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Exercise-induced Changes in Venous Vascular Function in Nonpregnant Formerly Preeclamptic Women

Ineke Krabbendam, MD, Martje L. Maas, MD, Dick H. J. Thijssen, PhD, Wim J. G. Oyen, MD, PhD, Fred K. Lotgering, MD, PhD, Maria T. E. Hopman, MD, PhD, and Marc E. A. Spaanderman, MD, PhD

Objective: Formerly preeclamptic women with low plasma volume are at increased risk of recurrent gestational hypertensive disease. We hypothesized that a 4-week cycling training in formerly preeclamptic women improves (venous) hemodynamic function. **Methods:** In 9 formerly preeclamptic women, we examined physical fitness and hemodynamic function, before and after the training. We assessed blood pressure, heart rate, cardiac output, plasma volume, and calf and forearm venous compliance. **Results:** After the training, baseline blood pressure and cardiac output remained unchanged, but resting heart rate decreased (-7% , $P = .02$). Plasma volume was 8% higher after training ($P = .01$). Calf venous compliance increased ($+18\%$, $P = .02$) but not forearm venous compliance ($+14\%$, $P = .09$). **Conclusion:** Cycling training improves venous vascular function in formerly preeclamptic women. The decreased resting heart rate and improvement of venous compliance suggest reduced sympathetic activity. These rapid exercise-induced changes may improve maternal vascular adaptation in early pregnancy and with it the risk of (recurrent) gestational hypertensive disease.

KEY WORDS: Preeclampsia, plasma volume, venous compliance, exercise, training.

INTRODUCTION

Preeclampsia complicates almost 8% of pregnancies and is a major cause of maternal morbidity and mortality worldwide.^{1,2} It is associated with preexistent vascular, metabolic, and clotting abnormalities.²⁻⁴ Formerly preeclamptic women are at increased risk of hypertension, cardiovascular disease, venous thromboembolism, and stroke in later life.^{5,6}

After gestation, the majority of normotensive formerly preeclamptic women exhibit subnormal plasma volume (PV), a characteristic associated with reduced venous capacitance and elevated sympathetic tone.^{3,7,8} This condition results in predisposition to recurrent gestational hypertensive disease and fetal growth restriction in a subsequent pregnancy.^{9,10} In healthy pregnancy, PV increases in response to the drop in peripheral vascular resistance to maintain blood pressure. This PV expansion, necessary to meet the increased arterial demands of advanced pregnancy, can only be accommodated when venous compliance (VeC) increases as well. Subnormal PV prior to pregnancy hampers normal venous adaptation and PV expansion in the first weeks of gestation.¹¹ Interventions that improve venous capacitance may contribute to lowering the risk of recurrent gestational hypertensive disease.

Physical activity is associated with a reduced risk of preeclampsia and cardiovascular disease.¹²⁻¹⁶ In sedentary and moderately active participants, exercise training increases PV^{17,18} and VeC.¹⁹⁻²¹ Possibly, exercise-induced

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improvements in PV and VeC may contribute to the reduced risk of recurrent gestational hypertensive disease. However, no study has examined the effects of exercise training on these variables in (formerly) preeclamptic women. Therefore, the aim of this study was to examine the effect of a 4-week training program on hemodynamic function in nonpregnant formerly preeclamptic women. We hypothesize that exercise training in these women improves nonpregnant circulatory variables known to interfere with maternal vascular adaptation in early pregnancy.

METHODS

Participants

A total of 9 nonpregnant women, with a history of preeclampsia were included in this study. Women were recruited from the obstetric outpatient clinic at follow-up. Preeclampsia was defined according to the criteria of the International Society on the Study of Hypertension in Pregnancy (ISSHP).²² Participants with diabetes mellitus, hypertension, cardiovascular disease, and/or hyperhomocysteinemia were excluded. All participants were at least 6 months postpartum, were not breastfeeding, and were not taking any medication. A written, informed consent was obtained from all participants and the study was approved by the Institutional Review Board (CMO nr. 2006/080).

Protocol

Before and after a 4-week cycling training program, physical fitness and hemodynamic parameters were determined. All experiments were performed in the follicular phase of the menstrual cycle to minimize hormonal influence. Measurements were performed between 7:45 and 12:00 a.m., under standardized environmental conditions and after an overnight fast. Participants refrained from caffeine, alcohol, smoking, and vitamin C during a 12-hour period prior to the measurements.

Physical fitness test. To evaluate the physical fitness of the participants, we continuously recorded oxygen uptake ($\dot{V}O_2$, mL·min⁻¹·kg⁻¹), heart rate (HR, bpm), respiratory exchange ratio (RER, $[\text{CO}_2]/[\text{O}_2]$ ratio), and power output (Power_{max}, W) during an incremental maximal cycling test, before and after the training period. The test started at an intensity of 10 W and was increased every

minute by 10 W, until exhaustion. O₂ and CO₂ concentrations were measured using an automatic gas analyzer (Oxycon Alpha, Jaeger, Wuerzburg, Germany). An electrocardiogram was used to continuously record HR. Two minutes after the test, a capillary blood sample was taken from the tip of the finger to examine lactate levels.

Hemodynamic function. Before and after the training period, hemodynamic parameters were determined. After 10 minutes of rest in the supine position, arterial blood pressure and HR were recorded at 3-minute intervals using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846, Critikon Company LLC, Tampa, Fla). The median value of 5 consecutive measurements was used to represent systolic, diastolic, and mean arterial blood pressure and HR. Pulse pressure (PP) was calculated as the difference between systolic and diastolic blood pressure.

Cardiac output (CO, L·min⁻¹) was measured in the left lateral position using a validated, noninvasive, inert gas rebreathing method (Innocor, Innovision, Copenhagen, Denmark).^{23,24} All participants were familiarized with the technique. Prior to each rebreathing maneuver, the rebreathing bag was filled with 1.5 L of the test gas mixture, containing 0.5% N₂O and 0.1% SF₆. The nasal airway was blocked using a nasal clamp. A constant ventilation rate of 20·min⁻¹ was ensured, and it was emphasized that the bag was completely emptied with each inspiration. A pulse oximeter attached to the third digit of the right hand recorded HR and arterial oxygen saturation (SpO₂, %).^{23,24} The rebreathing technique is based on the changes in end-tidal concentration of N₂O inspired from the rebreathing bag, which determines the pulmonary blood flow. Concentrations of N₂O are corrected for total lung volume, measured by the change in concentrations of the used insoluble gas SF₆. Because CO is not necessarily equal to pulmonary blood flow, the pulmonary blood flow is corrected for the shunt flow, which is determined from the subsequently measured disappearance rate of oxygen and by using the Fick principle. Then, stroke volume (SV, mL) could be calculated as CO/HR, total peripheral vascular resistance (TPVR, dyne·s·cm⁻⁵) as $80 \cdot \text{MAP} / \text{CO}$, in which MAP is mean arterial pressure. Global vascular compliance (GVC; mL·mm Hg⁻¹) is calculated as SV/PP.

Plasma volume (mL) was measured using the iodine 125-labeled human serum albumin (¹²⁵I-HSA) indicator dilution method.^{3,25} During the measurement, the participants were in a semisupine position on a comfortable

bed. A catheter was inserted in the left antecubital vein to inject 0.2 MBq of ^{125}I . Plasma volume was obtained by dividing the total injected radioactivity by the virtual volume-specific radioactivity at time 0, as described elsewhere.³

We determined VeC ($\text{mL}\cdot\text{dL forearm volume}^{-1}\cdot\text{mm Hg}^{-1}$) from the plethysmographically derived slope of the relationship between venous volume and pressure change (Hokanson, Denmark). Mercury-in-silastic strain gauges were placed around the largest girth of the right calf and forearm, which were elevated to heart level. A pressure cuff was placed around the upper right leg and arm and connected to a rapid cuff inflator (Stople E-20, Hokanson, Denmark) to ensure rapid and accurate filling and deflating of the cuff. The test procedure was started with an occlusion pressure of 20 mm Hg, and subsequent cuff pressures of 40, 60, and 80 mm Hg were used for at least 2, 3, 4, and 5 minutes, respectively, to achieve a stable plateau in the plethysmographic signal. The effective pressure on the venous system was estimated as 0.8 times the cuff pressure.²⁶ Data were recorded at a sample frequency of 100 Hz (MIDAC, Instrumentation Department, Radboud University Nijmegen, The Netherlands) and analyzed by a customized computer program (Matlab, Mathworks, Natick, Mass). The venous volume variation (V_{VV}, $\text{mL}\cdot\text{dL}^{-1}$) was defined as the maximal relative volume increase in a limb at each chosen cuff pressure. The V_{VV} at different (effective) cuff pressures represents the pressure-volume curve, which was used to calculate the VeC.

Training program. The 4-week training program consisted of 2 supervised training sessions per week during the first 2 weeks and 3 sessions per week during the last 2 weeks. The training was performed on a cycle ergometer (Ergometric 818-E, Monark, Varberg, Sweden). Each training session started with a warm-up of 10 minutes at 50% of the heart rate reserve (HRR) above the resting HR, which was calculated using the formula:

$$\text{HRR} = \text{HR}_{\text{max}} - \text{HR}_{\text{rest}},$$

in which HR_{max} is the maximal HR measured during the physical fitness test and HR_{rest} is the HR determined at rest.

After the warm-up period, a training intensity of 60% to 70% of the HRR was applied for 30 minutes. Exercise intensity gradually increased throughout the training period by 2.5% of the HRR per training session. Each

training session was ended with a cooling down period of 10 minutes at 50% of the HRR.

Statistical Analysis

All values are represented as median (ranges), unless otherwise stated. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 14.0. A Wilcoxon signed rank test was used to determine the effect of exercise for all variables. We calculated the coefficient of correlation using Spearman correlation analysis. The response to the physical fitness test in HR for pretraining and posttraining measurements was quantified by linear regression analysis. A P value $\leq .05$ was considered statistically significant.

RESULTS

We included 9 normotensive nonpregnant formerly pre-eclamptic women with a median age of 34 (31-37) years and a body mass index (BMI) of 24 (21-30) $\text{kg}\cdot\text{m}^{-2}$. Participants were 17 (11-75) months postpartum at the time of inclusion. All participants completed the 4 weeks exercise training.

Physical Fitness

The 4 weeks exercise training resulted in an increase in maximal oxygen uptake and maximal work load, even though maximal HR had decreased and maximal RER remained unchanged (Table 1). Using RER 1.0 as a reference value for the start of significant anaerobic exercise, the training program resulted in a significantly higher workload, higher oxygen consumption, and longer time needed to reach the RER value of 1.0 (Table 1). The change in HR during the physical fitness test, before and after the training program, is presented in Figure 1. We compared each individual regression line of the HR response during the physical fitness test, as measured before and after the training period by pairwise testing. Linear regression analysis showed different regression lines of the HR responses during pretraining and posttraining measurements (regression coefficient .56 [.39-.98] vs. .45 [.21-.78], respectively, $P = .02$).

Hemodynamic Function

Exercise training did not alter baseline blood pressure, total peripheral resistance, and CO, while SV increased

Table 1. Physical Fitness Before and After the 4-week Training Protocol in 9 Normotensive Formerly Preeclamptic Women^a

Parameter	Before	After	Delta	P Value
$\dot{V}O_{2\max}$ ($\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$)	30.1 (24.5-37.1)	31.3 (21.8-38.8)	+3%	.05
Power _{max} (W)	170 (120-210)	190 (130-220)	+8%	.01
Maximal RER	1.22 (1.12-1.29)	1.17 (1.08-1.43)	-6%	.15
Maximal HR (bpm)	186 (164-212)	182 (151-204)	-4%	.02
$\dot{V}O_2$ at RER 1.0 ($\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$)	22.1 (15.8-25.4)	26.8 (15.0-31.0)	+20%	.03
Power at RER 1.0 (W)	90 (60-180)	120 (90-170)	+23%	.02
Time to reach RER 1.0 (min)	8 (6-18)	12 (9-16)	+25%	.02

Abbreviations: HR, heart rate; power, workload, at maximal strain (Power_{max}); RER, respiratory exchange ratio; $\dot{V}O_2$, lung oxygen uptake, at maximal strain ($\dot{V}O_{2\max}$).

^a Values are median (ranges).

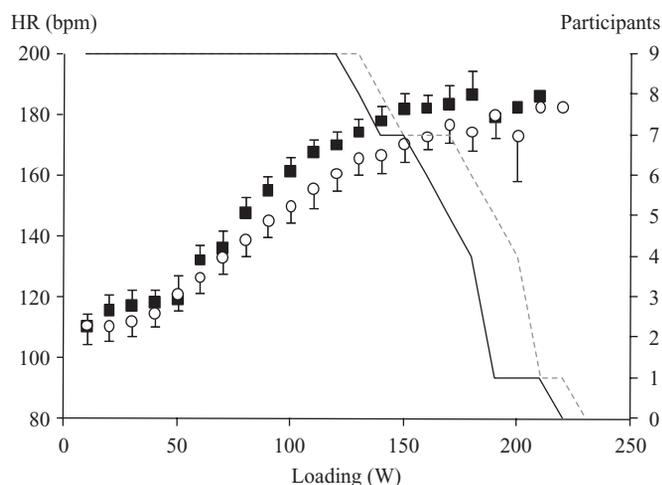


Figure 1. The change in heart rate (HR) in response to loading during the physical fitness test, before (■) and after (○) the training protocol. The number of participants (n) who sustained the various loading levels is shown at the secondary y-axis, before (—) and after (---) the training protocol. Values represent mean \pm SEM.

by 10% (Table 2). Resting HR was 7% lower after the training period ($P = .02$). In addition, PV rose by 8% from 2517 (2149-2927) to 2725 (2418-3211) mL ($P = .01$, Figure 2). Central hemodynamic function, as indicated by the GVC, improved by 13% ($P = .05$).

Calf VeC increased 18% ($P = .03$) in response to the 4-week training program (Figure 3). Despite the 14% increase in forearm VeC from 0.042 (0.031-0.061) to 0.048 (0.023-0.089) $\text{mL}\cdot\text{dL}^{-1}\cdot\text{mm Hg}^{-1}$, this change did not reach statistical significance ($P = .09$, Figure 3).

DISCUSSION

We hypothesized that hemodynamic function, primarily venous vascular dynamics, improves after 4 weeks of

cycle training in formerly preeclamptic women. We observed an exercise-mediated increase in PV and calf VeC, while resting SV was higher and resting HR was lower at the end of the training period. These findings suggest adaptations of the venous system, but also of the central hemodynamic function, in response to an elevated level of physical activity in formerly preeclamptic women. The rise in global compliance indicates a general improvement of vascular function. The adaptations in VeC and PV are of special interest, given the link between these parameters and an increased risk of recurrent gestational hypertensive disease in formerly preeclamptic women.

Earlier reports indicated that exercise induces changes in cardiovascular parameters in healthy individuals.^{12,17,21,27-30} Our study group consisted of parous women with a vascular complicated obstetric history. This group of women is reported to exhibit latent hemodynamic abnormalities consistent with the early stages of chronic hypertension, like low PV, low VeC, and higher sympathetic tone.^{3,31,32} The increase in PV and VeC in response to physical exercise is relatively high in our study group. It is tempting to speculate that these correcting cardiovascular effects may reduce the risk of recurrent hypertensive disease in a subsequent pregnancy and remotely the risk of cardiovascular disease in later life.

The design of our study was insufficient to study the mechanisms underlying either a primary increase in PV or a primary decrease in sympathetic activity. The current literature is not conclusive. The initial increase in PV is thought to be the result of acute shifts in plasma protein content, allowing the binding of additional water. We speculate that this initial increase in PV leads to a decrease in sympathetic activity, which, in turn, improves VeC. Consequently, the increased VeC will allow accommodation of at least part of the extra PV in the venous

Table 2. Cardiovascular Parameters Before and After the 4-week Training Protocol in 9 Normotensive Formerly Preeclamptic Women^a

Parameter	Before	After	Delta	P Value
Heart rate (bpm)	74 (61-86)	69 (57-79)	-7%	.02
Stroke volume (mL)	72 (59-90)	79 (57-109)	+10%	.04
Cardiac Output (L·min ⁻¹)	5.2 (4.4-7.1)	5.0 (4.3-8.4)	-4%	.58
MAP (mm Hg)	89 (76-99)	88 (74-101)	-1%	.72
Pulse pressure (mm Hg)	45 (41-55)	47 (40-55)	+4%	.94
TPVR (dyne·s·cm ⁻⁵)	1382 (890-1580)	1316 (780-1760)	-5%	.86
Global compliance (mL·mm Hg ⁻¹)	1.5 (1.3-1.8)	1.7 (1.2-2.3)	+13%	.05
Red cell volume (mL)	1448 (1197-2042)	1482 (1320-2141)	+2%	.68

Abbreviations: MAP, mean arterial pressure; TPVR, total peripheral vascular resistance.

^a Values are median (ranges).

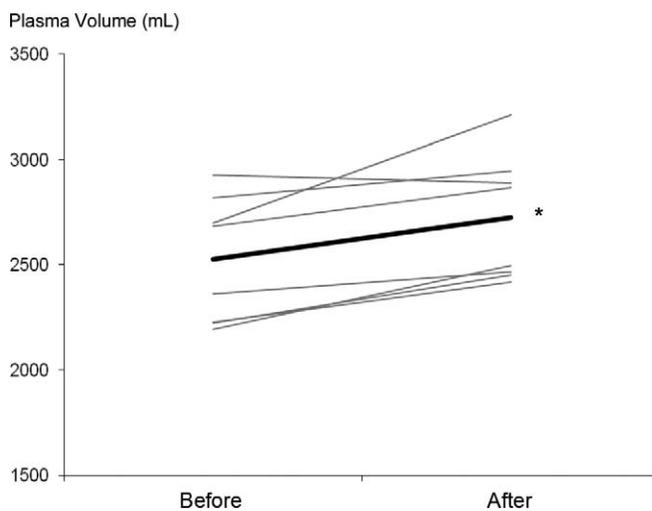


Figure 2. Plasma volume before and after the 4-week training protocol in 9 normotensive formerly preeclamptic women. * $P < 0.05$ as compared to start value.

compartment, which allows sympathetic activity to be persistently lower after training in this group of women.^{27,33,34} Physical activity is thought to reduce sympathetic tone by reducing baroreflex-mediated sympathoexcitation, leaving baroreflex sensitivity unaltered but reducing its activational action on the rostral ventrolateral medulla.³³ Although we did not assess sympathetic activity, the decrease in resting HR during the physical fitness test supports this view.³⁵ Alternatively, the decrease in HR may also originate from the ventricular hypertrophic response to increased cardiac preload and to the rise in SV.^{29,34} The training-induced hypervolemia may also contribute to this bradycardiac effect of training. A 6-week training protocol is reported to produce substantial lowering of resting HR, without structural cardiac hypertrophic changes,^{34,36} leaving HR primarily modulated by autonomic outflow after short-term training protocols. The improved HR response after the training

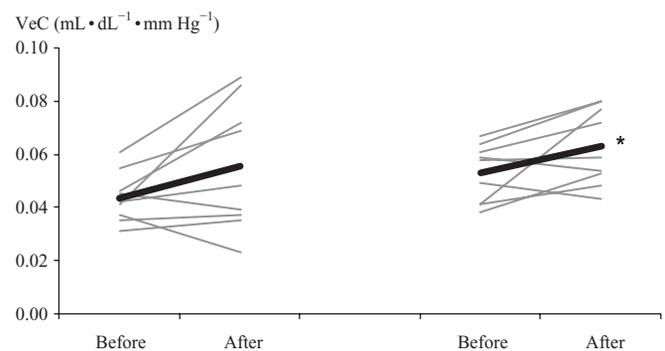


Figure 3. Venous compliance (VeC) of the forearm (left) and calf (right) before and after the 4-week training protocol in 9 normotensive formerly preeclamptic women. * $P < 0.05$ as compared to start value.

period also indicates adaptation of the sympathetic system. Therefore, the observed changes most likely result from multifactorial changes in endothelial function, vasculoelastic properties, and autonomic control of the circulation.

Under physiologic conditions, most of the blood volume is located in the venous compartment, where it serves as a readily available buffer to raise venous return in response to higher demands for systemic blood flow. In pregnancy, the rise in VeC enables accommodation of the expanding PV without leading directly to circulatory overfill. To create an adequate blood supply for the growing conceptus, the development of a substantial amount of unstressed volume is necessary to meet the uterine demands of advanced pregnancy. In women with prepregnant low PV, VeC is decreased resulting in a blunted (venous) adaptation to early pregnancy.^{8,11,37} Our data indicate that even 4 weeks of moderate exercise in formerly preeclamptic women induces consistent improvement of VeC and PV. However, one should realize that the splanchnic veins contain most of the venous blood.

Active distribution of venous volume, by reducing VeC in the remaining part of the venous system, accounts for only 25% of the total blood transfer. We did not study the splanchnic venous response in this study, because of methodological factors, but it might be a worthwhile aspect to study in formerly preeclamptic women after training.

Venous compliance and PV are potent prepregnancy marker for recurrent gestational hypertensive disease.⁹ Rudra et al and Sorenson et al demonstrated that physical activity before and during pregnancy is associated with a reduced risk of preeclampsia.^{14,15} Accordingly, our novel findings in formerly preeclamptic women may suggest that improvement of the venous vascular function by physical activity prior to pregnancy could play an important role in healthy circulatory adaptation to pregnancy and the prevention of gestational hypertensive disease in advanced gestation.

We included a heterogeneous group of 9 women with a history of preeclampsia. One may hypothesize that variation in BMI may influence our results. As all women served as their own control in the comparison, it is unlikely that variation in BMI affected our observations. In addition, the variation in time since the last pregnancy may have influenced our results.³⁸ Correlation analysis showed that the duration of the postpartum period did not relate to any of the measured variables. Therefore, we assume that the observed changes in hemodynamic function are mediated by the training protocol, irrespective of participant characteristics.

The training program was of only moderate intensity and duration. Nonetheless, maximal oxygen uptake increased, and the higher oxygen consumption and higher workload at RER 1.0 suggests that physical fitness improved after the 4-week cycle training. Even a short duration training protocol seems to be sufficient to induce an improvement of the vascular function and cardiovascular reserve capacity among women at risk of vascular complications. A longer duration may lead to more profound changes.

In conclusion, a 4-week cycling training program improves total PV and calf VeC in normotensive formerly preeclamptic women. When low, both vascular characteristics are prepregnancy risk indicators of recurrent gestational hypertensive disease. We speculate that moderate intensity exercise might reduce recurrence rates of gestational hypertensive disease.

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