Oxygen uptake kinetics during low level exercise in patients with heart failure: relation to neurohormones, peak oxygen consumption, and clinical findings

H P Brunner-La Rocca, D Weilenmann, F Follath, M Schlumpf, H Rickli, C Schalcher, F E Maly, R Candinas, W Kiowski

Abstract

Objective—To investigate whether oxygen uptake (Vo2) kinetics during low intensity exercise are related to clinical signs, symptoms, and neurohumoral activation independently of peak oxygen consumption in chronic heart failure.

Design—Comparison of Vo2 kinetics with peak Vo2, neurohormones, and clinical signs of chronic heart failure.

Setting—Tertiary care centre.

Patients—48 patients with mild to moderate chronic heart failure.

Interventions—Treadmill exercise testing with “breath by breath” gas exchange monitoring. Measurement of atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), and noradrenaline. Assessment of clinical findings by questionnaire.

Main outcome measures—O2 kinetics were defined as O2 deficit (time [rest to steady state] × ΔVo2 - ΣVo2 [rest to steady state]; normalised to body weight) and mean response time of oxygen consumption (MRT; O2 deficit/ΔVo2). Results—Vo2 kinetics were weakly to moderately correlated to the peak Vo2 (O2 deficit, r = -0.37, p < 0.05; MRT, r = -0.49, p < 0.001). Natriuretic peptides were more closely correlated with MRT (ANF, r = 0.58; BNP, r = 0.53, p < 0.001) than with O2 deficit (ANF, r = 0.48, p = 0.001; BNP, r = 0.37, p < 0.01) or peak Vo2 (ANF, r = -0.40; BNP, r = -0.31, p < 0.05). Noradrenaline was correlated with MRT (r = 0.33, p < 0.05) and O2 deficit (r = 0.39, p < 0.01) but not with peak Vo2 (r = -0.20, NS). Symptoms of chronic heart failure were correlated with all indices of oxygen consumption (MRT, r = 0.47, p < 0.01; O2 deficit, r = 0.39, p < 0.01; peak Vo2, r = -0.48, p < 0.01). Multivariate analysis showed that the correlation of Vo2 kinetics with neurohormones and symptoms of chronic heart failure were independent of peak Vo2 and other variables.

Conclusions—Oxygen kinetics during low intensity exercise may provide additional information over peak Vo2 in patients with chronic heart failure, given the better correlation with neurohormones which represent an index of homeostasis of the cardiovascular system.

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Keywords: oxygen consumption; low intensity exercise; heart failure; neurohormones

Oxygen uptake is directly related to cardiac output and tissue oxygen extraction, and the rate of change of oxygen uptake at exercise onset—that is, the oxygen kinetics—are related to the increase in cardiac output.1 Although cardiac output at rest may be normal even in patients with severe left ventricular dysfunction, stroke volume may increase inadequately during exercise. On the one hand, this leads to a reduced peak oxygen consumption at maximal exercise;4 on the other hand, it has been shown that oxygen kinetics at exercise onset are altered in patients with congestive heart failure.1 3 5

While peak oxygen consumption is widely accepted as a good marker of prognosis in patients with congestive heart failure,2−4 the meaning of altered oxygen kinetics in these patients is less well defined. Apart from the unknown prognostic significance of oxygen kinetics, their relation to symptoms, signs, and other features of congestive heart failure such as neurohumoral stimulation is largely unknown. In addition, studies investigating the relation between oxygen kinetics and the oxygen kinetics at exercise onset have provided conflicting results.5 7 8 11 This may partly be explained by the fact that measurements of oxygen kinetics are not yet standardised and different approaches have been used.

It was therefore our aim in this study to investigate the relation between oxygen kinetics and a broad spectrum of indicators of congestive heart failure. We hypothesised that oxygen kinetics, expressed as oxygen deficit and mean response time of oxygen consumption, are related to clinical signs, symptoms, and neurohumoral activation independently of peak oxygen consumption in patients with mild to moderate congestive heart failure.

Methods

PATIENT POPULATION

The study comprised 48 patients (44 male, four female) aged 33 to 74 years (mean (SD), 55 (10) years); 26 (54%) had mild to moderate chronic congestive heart failure secondary to coronary artery disease (as documented by coronary angiography); 18 (38%) had dilated cardiomyopathy; and four (8%) had valvar heart disease. All patients had an ejection...
fraction of ≤ 40% (mean (SD) 28 (7)%) and had been in a stable condition for at least three months. All were on angiotensin converting enzyme (ACE) inhibitors and diuretics, 28 were on digitals, and 22 were on amiodarone; no patients were on β blockers. Patients whose exercise capacity was limited for reasons other than congestive heart failure were excluded from the study.

The protocol was approved by the local ethics committee, and patients gave informed consent for their participation in the study.

EVALUATION CRITERIA

All patients were examined in the morning. A history of symptoms of congestive heart failure was elicited by a standard questionnaire, and severity of dyspnoea, orthopnoea, ankle oedema, and nocturia were judged on a scale from 0 to 3. After insertion of a venous line for blood sampling, patients rested in supine position for 30 minutes. Thereafter, blood samples were taken and clinical examination was performed. Rales on chest auscultation, ankle oedema, and examination of the jugular vein were used to assess whether physical signs of congestive heart failure were present.

Blood pressure was recorded at rest and during a Valsalva manoeuvre. Data were recorded on a computer and analysed offline by a person who was blinded to the results of the ergospirometry. The Valsalva manoeuvre was performed as follows. Patients were asked to initiate and maintain expiratory straining for 15 seconds after normal inspiration by blowing into a tube which was connected to a sphygmomanometer. The straining pressure was controlled at 30 mm Hg. The ratio of the blood pressure amplitude between the beginning and the end of the Valsalva manoeuvre was calculated using the first three beats and the last two beats during the straining period. This ratio was shown to correlate well with pulmonary capillary wedge pressure. The manoeuvre was repeated if the recording obtained was unsatisfactory.

ERGOSPIROMETRY

Exercise testing was performed on a treadmill using a two step protocol. The ECG was monitored continuously with a CASE 12 monitor (Marquette Corporation, Milwaukee, Wisconsin, USA). Gas exchange was assessed breath by breath using a CPX/D system from Medical Graphics Corporation (St Paul, Minnesota, USA). The system was calibrated before each test. Oxygen was analysed by a rapidly responding zirconia fuel cell and carbon dioxide by an infrared analyser. Flow measurements were performed using a disposable pneumotachograph.

Patients started walking after reaching a steady state of gas exchange for at least one minute while standing quietly on the treadmill. In order to define the starting point of walking precisely, patients stood with their feet on the edge of the treadmill and started walking after the device had reached a steady state level of programmed speed and elevation. Initially, they walked at 1.0 mph with an elevation of 6% for six minutes, corresponding to approximately 0.5 W/kg body weight. Thereafter, both speed and elevation were increased to augment work load by approximately 0.15 W/kg body weight/minute until exhaustion. Work load was assessed by calculating the power to overcome the elevation (speed * tan[grade] * g) and cover the distance. Horizontal energy exposure was estimated by rearrangement of the formula by the American College of Sports Medicine.

Oxygen uptake kinetics were assessed during the first six minutes of exercise. As previously reported, oxygen deficit was calculated according to the following formula:

\[ \text{O}_2 \text{ deficit} = t \times \Delta \text{VO}_2 - \Sigma \text{VO}_2 \]  

(1)

where \( t \) is time from rest to steady state (min), \( \Delta \text{VO}_2 \) is the difference between rest and steady state (ml/min), and \( \Sigma \text{VO}_2 \) is the sum of consumed oxygen from rest to steady state (ml). Two different methods were used to calculate the \( \Delta \text{VO}_2 \) deficit. First, software BreezeEx version 3.0 (Medical Graphics Corporation) was used and particular care was taken to optimise the correlation coefficient of curve fitting (fig 1). Second, \( \Delta \text{VO}_2 \) was summed by breath to determine the cumulative sum of oxygen consumption in excess of resting \( \text{VO}_2 \) over six minutes. This sum was subtracted from the product of the difference between resting and steady state \( \text{VO}_2 \) and six minutes according to formula 1, where \( t \) was set to six minutes. Since the results of these methods did not differ significantly, only the first was used. \( \text{O}_2 \) deficit is expressed as ml/kg body weight.
The mean response time (MRT) of oxygen consumption was calculated using the following formula:

\[ \text{MRT} = \frac{O_2 - \text{deficit}}{\Delta VO_2} \]  

(2)

Peak oxygen consumption was defined as maximum oxygen uptake during ramp exercise by averaging five of seven consecutive breaths; it is expressed in ml/min/kg body weight.

The same analysis was used to calculate the mean response time of heart rate increases during low intensity exercise. Data over 5 second periods were used for the calculations.

LABORATORY MEASUREMENTS

Venous blood was collected into chilled tubes containing EDTA and aprotinin (500 kU/ml blood) for assessment of natriuretic peptides, and into tubes containing lithium heparin for measurement of noradrenaline. Plasma was separated immediately using a refrigerated centrifuge and stored at ~80°C until measurement. Noradrenaline was measured by a high performance liquid chromatography separation method after solvent extraction.17 Atrial natriuretic factor (ANF) was determined directly—that is, without prior extraction, in duplicate by a competitive radioimmunoassay with 125I as tracer (Shionogi Chemical Company, Osaka, Japan). All analyses were performed by individuals who were blinded to results of ergospirometry.

STATISTICS

Values are expressed as frequencies and means (SD) as indicated. Correlations between continuous variables were assessed using the Pearson correlation test. For ordinal data (that is, history and clinical signs of heart failure), the Spearman rank correlation was used. Partial correlation and linear regression were used to test the independence of statistically significant correlations between two variables on covariables. Group comparisons were made using the unpaired Student’s t test or the Mann–Whitney U test, as appropriate. A two tailed significance level of 0.05 was considered statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 6.0).

Results

Patient characteristics are shown in table 1. Indices of neurohumoral stimulation were increased in most patients, although 65% were in New York Heart Association class II, and mean peak oxygen consumption was > 20 ml/kg/min. Mean respiratory exchange ratio at peak oxygen consumption was 1.11 (0.09), confirming the achievement of the anaerobic stage of exercise testing. In all but four patients, the respiratory exchange ratio was > 1.0. Calculations after exclusion of these four patients did not affect the results.

Twelve patients (25%) had chronotropic incompetence, defined as a maximum heart rate < 80% of the age predicted value. Although these patients had a significantly lower peak oxygen consumption (18.2 (3.3) ml/kg/min, p < 0.01) and a shorter exercise duration (8.4 (3.9) min, p < 0.05), neither oxygen kinetics during low intensity exercise nor neurohormonal measurements differed from the values found in the remaining patients. Heart rate increased similarly in both groups during low intensity exercise (19 (14) v 19 (11) beats/min, p > 0.1) but much less in those with chronotropic incompetence during maximum exercise (47 (14) v 76 (20) beats/min, p < 0.001). Mean response time of heart rate during low intensity exercise was not significantly prolonged in the patients with chronotropic incompetence (54 (28) v 44 (27) seconds, p > 0.1).

The correlation between the spirometry measurements is shown in table 2. As expected, there were close correlations between maximum work load and peak oxygen consumption, and between O2 deficit and mean response time of oxygen consumption at exercise onset. Although statistically significant, the correlation between peak exercise and oxygen kinetics at exercise onset was less close. Mean response time of heart rate at exercise onset was weakly but significantly correlated with oxygen kinetics and peak oxygen consumption.

Table 3 shows the correlations between spiroergometry, neurohormone measurements, signs

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Mean (SD)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55 (10)</td>
<td>33 to 74</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.3 (13.9)</td>
<td>50 to 123</td>
</tr>
<tr>
<td>Symptom score</td>
<td>3.3 (1.4)</td>
<td>1 to 7</td>
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<tr>
<td>Physical signs of CHF</td>
<td>17% (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Physical examination score</td>
<td>0.31 (0.85)</td>
<td>0 to 4</td>
</tr>
<tr>
<td>NYHA class (II/III)</td>
<td>31/17</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>27.6 (7.1)</td>
<td>11 to 40</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>117 (16)</td>
<td>92 to 150</td>
</tr>
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<td>Diastolic blood pressure (mm Hg)</td>
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<td>78 (15)</td>
<td>51 to 114</td>
</tr>
<tr>
<td>PAR during Valsalva manoeuvre (%)</td>
<td>69 (22)</td>
<td>18 to 106</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>169.2 (138.8)</td>
<td>24 to 738</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>289.4 (232.3)</td>
<td>3 to 1270</td>
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<table>
<thead>
<tr>
<th>Table 2 Correlation between spiroergometric variables</th>
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<tr>
<td>Peak VO2</td>
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<tr>
<td>Exercise capacity</td>
</tr>
<tr>
<td>O2 deficit</td>
</tr>
<tr>
<td>MRT O2</td>
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<tr>
<td>MRT HR</td>
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</tbody>
</table>

MRT O2, mean response time of oxygen consumption at exercise onset; MRT HR, mean response time of heart rate at exercise onset.
and symptoms of heart failure, and the response of the pulse amplitude to the Valsalva manoeuvre. These variables were also compared between patients with spiroergometric data below and above the median value. The data show that neurohormones were more closely related to oxygen kinetics than to peak oxygen consumption and maximum work load, respectively. Figure 2 gives scatterplots showing the relation of natriuretic peptides to peak oxygen consumption and mean response time at exercise onset, respectively. Although a wide range of variation existed between natriuretic peptides and mean response time, correlation was closer than between natriuretic peptides and peak oxygen consumption. While there was no correlation between noradrenaline and peak oxygen consumption, oxygen kinetics were significantly related to noradrenaline (fig 3).

The ratio of pulse amplitude of phase 2 and phase 1 of the Valsalva manoeuvre was significantly related only to mean response time of oxygen consumption. Signs and symptoms of congestive heart failure were equally related to peak oxygen consumption, maximum work load, and oxygen kinetics at exercise onset. Partial correlation analysis showed that the relations of oxygen kinetics to neurohormones, pulse amplitude ratio during the Valsalva manoeuvre, and symptoms of congestive heart failure, respectively, were not influenced by peak oxygen consumption, maximum work load, heart rate changes during exercise, ejection fraction, or body weight. However, the signs of congestive heart failure were not related to oxygen kinetics independently of peak oxygen consumption and exercise capacity. The relation of peak oxygen consumption

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<th>O₂ deficit</th>
<th>MRT</th>
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<td>135 (108)</td>
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<td>BNP (pg/ml)</td>
<td>266 (294)</td>
<td>254 (306)</td>
<td>140 (165)</td>
</tr>
<tr>
<td>NA (mmol/l)</td>
<td>4.1 (1.7)</td>
<td>3.9 (1.6)</td>
<td>3.3 (1.8)</td>
</tr>
<tr>
<td>PAR (%)</td>
<td>72 (24)</td>
<td>74 (24)</td>
<td>65 (25)</td>
</tr>
<tr>
<td>Symptoms present</td>
<td>27%</td>
<td>32%</td>
<td>4%</td>
</tr>
<tr>
<td>Signs present</td>
<td>27%</td>
<td>4%*</td>
<td>4%</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001.

ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; MRT, mean response time; NA, noradrenaline; PAR, pulse amplitude ratio (phase 2 and phase 1 of Valsalva manoeuvre); Signs, signs of congestive heart failure; Symptoms, symptoms of congestive heart failure.
and maximum work load to neurohormones was not influenced by heart rate changes during exercise, by chronotropic incompetence, or by the ejection fraction. Drugs did not influence the results. Multivariate regression analysis showed that all variables were removed from the equation except mean response time for natriuretic peptides and symptoms of heart failure, and oxygen deficit for noradrenaline.

Discussion

It has been shown that oxygen kinetics are delayed in patients with congestive heart failure,1 5–9 but no investigation has been done on which features of congestive heart failure are related to oxygen kinetics at exercise onset. In this prospective study, we observed correlations of neurohormones with oxygen kinetics at exercise onset which exceeded their correlations with variables related to maximum exercise (that is, peak oxygen consumption and maximal work load). These relations were independent of other indices of congestive heart failure. In addition, the mean response time of oxygen consumption at exercise onset showed a significant correlation only with the change in pulse amplitude induced by the Val-salva manoeuvre, which is closely related to the pulmonary capillary wedge pressure.11 17 The findings suggest that oxygen kinetics may provide additional information over measures obtained at peak exercise in the assessment of patients with congestive heart failure.

The response of oxygen consumption has three phases: phase I represents an immediate increase in oxygen consumption during the first 20 seconds of exercise; phase II is an exponential increase lasting two to three minutes; and phase III a steady state or slow drift depending whether the work load is below or above the anaerobic threshold.18 While phase I is caused by an immediate increase in blood flow through the lungs resulting from increased inotropy and increased venous return,19 phase II oxygen kinetics closely reflect muscular oxygen uptake after the onset of constant work rate exercise.20 Thus the delayed oxygen kinetics in patients with congestive heart failure are most probably caused by a decrease in oxygen availability to poorly perfused segments of exercising muscles as a result of an insufficient increase in cardiac output.1 Other factors linked to reduced ventilatory efficiency21 may also contribute to delayed oxygen kinetics.

In recent years, submaximal exercise testing has become more popular in assessing patients with congestive heart failure.1 5–9 21–26 In particular, the six minute walking test was shown to predict survival27 and was incorporated into studies of new therapeutic agents for patients with heart disease.28 29 The major advantages of a submaximal exercise test are threefold. First, it may more effectively evaluate the impairment and functional status during daily activities than maximal exercise testing, although in this study symptoms of congestive heart failure were equally related to both oxygen kinetics and indices of maximum work load testing. Nevertheless, significant correlations existed between these variables independently of each other. Second, patients in whom exercise capacity is limited for reasons other than cardiopulmonary disease may be examined by exercise testing during low intensity exercise only. Although the six minute walking test has been used increasingly, oxygen kinetics at exercise onset may provide some advantages since this test is largely independent of the compliance of the patient. Third, it has recently been shown that in patients with impaired ejection fraction early after myocardial infarction the increase in cardiac output at exercise onset may be delayed while the maximal cardiac output is still normal,1 although advanced impairment of systolic function leads to a reduction in cardiac output at every stage of exercise.30

Attempts have been made to predict peak oxygen consumption by submaximal exercise testing (for example, the six minute walk test).35 However, the kinetics of the increase and the maximum cardiac output achieved do not necessarily correspond.1 Low intensity exercise and peak exercise represent different types of cardiopulmonary response in terms of increment of cardiac output and ventilatory response. At the start of exercise, stroke volume increases first.36 However, the magnitude of the increase depends on factors such as the cardiac output and other factors.32 Further increases in cardiac output depend mainly on the increase in heart rate.36 Thus it may be that oxygen kinetics at exercise onset, with a low work load, are more dependent on changes of pump function than heart rate, while peak oxygen consumption is more heart rate dependent, in agreement with our results. This may also explain the influence of chronotropic incompetence on peak oxygen consumption while oxygen kinetics are unaffected. One could further speculate that the higher the work load, the more heart rate dependent oxygen kinetics become. This could explain the finding that the correlation between mean response time and peak oxygen consumption is better with a higher work load at steady state.33 This may also explain the better correlation between the two methods in heart failure patients using a higher work load than in the present study.37 Interestingly, a study in healthy volunteers using a low work load of 35 watts found a similar relation to the one shown in our present study.35 Nevertheless, comparison between different studies might be complicated by the difficulty in assessing peak oxygen consumption because of the influence of patient motivation and the subjective evaluation of the physician with regard to the end point of the exercise test.34 Several clinical trials have shown that neurohormonal stimulation is associated with the clinical progression of heart failure and indicates a poor prognosis independent of other clinical variables.5 35–39 In particular, levels of natriuretic peptides and noradrenaline seem to be good indices of the severity of heart failure, and clinical progression is reflected in their plasma levels. Against this background, it is tempting to speculate that oxygen kinetics at exercise onset may be a marker of prognosis in patients with congestive heart failure which is independent of peak oxygen
consumption, given the significant and independent correlations with natriuretic peptide and noradrenaline concentrations. However, larger trials would be required to address this question.

LIMITATIONS
There are several limitation of this study. The number of patients investigated is relatively small, making multivariate analysis difficult. Thus it is conceivable that the closer relations between oxygen kinetics and neurohormones than indices of maximum work load was a chance finding. However, the findings with two different neurohormones (natriuretic peptides and noradrenaline), symptoms of congestive heart failure, and an indirect assessment of pulmonary capillary wedge pressure were consistent. In addition, partial correlation showed that correlations between oxygen kinetics and the other variables were independent of maximal exercise testing. Multivariate regression further supported that finding. Hence it seems likely that oxygen kinetics provide additional information to peak oxygen consumption.

The work load at exercise onset was relatively low, making an influence of phase I of the oxygen uptake on oxygen kinetics likely. However, this work load was chosen to allow all patients to reach a steady state of oxygen consumption within six minutes of exercise. Since some of our patients had advanced heart failure, a relatively low work load was necessary to achieve this aim. Nevertheless, assessment of oxygen kinetics was possible in all patients and comparison between two different methods of calculation (that is, breath by breath and curve fitting) did not influence the results. In addition, depressed pump function might be better detected at low work load, as discussed above.

Patients on drugs that may influence heart rate response (for example, digoxin or amiodarone) were not excluded from this study. This might have influenced our results since an effect of β blockade on oxygen kinetics has been shown in healthy people.49 However, we recruited relatively unselected patients with heart failure, making our results applicable to most heart failure patients. In addition, our analysis showed that drug treatment did not affect the results significantly.

Finally, we used a protocol with a fixed treadmill speed and elevation rather than a fixed workload, which might have affected our results. However, protocols for treadmill exercise testing generally use steps with fixed speed and elevation, and partial correlation showed that body weight did not influence our results. Nevertheless, this may complicate any direct comparison between our present study and previous studies, as may the lack of an accepted standard for assessment of oxygen kinetics. Thus, standardisation of this kind of exercise testing is needed.

CONCLUSION
Our study shows that mean response time of oxygen consumption at exercise onset and oxygen deficit normalised by body weight, which do not require the patient's maximum effort, are more closely correlated with neurohumoral stimulation than with variables of maximum exercise such as peak oxygen consumption or maximum work load. Since neurohumoral stimulation represents an index of homeostasis of the cardiovascular system and relates to the severity, progression, and prognosis of heart failure, assessment of oxygen consumption during low intensity exercise may provide additional information over indices of peak exercise in patients with congestive heart failure. Finally, oxygen kinetics during low intensity exercise may be more suitable than peak exercise testing in patients whose exercise capacity is limited for reasons other than cardiopulmonary disease (mainly musculoskeletal disability).

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