Forearm training reduces the exercise pressor reflex during ischemic rhythmic handgrip

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Mostoufi-Moab, Sogol, Eric J. Widmaier, Jacob A. Cornett, Kristen Gray, and Lawrence I. Sinoway. Forearm training reduces the exercise pressor reflex during ischemic rhythmic handgrip. J. Appl. Physiol. 84(1): 277–283, 1998.—We examined the effects of unilateral, nondominant forearm training (4 wk) on blood pressure and forearm metabolites during ischemic and nonischemic rhythmic handgrip (30 1-s contractions/min at 25% maximal voluntary contraction). Contractions were performed by 10 subjects with the forearm enclosed in a pressurized Plexiglas tank to induce ischemic conditions. Training increased the endurance time in the nondominant arm by 102% (protocol 1). In protocol 2, tank pressure was increased in increments of 10 mmHg/min to +50 mmHg. Training raised the positive-pressure threshold necessary to engage the pressor response. In protocol 3, handgrip was performed at +50 mmHg and venous blood samples were analyzed. Training attenuated mean arterial pressure (109 ± 5 and 98 ± 4 mmHg pre- and posttraining, respectively, P < 0.01), venous lactate (2.9 ± 0.4 and 1.8 ± 0.3 mmol/l pre- and posttraining, respectively, P < 0.01), and the pH response (7.21 ± 0.02 and 7.25 ± 0.01, pre-and posttraining, respectively, P < 0.01). However, deep venous O2 saturation was unchanged. Training increased the positive-pressure threshold for metaboreceptor engagement, reduced metabolite concentrations, and reduced mean arterial pressure during ischemic exercise.

metaboreceptor; reflex pressor response; sympathetic nervous system; ischemic exercise

During systemic exercise, vascular conductance in exercising skeletal muscle is tightly linked to cardiac output. This linkage is present, despite the fact that intrinsic skeletal muscle vasodilator capacity can greatly exceed maximal cardiac output (33, 34). Therefore, some vasconstrictor system must be activated during exercise to oppose this potent vasodilator system (6, 13, 14, 16, 42, 52). Previous studies have shown that increased sympathetic nervous system tone plays an important role in constricting dilated skeletal muscle blood vessels during exercise, preventing a fall in blood pressure (BP) (15, 22, 30, 52).

During rhythmic exercise, muscle metabolites byproducts are released into the muscle interstitium, stimulating muscle afferents in the contracting muscle, thereby evoking a potent reflex. This reflex increases BP and may oppose the potent metabolic dilator systems in skeletal muscle. Previous work in humans has demonstrated that exercise increases sympathetic discharge to active and inactive muscle (10). Additionally, measures designed to block sympathetic constrictor outflow augment flow to exercising muscle (14, 23). This indicates that the sympathetic nervous system acts to restrain skeletal muscle blood flow during exercise.

In humans, exercise conditioning increases skeletal muscle dilator capacity (40, 41, 48) and reduces sympathetic vasoconstrictor responses (25, 44, 49). This reduction in sympathoexcitation during exercise may be due in part to a reduction in metaboreceptor-mediated activation of muscle reflex (49). We examined the effects of forearm conditioning on the autonomic and metabolic responses to forearm exercise under normal and low-flow conditions. We speculated that conditioning would reduce metabolite production and would, in the process, reduce BP and raise forearm venous O2 saturation. To accomplish this goal, exercise was performed while the forearm was sealed in a Plexiglas tank capable of generating and sustaining high levels of positive or negative pressure. Previous studies (7) have shown that the external pressure generated in the tank is fully transmitted throughout the muscle tissue and its vessels. Although arterial pressure is not affected by increasing external pressure, local transmural venous pressure rises until it exceeds the elevated tissue pressure. As a result, perfusion pressure is reduced and a point is reached where a mismatch between O2 demand and delivery generates ischemic conditions. This type of device was originally designed for lower extremity use (7) and was later modified for forearm exercise (12). The results of our study demonstrate that conditioning reduced the forearm metabolic and pressor responses to ischemic exercise. On the other hand, mixed venous O2 saturation was unchanged by the conditioning paradigm.

METHODS

Ten healthy men (22 ± 1 yr) participated in the study. The subjects were normotensive nonsmokers who were not taking any medications. Each subject gave written informed consent, and procedures used in the study had prior approval of the Institutional Review Board. Three separate protocols were performed by the subjects.

In protocol 1, subjects performed rhythmic handgrip with both forearms at ~35% maximal voluntary contraction (MVC; 12 2-s contractions/min) until fatigue. Protocol 1 was designed to determine whether the conditioning paradigm elicited a training effect.

Protocol 2, a modified version of the exercise protocol described by Joyner et al. (13, 14), was designed to evaluate reflex increases in mean arterial pressure (MAP) in response to graded reductions in exercising muscle perfusion pressure. Protocol 3 was designed to examine muscle metabolism, the O2 saturation of hemoglobin, and BP regulation during a given level of flow reduction. All protocols were repeated at the end of a 4-wk training period to examine the effects of the
training. Protocols 2 and 3 are presented schematically in Figs. 1 and 2, respectively.

Protocol 2

All 10 subjects performed two 6-min trials of rhythmic forearm exercise (30 1-s contractions/min) at 25% MVC. One trial was a 6-min bout of exercise at 25% MVC at ambient pressure. In the other exercise trial the pressure in the tank was increased in increments of 10 mmHg/min after 1 min of exercise until +50 mmHg was reached (total 6 min). The ambient pressure and positive-pressure trials were randomized, with a 10- to 15-min rest period separating each trial.

Instrumentation for protocol 2. To obtain low-flow conditions during contraction of forearm muscles, each subject performed the rhythmic handgrip exercise while lying supine on a table, with the hand, forearm, and arm immediately proximal to the elbow enclosed in a Plexiglas tank. A seal was formed around the arm. By increasing the pressure in the tank, it was possible to reduce the perfusion pressure in the exercising muscles. MAP and heart rate (HR) were measured continuously throughout the protocol using a Finapres device (Ohmeda, Madison, WI).

Protocol 3

All 10 subjects performed two 6-min trials of rhythmic forearm exercise (25% MVC) at a cadence of 30 1-s contractions/min preceded by 5 min of baseline. In the time control trial, exercise without positive pressure was performed for 6 min. In the positive-pressure trial the pressure in the forearm tank was increased to +50 mmHg before the start of exercise and was maintained throughout the 6-min exercise period and a 5-min recovery period. There was a 10- to 15-min rest period between trials, and the order of trials was randomized.

Instrumentation for protocol 3. The subjects were placed supine on a padded table. HR and MAP were continually measured using a Finapres device. A 20-gauge intravenous catheter was inserted retrogradely into an antecubital vein in the nondominant forearm. Venous blood was sampled for pH, PO₂, PCO₂, and calculated hemoglobin O₂ saturation (model ABL 510, Radiometer). Venous lactate was also measured (2300 Stat Plus, Yellow Springs Instruments, Yellow Springs, OH). Care was taken to note the exact location of catheter insertion to ensure appropriate pre- and posttraining comparisons. The subjects wore a nonrebreathing facemask, and minute ventilation and end-tidal PCO₂ were measured using a respiratory gas monitor (Ohmeda).

After instrumentation the subjects rested for a 5-min baseline period. In the last 30 s of the baseline period (at 4.5 min), a 0.5-ml blood sample was drawn. Blood samples were obtained 30 s into minutes 1, 3, and 5 of rhythmic handgrip exercise (G1, G3, and G5) of both trials.

Training Regimen

The training regimen was similar to that used previously by our laboratory (44). Subjects were given a spring-loaded variable-tension handgrip dynamometer and were instructed to exercise 5 days/wk. The subjects exercised the nondominant forearm at a cadence of 12 contractions/min beginning at 30–35% MVC until fatigue. When the subject was able to exercise at a given workload for 30 min, the workload was increased. The investigators were in verbal contact with the subjects on a weekly basis to monitor compliance and change the workloads.

Statistical Analysis

Protocol 1. Pre- and post-MVC and endurance times were compared using a paired t-test.

Protocol 2. The MAP values were recorded for each minute of handgrip exercise during the ambient pressure and graded positive-pressure trials. A one-way analysis of variance was performed for each of the four trials (ambient and positive pressure before and after training). In this analysis, comparisons were made between G1 and each successive minute. We observed significant P values during the positive-pressure, but not the ambient pressure, runs; therefore, MAP differ-

<table>
<thead>
<tr>
<th>A</th>
<th>Base</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>Recovery</th>
</tr>
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<tr>
<td></td>
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<td>25% MVC</td>
<td>Rhythmic</td>
<td>Handgrip</td>
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<thead>
<tr>
<th>B</th>
<th>Base</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>Recovery</th>
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<td>Rhythmic</td>
<td>Handgrip</td>
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Fig. 1. Protocol used to evaluate reflex increases in blood pressure in response to graded reduction in exercising muscle perfusion pressure. Subjects (n = 10) performed two 6-min trials (G1–G6) of rhythmic forearm exercise [25% maximum voluntary contraction (MVC); 30 1-s contractions/min]. Exercise was performed at ambient pressure (A) and at graded positive-pressure increments of +10 mmHg (B). Both trials were repeated at end of a 4-wk training period to assess effects of training. Base, baseline.

Fig. 2. Protocol used to evaluate effects of training on ischemic rhythmic forearm exercise (25% MVC). Subjects (n = 10) performed two 6-min trials of forearm grip exercise (G1–G6) at a cadence of 30 1-s contractions/min at ambient pressure (A) and at +50 mmHg (B). Both trials were repeated at end of 4-wk training period.
ences between G1 and ensuing minutes during the positive-pressure trials were due predominantly to engagement of the ischemic pressor reflex. Pairwise comparisons between G1 and the ensuing minutes of exercise were performed using Tukey's test.

Protocol 3. A two-way analysis of variance was used to analyze the effects of exercise and conditioning on the various measured parameters. Ambient pressure and positive-pressure trials were analyzed separately. Post hoc comparisons were performed using Tukey's test.

For all analyses, \( P < 0.05 \) was considered statistically significant. Values are means \( \pm SE \).

RESULTS

Protocol 1

The conditioning paradigm had no effect on MVC in the trained or the untrained forearm (Table 1). Endurance time was increased in both forearms: in the trained forearm, endurance time more than doubled; in the untrained forearm the increase in endurance time was much smaller. These training effects are similar to those previously reported by our laboratory (44).

Protocol 2

During the ambient pressure runs before and after training, MAP did not increase after G1. Before training the MAP values during +40- and +50-mmHg trials were greater than the G1 value. After training, MAP during the +40-mmHg trial was no longer different from the G1 value (Fig. 3). Thus training increased the positive-pressure value necessary to engage the ischemic pressor reflex.

Protocol 3

Training led to attenuated MAP responses during the +50-mmHg exercise trial (Fig. 4). No effect of training was seen during the ambient pressure trial (\( P > 0.12 \)). A conditioning effect on the MAP response was evident during the ischemic exercise trial. Post hoc analysis demonstrated a significant training effect by 3 min of ischemic handgrip.

Training had no effect on the lactate responses during the ambient pressure trial. However, 4 wk of forearm training led to a large reduction in the venous lactate response seen with ischemic exercise (Fig. 5).

Table 1. Resting values and results of endurance test: protocol 1

<table>
<thead>
<tr>
<th></th>
<th>Trained Arm</th>
<th>Untrained Arm</th>
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<tbody>
<tr>
<td></td>
<td>Pretest</td>
<td>Posttest</td>
</tr>
<tr>
<td>Endurance time, min</td>
<td>16.2 ± 2.2</td>
<td>32.7 ± 4.3*</td>
</tr>
<tr>
<td>MVC, kg</td>
<td>46 ± 2</td>
<td>46 ± 2</td>
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</table>

Values are means \( \pm SE \). Endurance time for rhythmic forearm exercise was measured in 9 of 10 subjects. Maximal voluntary contraction (MVC) was measured in trained (nondominant) forearm in 8 subjects and in untrained (dominant) forearm in 7 subjects. * \( P < 0.05 \).
After conditioning, forearm venous lactate after 3 min of exercise was 61.5% of the pretraining value, and at 5 min of handgrip the posttraining value was 61.0% of the pretraining value.

During the ambient pressure trial, pointwise comparisons did not demonstrate an effect of training on venous pH, although a significant statistical interaction was noted. However, during ischemic handgrip we observed an attenuated fall in pH during the measurements at 3 and 5 min (Fig. 6).

Forearm training had no effect on the minute ventilation. There was a trend toward a training effect on Pco₂; however, the magnitude of this effect was small, and its physiological significance is unclear. Training also had no effect on venous O₂ saturation levels at ambient pressure and +50 mmHg (Fig. 7). A significant interaction was noted for the HR response during the +50-mmHg trial; however, pointwise differences (Tukey’s test) were not significant, and a training main effect was not seen (Table 2).

**DISCUSSION**

We have demonstrated that the selected exercise-conditioning paradigm decreased lactate accumulation and venous pH values during ischemic exercise. We also observed an attenuated pressor response during ischemic exercise, suggesting that muscle metaboreceptor responses were attenuated by training. We did not observe an effect of training on forearm venous O₂ saturation. In addition, the results of protocol 2 suggest that training altered the relationship between graded flow reductions and the threshold for engagement of the ischemic pressor reflex. In the remainder of this discussion, we will consider the mechanisms responsible for the autonomic adjustments to exercise and training, possible explanations for our findings, and the potential application of our observations to specific cardiovascular conditions.

**Reflex Responses to Exercise and the Effects of Conditioning**

Rhythmic handgrip exercise results in increases in BP, HR, and sympathetic nerve activity (2, 8, 17, 24, 29, 44). The rise in BP is due, in part, to increases in HR and cardiac output through vagal withdrawal (20, 53,
Table 2. Effects of training on HR, ventilation, and PCO2 responses: protocol 3

<table>
<thead>
<tr>
<th>Ambient trial</th>
<th>Training G1</th>
<th>Training G2</th>
<th>Training G3</th>
<th>Training G4</th>
<th>Training G5</th>
<th>Training G6</th>
<th>P</th>
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<tr>
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<tr>
<td>Pretraining</td>
<td>58 ± 1</td>
<td>64 ± 3</td>
<td>61 ± 3</td>
<td>64 ± 3</td>
<td>64 ± 2</td>
<td>64 ± 3</td>
<td></td>
</tr>
<tr>
<td>Posttraining</td>
<td>61 ± 5</td>
<td>63 ± 5</td>
<td>61 ± 5</td>
<td>61 ± 5</td>
<td>65 ± 5</td>
<td>63 ± 5</td>
<td>NS &lt;0.001 NS</td>
</tr>
<tr>
<td>Ventilation, l/min</td>
<td>7.8 ± 0.4</td>
<td>8.6 ± 0.5</td>
<td>8.9 ± 0.5</td>
<td>8.5 ± 0.3</td>
<td>9.0 ± 0.5</td>
<td>8.9 ± 0.4</td>
<td>9.0 ± 0.3</td>
</tr>
<tr>
<td>PCO2, Torr</td>
<td>40 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>40 ± 1</td>
<td></td>
</tr>
<tr>
<td>Posttraining</td>
<td>41 ± 1</td>
<td>42 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>42 ± 1</td>
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<td>NS NS NS</td>
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<td>+50-mmHg trial</td>
<td></td>
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<td>HR, beats/min</td>
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<tr>
<td>Pretraining</td>
<td>57 ± 1</td>
<td>61 ± 3</td>
<td>63 ± 3</td>
<td>65 ± 3</td>
<td>67 ± 3</td>
<td>69 ± 4</td>
<td>69 ± 3</td>
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<tr>
<td>Posttraining</td>
<td>63 ± 5</td>
<td>66 ± 6</td>
<td>68 ± 6</td>
<td>66 ± 6</td>
<td>67 ± 5</td>
<td>68 ± 6</td>
<td>70 ± 7</td>
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<td>Ventilation, l/min</td>
<td>7.8 ± 0.5</td>
<td>8.4 ± 0.5</td>
<td>8.4 ± 0.5</td>
<td>8.6 ± 0.6</td>
<td>9.0 ± 0.5</td>
<td>8.8 ± 0.5</td>
<td>8.9 ± 0.6</td>
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<tr>
<td>PCO2, Torr</td>
<td>40 ± 0</td>
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<tr>
<td>Posttraining</td>
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<td>42 ± 1</td>
<td>41 ± 1</td>
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Values are means ± SE. HR, heart rate; PCO2, end-tidal PCO2; Base, mean of 5 min of baseline; G1–G6, 6 min of rhythmic handgrip exercise at 25% MVC.

54). These changes in HR are thought to be due to central command activation, a central neural process linking motor outflow to autonomic activity (11, 19, 21, 31, 54).

A mismatch between blood flow and metabolism in the exercising muscle causes a change in the concentrations of metabolites that are detected by metabolite-sensitive nerve endings within the skeletal muscle interstitium. Lactic acid (27), hydrogen ions (53), arachidonic acid (26, 28), potassium (35, 36), adenosine (4, 5), and diprotonated phosphate (46) have been suggested as potential afferent stimulants. One or more of these substances are likely to increase the discharge of group IV (metaboreceptor) afferent fibers (27, 33, 51), initiating a potent reflex that increases sympathetic nerve activity directed to skeletal muscle in humans (53). This leads to vasoconstriction, which contributes to the rise in BP seen with exercise (39, 43). Metaboreceptor activation may also increase HR and cardiac output (32, 47). Because mismatches between blood flow and metabolism trigger the reflex, reductions in flow during exercise will effectively engage this system, evoking prominent increases in BP (33).

The effects of endurance training on skeletal muscle include increased capillary density (1), increased mitochondrial density (3, 9), activation of oxidative enzymes (9), and increased O2 extraction (38). β-Oxidation of free fatty acids and aerobic utilization of muscle glycogen are affected by conditioning, whereas anaerobic glycolysis appears to be influenced by conditioning to a far smaller degree (37). Increased vascular flow, together with an increased ability of trained muscle to maintain aerobic metabolism, decreases the reliance on anaerobic metabolism for a given level of muscle contraction. This in turn should lower interstitial concentrations of metabolites, causing less stimulation of metaboreceptors, thereby evoking a smaller sympathetic response (53).

Experimental Findings

We have speculated that after exercise conditioning a greater fall in blood flow would be necessary to engage the metaboreflex, and this would decrease the magnitude of the pressor response at a given level of positive external pressure. In addition, we hypothesized that conditioning would reduce metaboreceptor-induced vasoconstriction within the exercising muscle and thereby raise O2 saturation in the blood draining the working forearm skeletal muscle. In protocol 2 we used incremental forearm positive pressure to examine the effects of training on the pressor response seen with graded ischemic exercise. We reasoned that by gradually impeding blood flow to the actively contracting muscle (instead of rapidly decreasing muscle blood flow before or at the end of exercise) we would be able to examine skeletal muscle metaboreceptor activity during exercise itself, rather than during a period of postexercise muscle ischemia.

Incremental flow reductions were achieved by the application of external positive pressure around the exercising forearm, which was enclosed in a Plexiglas tank. Positive pressure in the tank reduced transmural intravascular pressure in the exercising forearm and thus lowered flow. This approach has been well characterized in previous reports (7, 12, 55). After training, a higher level of positive pressure was necessary to engage the reflex, and the magnitude of pressor response was attenuated. In pretraining trials an external pressure of +40 mmHg was needed to engage the reflex, whereas after training +50 mmHg was neces-
nary. We interpreted these findings as suggesting that training raised the "ischemic threshold" for engagement of the muscle metaboreflex. To our knowledge, this is the first report demonstrating this phenomenon.

In protocol 3 we demonstrated a training-induced reduction in venous lactate accumulation and the pH response during the +50-mmHg trial. These results, coupled with the attenuated rise in BP after training, suggest that metaboreceptor activation was reduced by conditioning. Previous studies by Somers et al. (49) and our group (45) suggest that training reduces sympathetic nerve responses to isometric exercise. The results of the present report provide strong evidence that BP responses to metaboreceptor engagement are also reduced by training. Moreover, our results suggest that reduced metaboreceptor activity is present not only during a period of postexercise ischemia but also during exercise, if a mismatch between muscle metabolism and flow is present.

In protocol 3 we also noted that deep venous O₂ saturation responses to exercise during forearm pressure were unchanged by training. The fact that exercise training did not alter venous O₂ saturation during ambient pressure or positive-pressure runs suggests that flow was unchanged by training. A similar level of flow and a reduction in BP would be consistent with a fall in forearm vascular resistance in the exercising forearm after training. However, it must be emphasized that venous O₂ saturation measurements provide only a relative index of changes in flow. It must be understood that solely examining the effects of training on O₂ saturation does not take into consideration any potential effects of training on O₂ extraction or consumption. Additionally, changes in blood flow that are calculated from changes in venous O₂ saturation may underestimate changes in flow determined by plethysmography or xenon clearance (50).

Piepoli and colleagues (25), studying patients with heart failure and control subjects, demonstrated large increases in ventilation with forearm exercise that were attenuated by conditioning. We did not observe a large ventilatory response to handgrip or an attenuating influence of training. An explanation for the different observations in the two reports remains unclear. Perhaps some of the difference is due to the higher workload used by Piepoli et al. (50%MVC vs. 25%MVC in our study). It is possible that this led to a greater ventilatory response, and this allowed Piepoli et al. to detect a training-induced reduction in the ventilatory response to metaboreceptor engagement.

Potential Application of Our Results

The attenuated rise in BP response to exercise may be of value for patients suffering from congestive heart failure. In congestive heart failure, metaboreceptor-mediated increases in BP will increase the afterload on the already impaired left ventricle. Training-induced reductions in BP could alleviate this deleterious hindrance on the failing heart. Additionally, it is possible that the reduced vascular resistance within the exercising muscle may act to enhance flow delivery. Further studies are necessary to test this hypothesis.

Similarly, a reduced BP response to exercise could also benefit patients suffering from exertional angina, since posttraining reductions in BP will decrease myocardial O₂ consumption and the flow requirements of the ischemic heart. Thus reduced metaboreceptor activity could raise the threshold for angina development. It should also be mentioned that metaboreceptor activation causes coronary vasoconstriction, which could reduce flow delivery to an already ischemic heart (18).

In conclusion, handgrip exercise training reduces metabolite production during ischemic exercise. This results in an attenuated metaboreceptor-mediated rise in BP but has no effect on ventilation. Finally, forearm training raises the level of positive pressure necessary to engage the metaboreflex, suggesting that the ischemic threshold necessary to engage this reflex is raised by conditioning.

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