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# Formerly Preeclamptic Women With a Subnormal Plasma Volume Are Unable to Maintain a Rise in Stroke Volume During Moderate Exercise

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**INTRODUCTION:** In formerly preeclamptic women with a low plasma volume, the recurrence rate of preeclampsia is higher than in women with a normal prepregnant plasma volume. In a recent study, we demonstrated that the low plasma volume subgroup also had a subnormal venous capacitance. In the present study, we determined the impact of subnormal plasma volume on the hemodynamic response to moderate exercise.

**PATIENTS AND METHODS:** We performed this study in the follicular phase of the menstrual cycle, in 31 formerly preeclamptic women with a subnormal plasma volume (low-PV) and eight parous controls. The exercise consisted of 60 minutes of cycling in the supine position at 35% of the individualized maximum capacity. Before, during, and after cycling, we measured the percentage change in heart rate, stroke volume, and cardiac output. Before and after exercise, we measured the effective renal plasma flow (ERPF, para-amino-hippurate [PAH] clearance), glomerular filtration rate (GFR, inulin clearance), circulating levels of alpha-atrial natriuretic peptide ( $\alpha$ -ANP), and active plasma renin concentration (APRC).

**RESULTS:** The response to exercise of formerly preeclamptic women with a subnormal plasma volume differed from that in controls by a lack of rise in stroke volume, a smaller rise in cardiac output and  $\alpha$ -ANP, and a greater fall in GFR. The responses in heart rate, ERPF, and APRC did not differ between the two groups.

**CONCLUSION:** The response to moderate exercise of formerly preeclamptic women with a subnormal plasma volume differs from that in healthy parous controls with a normal plasma volume and suggests a lower capacity to raise venous return in conditions of a higher demand for systemic flow. The lower capacity to raise venous return in these conditions is associated with more cardiovascular drift. The physiologic consequence is a lower aerobic endurance performance during moderate exercise. (*J Soc Gynecol Investig* 2005;12: 599–603) Copyright © 2005 by the Society for Gynecologic Investigation.

**KEY WORDS:** Pre-eclampsia, plasma volume, venous capacitance, exercise.

In formerly preeclamptic women, the prevalence of a subnormal plasma volume is approximately 50%.<sup>1</sup> We and others observed that a subnormal plasma volume predisposes to recurrent hypertensive complications in a next pregnancy.<sup>2–7</sup> In the non-pregnant state, these women with a subnormal plasma volume differed from their counterparts with a normal plasma volume by a lower stroke volume, lower cardiac index, and shorter estimated systemic circulation time.<sup>2</sup> Although their health state in resting conditions appears to be good, it is not clear whether these women have less cardiovascular reserves in conjunction with a lower capacity to raise and maintain cardiac preload. If so, their ability to deal with conditions of

chronically elevated cardiac output may be compromised and cardiovascular drift might be increased.

A decline in circulating volume due to dehydration reduces the aerobic endurance performance during exercise.<sup>8</sup> Furthermore, an experimentally induced acute reduction in total blood volume by withdrawal of approximately 0.5 L of blood attenuates the normal rise in stroke volume in response to exercise.<sup>9</sup> These observations suggest that a (sub)acute decrease in blood volume diminishes the exercise-induced rise in both stroke volume and total body oxygen uptake. The negative impact of a reduced plasma volume on aerobic endurance performance causes “cardiovascular drift,” defined as a decline in stroke volume that may occur in conditions of prolonged moderately intensive exercise.<sup>10</sup>

The present study was designed to test the hypothesis that the response to exercise of formerly preeclamptic women with a subnormal plasma volume differs from that in parous controls with a normal plasma volume by more cardiovascular drift. To

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**Table 1.** Demographics of the Participants in the Two Study Groups

	Low-PV	Controls	P value
Age (y)	31.1 ± 0.7	35.2 ± 1.0	<.05
BMI (kg/m <sup>2</sup> )	25.5 ± 0.7	22.1 ± 1.1	<.05
Primiparity (%)	80.0%	75.0%	NS
Plasma volume (mL/kg lean body mass)	44 ± 2	55 ± 3	<.05
Mean arterial pressure (mm Hg)	91 ± 13	87 ± 11	NS
Plasma volume (mL)	2,576 ± 67	3,015 ± 176	<.05
Microalbuminuria (g albumin/mol creatinin)	0.8 ± 0.5	0.7 ± 0.8	NS

NS = not significant.

this end, we compared the response in heart rate, stroke volume, cardiac output, renal perfusion (effective renal plasma flow [ERPF] and glomerular filtration rate [GFR]) and that in two important hormones involved in volume regulation (alpha-atrial natriuretic peptide [ $\alpha$ -ANP] and active plasma renin concentration [APRC]), to 60 minutes of moderate intensive exercise in 31 formerly preeclamptic women with a subnormal plasma volume, with that in eight parous controls with a normal plasma volume.

## PATIENTS AND METHODS

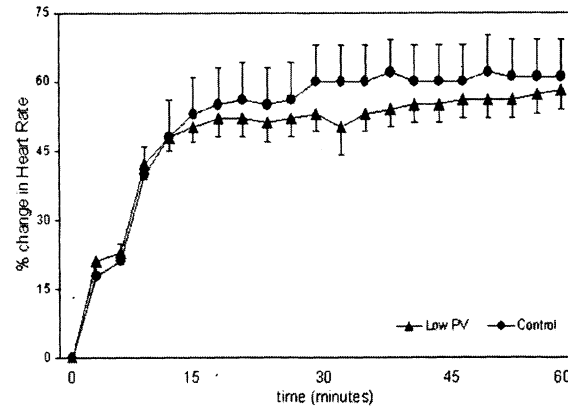
### Patients

This study was performed in eight healthy parous controls and in 31 non-pregnant seemingly healthy normotensive women with a recent history of early-onset (<34 weeks) preeclampsia/hemolysis, elevated liver enzymes, low platelets (HELLP) as well as a plasma volume of at least 2 SD below the mean of the control group (<48 mL/kg lean body mass)<sup>1</sup> determined at least 6 months postpartum at the time of postpartum counseling for recurrent hypertensive complications in a next pregnancy. Former patients were invited to participate in this study when they seemed to be healthy, when their plasma volume turned out to be subnormal, and finally, when no other abnormalities could be detected. We used the definitions for hypertensive complications in pregnancy as detailed else-

**Table 2.** Exercise Variables Obtained in the Two Study Groups

	Low-PV	Controls	P value
Maximal power (watt)	124 ± 19	142 ± 17	NS
Heart rate (basal, beats/min)	76 ± 9	76 ± 9	NS
Heart rate (maximal, beats/min)	173 ± 14	174 ± 12	NS
ERPF (basal, mL · min <sup>-1</sup> · 1.73 <sup>-2</sup> )	506 ± 18	550 ± 50	NS
ERPF (exercise, mL · min <sup>-1</sup> · 1.73 <sup>-2</sup> )	407 ± 13	447 ± 43	NS
GFR (basal, mL · min <sup>-1</sup> · 1.73 <sup>-2</sup> )	121 ± 3	120 ± 10	NS
GFR (exercise, mL · min <sup>-1</sup> · 1.73 <sup>-2</sup> )	112 ± 3	116 ± 9	NS

NS = not significant.

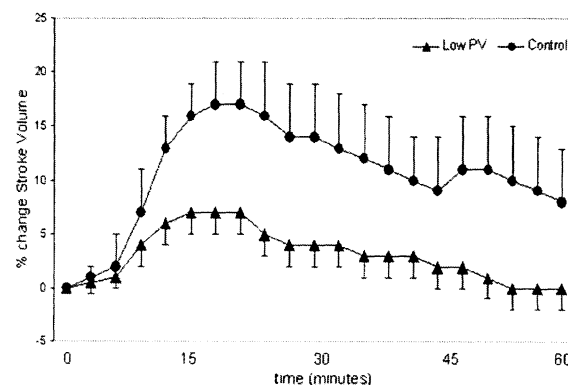
**Figure 1.** Heart rate response to exercise. The area under the curve is not different between groups.

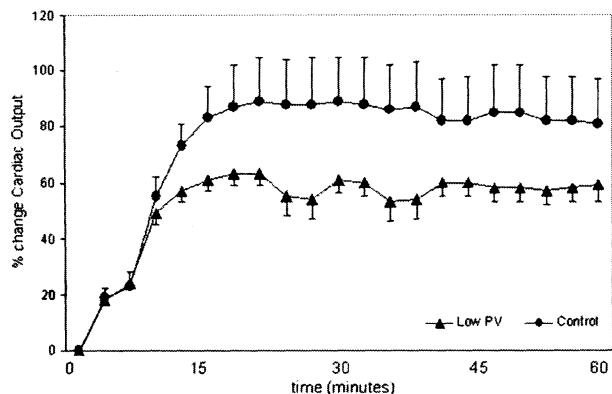
where.<sup>11</sup> Controls, recruited by advertisement, were all normotensive and had a history of uneventful pregnancies only. We started recruitment after approval of the study protocol by the University hospital's medical-ethical committee. After careful explanation of the protocol all participants gave written informed consent.

### Methods

All exercise experiments were performed in the follicular phase of the menstrual cycle (cycle day 5 ± 3) and were preceded by a "max-test" on the preceding day. The latter implied the assessment of maximum cycling capacity in all participants, defined as the maximum power at which a subject was able to cycle in our experimental set-up. To this end, all women cycled on the same ergometer at a starting power of 60 watts, with power being raised by increments of 30-20-10-10-etc watts, every 2 minutes. Women were instructed to continue cycling until unable to comply. The maximum power was defined as the highest power level during which they were able to keep cycling for at least 1 minute.

Participants refrained from smoking and consuming caffeine- and/or alcohol-containing substances after the max-test until the exercise experiment on the subsequent day. During that experiment, the participants were quietly laying in supine

**Figure 2.** Stroke volume response to exercise. The area under the curve differs between groups ( $P < .05$ ).

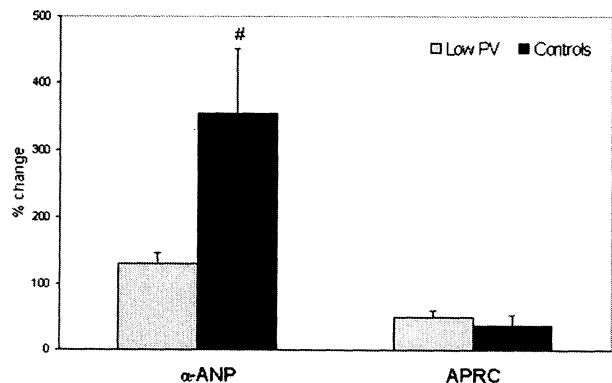


**Figure 3.** Cardiac output response to exercise. The area under the curve differs between groups ( $P < .05$ ).

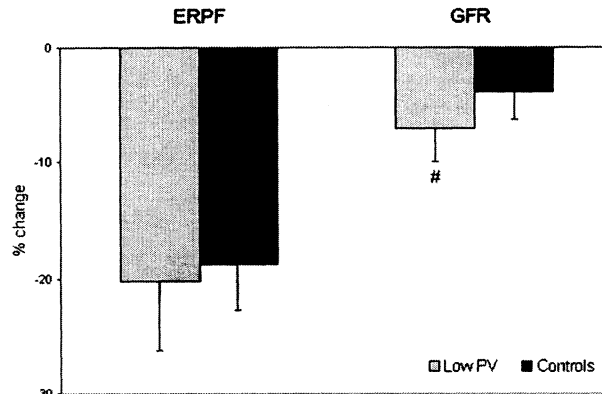
position in a room standardized for temperature ( $23 \pm 1$ C), humidity and noise level. Before and during exercise, we sampled blood for the measurement of circulating levels of  $\alpha$ -ANP ( $\text{ng} \cdot \text{L}^{-1}$ ) and APRC ( $\text{mU} \cdot \text{L}^{-1}$ ). For this purpose, we collected blood samples in chilled tubes, which were put on ice during transport and processed within minutes after collection. Processed samples were stored at  $-70$ C until analysis.  $\alpha$ -ANP and APRC were measured as detailed previously.<sup>12</sup> One hundred twenty minutes prior to the exercise experiment, we determined plasma volume by the dextran-70 indicator dilution method.<sup>13</sup> Plasma volume is expressed in mL per kg calculated lean body mass.<sup>1</sup>

We measured ERPF and GFR on the basis of a continuous intravenous infusion of para-amino-hippurate sodium (PAH) and inulin.<sup>1</sup> After at least 120 minutes of PAH/inulin infusion, blood samples were collected to measure basal  $\alpha$ -ANP, APRC, ERPF, and GFR. After blood sampling, each participant was carefully positioned on a supine cycle ergometer (Echo Cardiac Stress Table, Lode Medical Technology, Groningen, The Netherlands) and allowed to acclimatize to this position for 30 minutes. Then they started exercise for a period of 60 minutes at a power (watt), corresponding with 35% of each individual's own maximum power as determined on the previous day.

We recorded the percentage change in stroke volume, heart



**Figure 4.** Responses in  $\alpha$ -ANP and APRC to exercise. Exercise-induced values were significantly different from baseline values within each group ( $P < .05$ ). #Difference between groups ( $P < .05$ ).



**Figure 5.** Responses in ERPF and GFR to exercise. Exercise-induced values were significantly different from baseline values within each group ( $P < .05$ ). #Difference between groups ( $P < .05$ ).

rate and cardiac output during exercise, using the mean values of 3 minutes of beat-to-beat analysis by the Portapress device for continuous pulse contour analysis (TNO-Biomedical Instrumentation, Amsterdam, The Netherlands).<sup>14</sup> This technique has been validated for estimating intra-individual changes in stroke volume over time, without providing information on absolute values.<sup>15-17</sup>

### Statistical Methods

We compared patient and control groups with respect to basal levels of  $\alpha$ -ANP and APRC and the response to exercise in heart rate, stroke volume, and cardiac output by calculating the area-under-the-curve (AUC). The AUC for percent change in stroke volume relative to baseline throughout 60 minutes of exercise provides an estimate for "cumulative" rise in stroke volume. The latter varies as a function of the decline in stroke volume throughout the exercise period, and therefore was used in this study as an estimate for relative cardiovascular drift. Differences between the two groups in the three AUCs were tested using the Mann-Whitney  $U$  test. The Wilcoxon signed rank test was used to compare in each group the pre- and post-exercise values for  $\alpha$ -ANP, APRC, ERPF, and GFR. A  $P$  value less than .05 was considered statistically significant.

To determine whether plasma volume was an independent predictor of stroke volume changes or whether these changes were confounded by differences in body mass index (BMI), we performed a logistic regression analysis with stroke volume change as dependent, and plasma volume and BMI as independent variables.

## RESULTS

Table 1 lists the demographic characteristics of the two study groups. As compared to the control group, the patient group (low-PV) was younger, had a higher BMI, comparable parity, and by definition, a lower plasma volume and were comparable regarding microalbuminuria. Table 2 indicates that maximal power, basal heart rate, and heart rate at maximal power were comparable in the patient and control groups. The same



holds for absolute values of ERPF and GFR before and after 60 minutes of exercise. The coefficient of variation (CV) in ERPF and GFR was clearly higher in controls (CV = 9% to 10%) than in the patient groups (CV = 3% to 4%), most likely in conjunction with the limited size of the control group.

Figures 1, 2, and 3 illustrate the relative changes in response to exercise, in heart rate, stroke volume, and cardiac output, respectively. In both groups, exercise induced a rapid rise in heart rate, which reached a comparable and stable plateau of about 50% to 60% above baseline, 173 beats/min  $\pm$  14 in low-PV versus 174 beats/min  $\pm$  12 in controls, after about 15 minutes (Figure 1). In contrast, the response of stroke volume to exercise differed between the low-PV and control groups. Although the pattern of response—transient initial rise in stroke volume followed by cardiovascular drift after 15 minutes—was comparable in the two groups, the average percentage rise in stroke volume was clearly higher in the control group (Figure 2; 17%  $\pm$  3% vs 7%  $\pm$  2%;  $P < .05$ ). Figure 3 shows that exercise induced a smaller rise in cardiac output in the low-PV group than in the control group (70%  $\pm$  5% vs 90%  $\pm$  17%;  $P < .05$ ).

The percentage changes in  $\alpha$ -ANP and APRC are displayed in Figure 4. The exercise-induced increase in absolute values in circulating  $\alpha$ -ANP levels was smaller in women in the low-PV group than in the controls (101  $\pm$  15 and 166  $\pm$  44 ng  $\cdot$  L<sup>-1</sup>;  $P < .05$ ). The two study groups were comparable with respect to the exercise-induced response in APRC. Finally, Figure 5 depicts the effect of exercise on ERPF and GFR. In both groups, ERPF and GFR decreased during exercise. Absolute values in ERPF and GFR did not differ, most likely due to the limited size of the control group. On the other hand, the percent decrease in GFR was significantly larger in the low-PV group than in the control group (-7%  $\pm$  1% vs -4%  $\pm$  1%;  $P < .05$ ). The exercise-induced increase in filtration fraction was similar in the low-PV and control groups: from 25%  $\pm$  1% to 28%  $\pm$  1% and from 22%  $\pm$  1% to 26%  $\pm$  1%, respectively.

Logistic regression analysis showed that the changes in stroke volume during exercise were dependent to plasma volume ( $P = .017$ ) and not to differences in BMI ( $P = .762$ ).

## DISCUSSION

The response to moderate exercise in formerly preeclamptic women with a subnormal plasma volume differs from that in controls by a smaller rise in  $\alpha$ -ANP, a blunted rise in stroke volume, a smaller rise in cardiac output, and finally, a comparable pattern of cardiovascular drift. Although the absolute loss in surplus stroke volume by cardiovascular drift after 60 minutes exercise was larger in the control group, the remaining extra stroke volume above baseline was still larger in the control group than in the patient group (Figure 2). The observations in this study suggest that women with a subnormal plasma volume have a reduced capacity to raise cardiac preload and with it, stroke volume and cardiac output in response to exercise. As these women have a reduced venous capacitance,<sup>18</sup> we postulate that the impact of a certain degree of venoconstriction on cardiac preload is smaller in these women than in their counterparts with

a normal plasma volume. Although one would expect a greater rise in heart rate in the low PV-group, to compensate for the lack of rise in stroke volume, we observed the opposite, ie, a tendency towards a lower heart rate (Figure 1). We speculate that the inadequate rise in heart rate to compensate for the relatively small increase in stroke volume may be explained by a blunted rise in sympathetic nervous activity in the low PV-group, possibly in conjunction with an already elevated basal sympathetic activity in these women.<sup>19</sup>

In both the low-PV group and the controls, exercise triggered a comparable fall in ERPF, an observation that is in line with observations by others<sup>20</sup> and which probably results from a higher sympathetic nervous activity. Interestingly, our low-PV group differed from controls by responding to exercise with a significant fall in GFR, similarly as previously reported for subjects with impaired renal function.<sup>21</sup> However, it was not possible to deduce from our data whether the larger fall in GFR in our low-PV patients was related to latent renal dysfunction or to the subnormal vascular filling state. Microalbuminuria in basal conditions did not differ between the two groups (0.8  $\pm$  0.5 g albumin/mol creatinin in low-PV vs 0.7  $\pm$  0.8 g albumin/mol creatinin in controls). And macroalbuminuria did not occur in the low-PV group. In addition, all renal PAH/inulin clearances were within the normal range for all participants. Therefore, the abnormal hemodynamic response to exercise in the low-PV group is most likely a direct consequence of the subnormal filling state. The women in the low PV-group had a slightly higher BMI. The latter may be of some influence on the hemodynamic response to exercise. However, we think that the difference in BMI between the two groups is too small to contribute to substantial differences in hemodynamic responses to exercise.

Exercise triggers a rise in cardiac output, which in turn, requires a higher venous return. The latter is achieved by venoconstriction, which reduces venous capacitance and with it, increases cardiac preload.<sup>22-25</sup> In a recent study, we provided experimental evidence for an association between plasma volume and venous capacitance.<sup>18</sup> From these data and the results in the present study, we conclude that women with a subnormal plasma volume have a reduced capacity to raise venous return during exercise as a result of a subnormal venous capacitance, which limits their capacity to increase preload.

Venous return is related to plasma volume. In trained athletes an increased plasma volume acts as a volume buffer during exercise, enabling a sustained elevation of stroke volume.<sup>26,27</sup> During exercise, mildly hypovolemic subjects have a lower increase in stroke volume and a compensatory higher rise in heart rate than their normovolemic counterparts.<sup>9,10</sup> Interestingly, the latter resembles the smaller rise in stroke volume in response to exercise in the low-PV group of this study, although the latter group fails to compensate for this effect by an appropriate rise in heart rate. At any rate, these inferences suggest that size of the plasma volume compartment and stroke volume are causally related.<sup>28</sup>

In the present study, we evaluated the cardiovascular reserves of formerly preeclamptic women with a subnormal

plasma volume. It is difficult to extrapolate these results obtained during a 1-hour period of moderate exercise to pregnancy, when cardiac output remains elevated for a period of months. Previous data on the adaptation of women with a subnormal plasma volume to pregnancy provide evidence for a blunted plasma volume expansion,<sup>12</sup> accompanied by signs of increased cardiovascular sympathetic tone.<sup>29</sup> A low pre-pregnant plasma volume and a lack of plasma volume expansion can be expected to hamper the institution of a high-flow/low-resistance circulation. Such an adaptive response predisposes to the development of preeclampsia.<sup>30</sup>

### Conclusion

Normotensive formerly preeclamptic women with a subnormal plasma volume are unable to keep stroke volume elevated during moderate exercise. We speculate that this response also applies to pregnancy, when cardiac output is elevated for a prolonged period. Their inability to preserve an elevated cardiac output raises their chance to develop a hypertensive disorder in pregnancy.

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