53] Given the commonly present low PV status in formerly preeclamptic women and the increased tendency to develop chronic hypertension, one could anticipate on a synergistic detrimental effect of volume and pressure load on concentric cardiac remodeling in these women while aging.[7–9,20,21] From this perspective, close monitoring of blood pressure and timely intervention with blood pressure–modulating medication, not only capable in lowering pressure load but also increasing volume load, may be most promising in the effective and preventive treatment of concentric remodeling. Along these lines, as such, diuretics as primary treatment option for hypertension in these women should not be advisable.

Limitations

There are a few limitations in this study. First, most women in our study were White. Therefore, our study results might not be entirely generalized to other populations. Second, although we adjusted for the use of antihypertensive medication in our analysis, we cannot completely exclude the effect of antihypertensive drugs at the time of the measurements, as cardiac remodeling also independently results from other biochemical factors apart from blood pressure and PV. Third, the observational nature of our study and the lack of a matched control group do not allow us to conclude whether the relationship between volume status and persistence of concentric remodeling is causal or not and to evaluate the potential effect of complicated or uncomplicated pregnancy itself on cardiac changes in time. Therefore, additional studies confirming our findings are needed.

CONCLUSIONS

Of 6 formerly preeclamptic women, 1 has a concentric remodeled LV 4.8 years after gestation. In these women, concentric remodeling is associated with low volume load and increased pressure load.

PERSPECTIVES

Recognizing the role of diminished volume load along with elevated blood pressure, even without reaching the threshold of overt hypertension, may help in the clinical fine-tuning of preventive measures in these women to prevent the development of heart failure.

ARTICLE INFORMATION

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Affiliations

From Department of Obstetrics and Gynecology, Research School Grow, Maastricht University Medical Center (MUMC), Maastricht (N.M.B., R.J.A., L.G, J.v.N., C.G.-D., M.E.A.S.); Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center (MUMC), Maastricht (S.M.J.v.K.); Department of Cardiology, Radboud University Medical Center (Radboudumc), Nijmegen (A.P.v.D., M.J.v.d.V.); Department of Obstetrics and Gynecology, Radboud University Medical Center (Radboudumc), Nijmegen (W.M.H., R.R.S.); Department of Cardiology, Maastricht University Medical Center (MUMC), Maastricht, The Netherlands (V.P.M.v.E., H.-P.B.-L.R).

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