Aerobic Exercise Training in Formerly Preeclamptic Women

Effects on Venous Reserve

Ralph R. Scholten, Maria T.E. Hopman, Fred K. Lotgering, Marc E.A. Spaanderman

Abstract—In women with a history of preeclampsia, low plasma volume (≤1373 mL/m²) is associated with recurrent preeclampsia and chronic hypertension. Interventions that improve volume reserve may reduce these risks in formerly preeclamptic women. In this study, we examined the effects of aerobic exercise training on venous reserves in 24 normotensive formerly preeclamptic women and 20 controls. Before and after 12-week aerobic exercise training, we measured plasma volume with albumin indicator dilution technique and venous compliance with venous occlusion plethysmography. Venous compliance and hemodynamic responses were assessed dynamically during graded head-up tilt (HUT). Formerly preeclamptic women had lower pretraining plasma volume and venous compliance than controls (1348±78 versus 1529±112 mL/m²; P<0.01 and 0.04±0.02 versus 0.07±0.01 mL-dL⁻¹·mmHg⁻¹; P<0.01, respectively). Blood pressure decreased comparably between groups in response to HUT (P=0.11); the increase in heart rate in response to HUT was however more pronounced in preeclamptic women than in controls (P=0.01) Training increased plasma volume comparably in both groups (+180 versus +135 mL/m², P=0.22) and similarly physical fitness (+3.4 and +3.7 mL·min⁻¹·kg⁻¹, P=0.43). Venous compliance increased twice as much in formerly preeclamptic women than in controls (supine +0.02 versus +0.01 mL-dL⁻¹·mmHg⁻¹; P<0.01). After training, HUT decreased mean blood pressure comparable with pretraining responses in both groups, whereas both groups fulfilled the HUT testing at a persistently lower heart rate. These results demonstrate that 12 weeks of aerobic exercise training improve venous reserve in postpartum women. Training normalized plasma volume and venous compliance in formerly preeclamptic women to pretraining levels of controls.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00900458.

Key Words: exercise ■ blood volume ■ blood pressure ■ hypertension ■ pre-eclampsia

Women with a history of preeclampsia are at increased risk of recurrent gestational hypertensive disease and cardiovascular disease later in life.1,2 Fifty percent of formerly preeclamptic women (formerly PE women) have low plasma volume (PV)3 and the recurrence risk of preeclampsia varies inversely with PV. In pregnancy, a marked PV expansion (+30% to 60%) is required to meet the physiological demands of advanced pregnancy.5,6 Formerly PE women with low PV show reduced PV expansion in pregnancy, which suggests that the adaptive capacity of the venous system in these women is limited.7 When PV expansion cannot meet the physiological demands, the circulation may compensate for it by an increase in sympathetic activity.7 The resulting low-volume high-output circulation will exert extra shear stress on the endothelium.5,7 This may set the stage for endothelial dysfunction, vascular damage, and hypertensive disease in pregnancy and later in life.

The venous compartment is the most prominent blood volume reservoir of the body. Although at rest two-thirds of PV is localized in the venous system, it can be rapidly mobilized by sympathetic-mediated venoconstriction in times of increased arterial demands, including pregnancy and exercise.8,9 Venous capacity is largely determined by venous compliance (VeC) and varies dynamically with sympathetic tone predominantly controlled by the baroreflex system.8 Dynamic changes in VeC can be tested through orthostatic stress testing. Previous studies demonstrated that formerly PE women at rest have low venous reserve, characterized by low PV, low VeC, and high sympathetic tone.10

Aerobic exercise is perhaps the best intervention to improve venous reserve. It increases PV and reduces sympathetic tone in healthy individuals.11,12 In formerly PE women with low PV, aerobic exercise training could help to normalize venous reserve and thereby reduce the risk of hypertensive disease in future pregnancy and later in life. The extent to which formerly PE women are able to improve their venous reserve by exercise training is unknown. Our study addresses the question to what extent an aerobic exercise training program...
(12 weeks of cycling at 70% to 80% VO\textsubscript{max}, 2–3 times per week) can improve venous reserve in formerly PE women compared with parous controls. Based on the observation that formerly PE women demonstrate reduced PV expansion in pregnancy, we hypothesized that formerly PE women may be less able to increase venous reserve in response to exercise training compared with parous controls.

### Methods

#### Subjects

We recruited 25 normotensive formerly PE women and 22 controls. Primiparous formerly PE women were recruited during their postpartum checkup at the Radboudumc, controls from the community by advertisement. Preeclampsia in prior pregnancy was defined by the combination of gestational hypertension (≥140/90 mmHg, measured twice, 6 hours or more apart) and proteinuria (consistently ≥300 mg/24 h) after 20 weeks of pregnancy in previously normotensive women. Controls were healthy primiparous women; their pregnancy charts were checked to ensure that the preceding pregnancy had been normal. All participants were white women, healthy and normotensive at the time of measurements. None had diabetes mellitus, autoimmune disease, or overt cardiovascular disease. None of the women smoked or used medication or supplements that might affect the cardiovascular system, and none of the women included were pregnant, breastfeeding, or using hormonal contraceptives. Excluded from analysis were women who became pregnant during the course of training and women who did not finish the exercise protocol. The study was approved by the Medical Ethics Committee of the Radboudumc (CMO: 2008/226). All participants gave written informed consent before entering the study.

#### Experimental Design

Measurements and training were performed in the nonpregnant state, 6 to 12 months after pregnancy to allow for cardiovascular recovery. Subjects were tested before and after 12 weeks of the exercise training. All measurements, except VO\textsubscript{max} testing, were performed during the same visit. VO\textsubscript{max} was tested 1 to 5 days from the other visit. In sequential order, we measured body characteristics, resting blood pressure, cardiac output, PV, and venous and hemodynamic responsiveness during head-up tilt (HUT). This study protocol is part of a more extensive protocol that also involves functional arterial measurements. Results of the arterial measurements are published elsewhere.

#### Experimental Procedures

Tests and measurements were performed between day 3 and 11 of the menstrual cycle to minimize possible endocrine influences of the sex hormones on the cardiovascular and autonomic nervous system. All measurements except VO\textsubscript{max} were performed after an overnight fast. Participants were instructed to abstain from strenuous physical activity in the 24 hours before testing. Participants collected urine in the 24 hours preceding the measurements. The 24-hour urine sample was assayed for albumin, protein, and creatinine to define the (micro) albuminuria corrected for creatinine output (g/mol creatinine) and total protein level (g/24 h; Aeroset, Abbott Laboratories, IL).

Tests were performed under standardized conditions in a temperature-controlled room (22±0.5°C). Measurements were performed at the same time in the morning to prevent diurnal variation. After 30-minute rest in supine position, blood pressure and heart rate (HR) were measured oscillometrically (Dinamap, Vital Signs Monitor 1846, Critikon, Tampa, FL) in the upright sitting position, at the right upper arm, with the cuff size recommended for the arm circumference, at 3-minute interval for 30 minutes. We recorded systolic (mmHg), diastolic (mmHg), and mean (MAP, mmHg) arterial pressures and HR (bpm) and used the median values of 9 consecutive measurements for analysis. Cardiac output (L/min) was measured in the left lateral position using a validated, noninvasive, inert gas rebreathing method (Innovation, Copenhagen) as detailed elsewhere. Stroke volume (mL) was calculated as cardiac output/HR. Venous blood samples were taken from the antecubital vein and analyzed for creatinine concentration (Aeroset, Abbott Laboratories, IL).

#### Plasma Volume

PV (mL) was measured using the iodine\textsuperscript{125} albumin indicator dilution technique (\textsuperscript{125}I-HSA). During the measurement, women were in semisupine position on a comfortable bed. An 18-gauge intravenous catheter was inserted in the left antecubital vein for repetitive blood sampling. A standardized dose (0.2 MBq) of labeled human serum albumin was injected intravenously in the right antecubital vein. Every 10 minutes a venous blood sample was taken from the contralateral intravenous catheter until 40 minutes after administration of the labeled human serum albumin. Blood samples were analyzed using a gamma counter. PV was calculated by dividing the total injected radioactivity by the virtual volume–specific radioactivity at time 0, as described elsewhere. PV was normalized for body surface area (PV, mL/m\textsuperscript{2}). Low PV was defined as PV≤1373 mL/m\textsuperscript{2}. The technician who measured PV was unaware of the medical history of participants.

#### HUT Test

HUT was performed after voiding the bladder and executed under standardized environmental conditions in a quiet and partially darkened room. Subjects were positioned on the tilt table on a comfortable mattress to minimize muscular activity, and both arms were positioned at heart level. Participants remained supine for 20 minutes; thereafter, HUT was imposed by passively changing the body posture from 20° head-down tilt (–20°) to 60° head-up tilt (+60°), in steps of 20° at 8-minute interval. Some women experienced presyncope and could not complete the whole test. Presyncope was defined by a precipitous fall in systolic arterial pressure >15 mmHg concurrent with symptoms, such as bradycardia, light-headedness, blurred vision, sweating, and nausea. Women who experienced presyncope were returned to supine position.

#### VeC During HUT

VeC (mL/dL per mmHg) was measured on the forearm using strain gauge venous occlusion plethysmography with direct intravenous pressure measurement. Venous pressure was directly measured through a catheter in the left antecubital vein connected to a pressure transducer system at atrial height. Changes in forearm volume were measured by a mercury-in-silastic strain gauge 5 cm distal to the antecubital crease. A venous collective cuff was placed 5 cm proximal to the antecubital crease. The pressure cuff was connected to a rapid cuff inflator (Hokanson E20, Denmark) to ensure rapid
and accurate filling and deflation of the cuff. Data signals were recorded by computer at a sampling rate of 100 Hz and stored for further analysis (MIDAC, Biomedical Engineering Department, Radboudumc, Nijmegen, The Netherlands). Cuff pressure was gradually increased from 0 to 40 mm Hg in 60 s. Changes in forearm volume and intravenous pressure were recorded at the end of each rotational step. VeC was defined as the ratio of the slope of the volume–time curve and the slope of the pressure–time curve:

$$\text{VeC} = \frac{\text{volume}}{\Delta \text{time}} / \frac{\text{pressure}}{\Delta \text{time}}$$

Only the data of the linear part of the relationship were used.

**Hemodynamic Responses During HUT**

During the HUT, HR and arterial blood pressure were measured continuously using a monitoring device attached to the third finger of the right hand and a sampling rate of 100 Hz (Finometer, Finapres BV, The Netherlands). We used the hemodynamic data only to study HR and relative changes of blood pressure in response to orthostatic stress. It is known that absolute values of blood pressure acquired from Finometer are not reliable enough as these values are reconstructed from waveform transformation. Changes in blood pressure can however be measured accurately.\(^1\)\(^2\) We excluded data of the first minute after postural change because we have shown in previous experiments that a new steady state is reached within 60 s after postural change.\(^2\)\(^3\) Head-down tilt was performed to test the responses with maximized venous return. Post hoc, the recordings were analyzed by calculating mean HR and mean blood pressure over 5 minutes starting 60 s after postural changes at each rotational step.

**Physical Fitness**

Physical fitness was measured before and after a 12-week aerobic training program. Fitness was defined as the peak oxygen uptake ($$\text{VO}_{2}\text{max}$, mL·min\(^{-1}\)·kg\(^{-1}\)) during a maximal test on a cycle ergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands). Tests were performed in the afternoon after a light lunch ad libitum. The initial workload was set at 10 W for 1 minute and followed by 10 W increments every minute until exhaustion. Breath by breath oxygen uptake was measured using spiro-ergometric equipment (Quark CPET, Cosmed, Italy). A 3-lead ECG continuously recorded HR and rhythm. Maximal workload (Workmax) was defined as the last completed workload before exhaustion. Test performance was considered to be adequate when (1) the increase in $$\text{VO}_{2}$$ during Workmax was <150 mL compared with the previous workload, indicating plateau formation in oxygen uptake; (2) HR at Workmax was <10 bpm from estimated maximal HR (220 – age); (3) respiratory exchange ratio ($$\text{CO}_2$/$$\text{O}_2$$) during Workmax was consistently >1.1; and (4) capillary lactate level was >8 mmol/L, 90 s after exhaustion. If the test failed to achieve these 4 qualifications, the test was repeated 2 to 3 days later. In 3 cases (2 formerly PE women, 1 control), the test had to be repeated, all tests eventually fulfilled the criteria.

**Exercise Training**

Exercise training consisted of 12 weeks of HR controlled, supervised cycle training (cycle ergometer, Corival, Lode BV, Groningen, The Netherlands) at 70% to 80% of $$\text{VO}_{2}\text{max}$$. Participants trained twice a week during the first 6 weeks and 3 times a week during the last 6 weeks. Each training session was supervised and executed in the gymnasium of our laboratory. Care was taken that each training session had at least 1 day in between to allow adequate recovery. Participants were instructed not to exercise in addition to the exercise protocol given. During each training session, HR was continuously monitored and recorded (RS800CX, Polar Electro Inc, NY). Each training session started with 10-minute warming up at 50% of the HR reserve (HRR) above resting HR. HRR was calculated as $$\text{HRR} = \text{HR}_{\text{max}} - \text{HR}_{\text{rest}}$$ in which $$\text{HR}_{\text{max}}$$ is maximal HR during the fitness test at study entry and $$\text{HR}_{\text{rest}}$$ is the HR determined at rest. Training consisted of 40 minutes of cycling at 70% to 80% of the individual HRR. Within their target HR zone, participants were free to choose the number of revolutions per minute. Cooling down for 5 minutes at warming up, workload completed the training.

**Statistics**

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) software. All normally distributed data are reported as mean±SD; other data are presented as median [interquartile range]. Normality of data was tested with a Kolmogorov–Smirnov test. Two-way repeated-measures ANOVA was used to examine differences between formerly PE women and controls group to assess the effects of training (intervention) and to determine whether training effects differed between formerly PE women and controls (training×group). A mixed linear model for repeated measures was performed to test differences between groups and effects of training on the response curves of venous and hemodynamic variables to HUT. When significant effects were found, Bonferroni post hoc comparison tests were used. Statistical significance was assumed at $$P<0.05$$. We based our group size calculation for the intervention part of our study on an anticipated difference in exercise-induced PV expansion (primary outcome measure) of 4% between groups, a power of 90% and an $$\alpha$$ of 0.05. Assumed SD of the exercise-induced PV expansion was based on a pilot study in 9 formerly PE women (4%).\(^2\)\(^4\) Based on these assumptions, 18 subjects were required per group. To anticipate possible dropout, we decided to include at least 20 subjects per group.

**Results**

Included in the analysis were 24 formerly PE women and 20 controls, after exclusion of 1 formerly PE woman (who became pregnant) and 2 controls (one who became pregnant and one who did not finish the training protocol). Mean age and interval from delivery to test were comparable between groups (32±4 versus 32±4 years, $$P=0.62$$ and 7±2 versus 7±1 months, $$P=0.88$$, respectively). Formerly PE women had delivered at an earlier gestational age compared with controls (32 [29–37] versus 40 [38–41] weeks, $$P<0.01$$), of children with a lower birth weight (1571±675 versus 3532±311 g, $$P<0.01$$).
Before Training

Physical and hemodynamic characteristics of formerly PE women and controls are shown in Table. Before training, mean physical fitness was comparable between both groups (VO2max: 27.0±4.0 and 28.2±3.7 mL·min⁻¹·kg⁻¹, P=0.32) as were body mass index, stroke volume, cardiac output, and serum creatinine concentration. All subjects were normotensive (by inclusion). In formerly PE women, average values of HR, systolic arterial pressure, diastolic arterial pressure, MAP, creatinine clearance, and albuminuria were higher than in controls. PV was 13% lower in formerly PE women than in controls (1348±78 versus 1529±112 mL/m², P<0.01), as shown in Figure 1.

The venous response curves to graded HUT are shown in Figure 2. Before training, VeC was lower in formerly PE women than in controls (supine: 0.04±0.02 versus 0.07±0.01 mL·dL⁻¹·mmHg⁻¹, P<0.01). Formerly PE women had lower VeC at all levels of HUT and a more gradual slope of the VeC response to progressive HUT than controls (P=0.004), indicating a relatively poor venous response to orthostatic stress.

Blood pressure decreases significantly secondary to orthostatic stress (P<0.01). The response curves of mean blood pressure to graded HUT show that before exercise training, blood pressure drops comparably between formerly PE women and controls in response to HUT (P=0.11; Figure 3). The increase in HR in response to HUT was however more pronounced in...
PE women than in controls ($P=0.01$). With progressive HUT, mean HR increased. From $20^\circ$ HUT onward, the slope of the orthostatically induced increase in HR was steeper in formerly PE women than in controls ($P=0.01$; Figure 4).

Presyncope at $60^\circ$ HUT tended to occur more frequently in formerly PE women than in controls (6/24 [25%] versus 1/20 [5%], $P=0.07$).

**Effects of Training**

Twelve weeks of training improved physical fitness comparably in both groups, as mean VO$_{2\text{max}}$ increased by +3.4 and +3.7 mL·min$^{-1}$·kg$^{-1}$, respectively. Training increased PV in both groups (+180 versus +135 mL/m$^2$, $P=0.22$; Figure 1) and it increased PV in formerly PE women up to pretraining values of controls ($P=0.84$).

As shown in Table, training reduced body mass index, systolic arterial pressure, arterial pressure, and MAP comparably in both groups. Although training increased stroke volume, cardiac output was unaffected because the reduction in HR was more pronounced in formerly PE women than in controls (interaction: $P=0.03$). Training abolished the differences in blood pressures between formerly PE women and controls, but did not affect serum creatinine levels and albuminuria, so that albuminuria remained higher in formerly PE women than in controls.

Training improved VeC (Figure 2). The improvement was significantly more pronounced in formerly PE women than in controls (supine VeC: +0.02 versus +0.01 mL·dL$^{-1}$·mmHg$^{-1}$, respectively; training×group: $P<0.01$), and supine VeC in trained formerly PE women became comparable with that
of untrained controls ($P=0.30$). The slope of the VeC curve in response to HUT increased with training (HUT×training: $P<0.01$), so that it became comparable for formerly PE women and controls (group×HUT: $P=0.78$).

After 12 weeks of training, the average MAP over the 5 rotational steps ($P=0.55$) and the slopes of the MAP curves in response to HUT ($P=0.54$) were similar in PE women and controls. Training shifted the HR response curve to HUT downwards in both groups. After 12-week exercise training, the slopes of the response curves of HR were comparable between formerly PE women and controls ($P=0.14$), although formerly PE women still performed at a higher HR at each level of HUT ($P=0.05$).

Training reduced the rate of presyncope in formerly PE women, albeit not significantly (from 6/24 [25%] to 3/24 [12.5%], $P=0.27$). After training, none of the control women showed symptoms of presyncope.

**Discussion**

The major finding in this study is that a 12-week aerobic exercise program increases PV and VeC in formerly PE women to pretraining levels of parous women without a history of preeclampsia.

Preeclampsia is a multifactorial disorder. In this study, we focused on the link between preeclampsia and reduced venous reserve. Although it has been repeatedly shown that formerly PE women have low PV, the exact cause for low PV is unknown. Formerly PE women had higher creatinine clearance and microalbuminuria, both characteristics of borderline hypertension. Therefore, one could argue that hyperfiltration may have contributed to reduced PV in formerly PE women. However, in pregnancy women with prepregnant low PV demonstrate reduced PV expansion with concurrent increased levels of atrial natriuretic peptide suggesting a restricted volume compartment rather than hyperfiltration.

Therefore, other possible pathogenic factors for low PV may be more likely such as a constitutionally small venous compartment or a constricted venous system. Both glomerular hyperfiltration and a constricted venous system are linked to sympathetic overactivity. Our results are consistent with a constricted, but not necessarily constitutionally small, venous compartment. A constitutionally small venous compartment most likely would have resulted in a small increase in PV with training in formerly PE women, yet our data show that PV increased at least as much in formerly PE women as in controls. The normal increase in PV and the larger increase in VeC in formerly PE women than in controls in response to training are consistent with a venous compartment that was initially constricted but was able to relax secondary to exercise-induced reduction of sympathetic tone. The magnitude of the exercise-induced PV expansion in our study is comparable with first trimester PV expansion in normal pregnancy ($\approx 10\%$). If pregnancy proceeds normally, PV expands further to more than $\pm 40\%$. It is conceivable that in pregnancy venous capacitance problems arise when $>10\%$ PV expansion needs to be accommodated. The effects of the exercise-induced PV expansion in formerly PE women on the subsequent recurrence risk of preeclampsia have not yet been studied.

Formerly PE women apparently have an increased venous tone and reduced VeC, similar to hypertensive subjects. The VeC at rest was lower in formerly PE women than in controls before training and improved markedly by exercise training. VeC modulation during HUT was initially blunted in formerly PE women compared with controls, but training shifted the curve upward and increased the slope. This implies that the ability of the veins to mobilize venous volume through venoconstriction was initially limited but improved markedly with exercise training. Twelve weeks of aerobic training allowed formerly PE women to effectively improve VeC modulation up to the pretraining level of controls. We presume that an increase in VeC before a new pregnancy will likely allow better accommodation of the necessary PV expansion in pregnancy at a lower sympathetic activity level.

We would like to address several methodological issues. First, a time control group could have strengthened our results to rule out effects of postpartum recovery resulting in an over-estimation of our training effects. We studied our participants.
6 to 12 months postpartum, which may not have been enough for full recovery. Yet, our data probably approach full recovery as venous functions have been reported to normalize within 3 months after delivery, and hemodynamic and metabolic recovery is at least 80% complete within 6 months. The postpartum interval was similar between groups; it is therefore unlikely that this has significantly affected our comparisons. Moreover, the fact that formerly PE women only improved up to a level that is comparable with that of untrained controls suggests that the observed training effects are not only reversal to the mean. Second, we measured VeC in a limb as a proxy for the whole body. One could argue that the splanchnic venous bed would have been more relevant because it contains the largest volume of venous blood and therefore plays a more important role in restoring venous return. However, measuring splanchnic VeC is technically too challenging, especially during dynamic testing. Measuring limb VeC is a well-accepted method for studying the venous vascular bed. Finally, controls were recruited from the community; therefore women with subjectively poor fitness may have had an incentive to participate in the study, knowing that their cardiovascular health would be assessed and improved by training.

Perspectives
Pregnancy represents a unique screening test in which preeclampsia indicates women at high risk for future gestational hypertension and cardiovascular disease later in life. Women at risk for cardiovascular disease are likely to be detected at a young age, early enough to benefit from subsequent preventative strategies. Although the reported effect of exercise before and during pregnancy on the reduction of recurrence risk of preeclampsia is conflicting, aerobic exercise training is a powerful nonpharmacological and low cost strategy to reduce blood pressure. The protective effects of exercise are complex and go beyond the effects on traditional cardiovascular risk factors alone. Our study has shown that formerly PE women can improve their venous reserve capacity through aerobic training to the level of that of untrained healthy control women who carried their pregnancy without developing hypertension. It is likely that if the active lifestyle is not maintained many of the exercise-induced venous and autonomic changes will reverse. Further studies are needed to demonstrate the extent to which aerobic training before pregnancy is of clinical benefit to reduce recurrent hypertensive disease in pregnancy and cardiovascular disease later in life.

Conclusions
Normotensive formerly PE women have reduced PV and lower VeC indicating reduced venous reserve capacity. Twelve weeks of aerobic training at 70% to 80% VO₂max 2 to 3 times per week significantly improves the venous reserve capacity in postpartum women. In formerly PE women, it restores these functions to the level of untrained healthy parous controls.

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The present research was performed without external funding.

Disclosures
None.

References
Exercise Induced Venous Changes After Preeclampsia

What Is Relevant?

- Women with a history of preeclampsia have approximately double the risk for subsequent cardiovascular disease over the 5 to 15 years after pregnancy. Pregnancy provides unique cardiovascular stress; therefore, a failed stress test can unmask early or pre-existing disease. Low plasma volume may reflect latent hypertension and relates linearly with recurrence rate of preeclampsia. Knowing the effects of nonpharmacological interventions (e.g., exercise) on cardiovascular and metabolic parameters may help in advocating a healthy lifestyle in these young formerly preeclamptic women.

Summary

We demonstrate that 12 weeks of aerobic exercise training effectively improves venous reserve capacity in postpartum women.
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