**OBJECTIVES**
This study evaluated the response to prostacyclin dose reduction in patients with primary pulmonary hypertension (PPH) who developed high cardiac outputs.

**BACKGROUND**
Patients on prostacyclin require chronic upward dose titration to overcome tolerance to the medication. No upper limit of effective dose has been described.

**METHODS**
We studied 12 patients with PPH treated with chronic prostacyclin therapy who presented in high cardiac output states. Each patient underwent prostacyclin dose reduction under hemodynamic guidance targeted to reduce the cardiac index to ≤4 liter/min/M², unless rebound pulmonary hypertension occurred. Following dose reduction, patients were observed for changes in the effectiveness of the prostacyclin.

**RESULTS**
Patients were treated for 39 ± 20 months, resulting in a 71% reduction in pulmonary vascular resistance compared to baseline. At the time of their most recent evaluation their cardiac outputs were increased to 10.1 ± 2.3 liter/min. The patients underwent a 39% dose reduction (range 12% to 78%) resulting in a change of mean PAP from 45 to 46 mm Hg (p = NS), cardiac index from 7.4 ± 1.4 to 4 ± 0.74 liter/min/M² (p = 0.01), and pulmonary vascular resistance from 3.7 ± 1.7 to 4.7 ± 1.5 units (p < 0.001). In no instance did rebound pulmonary hypertension occur. However, the patients all retained their clinical benefit without a return of tolerance.

**CONCLUSIONS**
Excessive prostacyclin in PPH can lead to a high cardiac output state, suggesting it has important positive inotropic effects. In this circumstance, reducing the dose can allow the cardiac output to return to normal without worsening the clinical state. (J Am Coll Cardiol 1999;34:1184–7) © 1999 by the American College of Cardiology

Prostacyclin (sodium epoprostenol) is an effective treatment for primary pulmonary hypertension (PPH) (1–3). The dosing of this medication, however, is complex and not fully understood. Tolerance to the beneficial effects of prostacyclin, which seems to occur in all patients (1–3), makes it difficult to know the optimal dose. The current practice is to initiate therapy at maximally tolerated doses that are usually limited by side effects such as headache, flushing, nausea and hypotension. Once these side effects diminish, the patient will typically be left with a period of improved symptomatology, which will lessen over time and result in a reversal of the initial improvement in dyspnea (tolerance). This can be overcome by increasing the dose. No upper limit of an effective prostacyclin dose has been described.

Recently, we have observed some patients with PPH on long-term prostacyclin who developed high cardiac outputs. Side effects to the drug diminished when the dose was reduced, but symptomatic improvement remained (loss of tolerance). Our data suggest that the effects of prostacyclin on the cardiac output and the appearance of side effects are related.

**METHODS**
We began treating patients with PPH with intravenous (IV) prostacyclin in January 1990, and have initiated therapy in more than 165 patients. Patients are seen at least biannually, and they are asked to undergo an objective assessment of the efficacy of their medication on an annual basis, which includes an exercise test and cardiac catheterization. The diagnosis of PPH was established according to the criteria of the National Institutes of Health Registry on Primary Pulmonary Hypertension (4). The patients were treated with prostacyclin if they had progressive symptoms of PPH and either a failure to improve with calcium channel blockers or lack of an adequate response to acute vasodilator challenge.
From January 1997 until April 1998, a total of 55 patients with PPH treated with prostacyclin for a year or longer returned for a follow-up right-heart catheterization. The present report focuses on 12 patients who, at the time of follow-up cardiac catheterization, were noted to be in a high cardiac output state, which was attributed to excessive prostacyclin. As prostacyclin causes a dose-related increase in cardiac output upon initiation, we reasoned that a reduction in the prostacyclin would result in a lowering of the cardiac output. All 12 patients had symptomatic improvement from prostacyclin, which was shown by a reduction in the symptom of dyspnea with effort and an improvement in exercise capacity. In addition, all patients experienced a return of symptoms, primarily dyspnea and fatigue, after a period of time; these were treated with periodic escalation of the prostacyclin dose at 2 ng/kg/min increments. The time interval for dose increases ranged between two weeks and six months. All patients acknowledged side effects to prostacyclin over the treatment period, which included jaw pain, diarrhea, flushing, rash and foot pain. At the time of their most recent evaluation, each patient remarked that he or she no longer had the symptom of dyspnea with effort. However, each also complained of a triad of symptoms that included severe flushing, rash and bloating, which appeared to worsen with each prostacyclin dose increase. In addition, on exam each patient had a bounding carotid pulse and a dynamic right ventricular impulse, and on echocardiography each had a normal to hypercontractile–appearing left ventricle.

Hemodynamic assessment of the patient was performed by means of a right-sided heart catheterization with a thermodilution balloon flotation catheter. Cardiac pressures and systemic and pulmonary arterial oxygen saturation, along with cardiac output, were measured in all patients. To qualify for a reduction in prostacyclin dose, the cardiac index had to exceed 4 liter/min/M² (the upper limit of normal). To monitor the effects of reducing the dose of prostacyclin the pulmonary artery catheter was left in place with the patient in the intensive care unit for bedside hemodynamic monitoring. Informed consent was obtained in every patient. The dose of IV prostacyclin was reduced every hour with a goal of reducing the cardiac index below 4 liter/min/M² unless it was noted that rebound pulmonary hypertension was occurring, defined as an increase in the mean pulmonary artery pressure of greater than 10 mm Hg. When an end point was reached, the dose of prostacyclin was kept constant, hemodynamics were recorded for an additional 2 to 4 h, and the catheters were subsequently removed.

**Statistical analysis.** Baseline demographic and hemodynamic variables were recorded and are presented as the mean value ± SD. Comparison of variables measured at the baseline state, upon restudy with the patient on prostacyclin, and subsequently after the dose was reduced to achieve a cardiac index under 4 liter/min/M², was made with repeated-measures analysis of variance (ANOVA) with multiple comparisons, with p values below 0.05 considered to indicate statistical significance.

**RESULTS**

The 12 patients studied consisted of nine women and three men with a mean age of 46 ± 7 years. At the time that they were initially treated for PPH they had severe symptoms, with 67% New York Heart Association (NYHA) functional class III and 33% NYHA functional class IV. Their baseline hemodynamics revealed a mean pulmonary artery pressure of 60 ± 11 mm Hg, a cardiac output of 4.4 ± 1.3 liter/min (cardiac index 2.2 ± 0.5 liter/min/M²), and a pulmonary vascular resistance of 13 ± 6 units.

At the time of the most recent evaluation, all patients were symptomatically improved, with 75% NYHA functional class I and 25% NYHA functional class II. Their hemodynamics before the reduction in their dose of prostacyclin are shown in Table 1. The mean duration of treatment was 39 ± 20 months, and the mean prostacyclin dose was 98 ± 61 ng/kg/min. Compared with the baseline state, they had a significant reduction in mean pulmonary artery pressure of 25% (p = 0.001) and pulmonary vascular resistance of 71% (p < 0.001). However, the patients were now in a relatively high cardiac output state, with the mean cardiac output 10.1 ± 2.3 liter/min (range 6.9 to 14.3 liter/min).

The dose of prostacyclin was titrated downward over 6 to 24 h under direct hemodynamic monitoring, to a mean dose of 60 ± 50 ng/kg/min. Individual patient doses were reduced 39% (range 12% to 78%). In response to this, there was a significant fall in the cardiac output to 7.4 ± 1.4 liter/min, corresponding to a cardiac index of 4.0 ± 0.74 liter/min/M² (p = 0.001) (see Fig. 1). Rebound pulmonary hypertension did not occur in any patient, as the mean pulmonary artery pressure went from 45 ± 12 to 46 ± 10 mm Hg (p = NS). In one patient, the dose reduction was limited by complaints of dyspnea.

Patients were followed for an average of 13.6 months (range 7 to 25 months). No patient required a dose adjustment for the initial three months. Two patients have had no further changes, three have had further dose reductions on an outpatient basis, and six have had minor dose increases. Their NYHA functional class at the time of their last visit has remained unchanged. In addition, every patient described an improvement in the side effects of flushing, bloating and fatigue related to prostacyclin, with some

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<th>Abbreviations and Acronyms</th>
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<tr>
<td>ANOVA = analysis of variance</td>
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<td>IV = intravenous</td>
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<td>NYHA = New York Heart Association</td>
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<td>PPH = primary pulmonary hypertension</td>
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noting a dramatic reduction in the severity in their leg pain, or severity of their rash.

**DISCUSSION**

**Prostacyclin and the renin-angiotensin system.** Prostacyclin has been a very efficacious medication for patients with PPH (1–3). However, drug administration is complex and its exact mechanism of action on the pulmonary vasculature in these patients is not completely understood. Published studies suggest that it works through vasodilatation, platelet inhibition, and vascular remodeling (3,5). The sudden withdrawal of prostacyclin from a patient can result in severe rebound pulmonary hypertension, which can be fatal (6,7). The mechanism of rebound pulmonary hypertension has not been fully elucidated, but based on animal studies it appears to be mediated by angiotension II rather than through sudden thromboxane release (8).

Prostacyclin has been shown in animals to be a potent stimulator of renin-angiotensin release, believed to be related to its effect on the afferent renal arteriole (9). In addition, patients with PPH develop neurohormonal activation, which is related to the severity of their disease (10). Thus, it is possible that the initiation of prostacyclin in a patient with PPH and heart failure could result in further neurohormonal activation, which opposes the effects of prostacyclin and results in the development of tolerance. Raising the prostacyclin dose would overcome the tolerance until further neurohormonal activation eventually negates it. The mediators of tolerance to prostacyclin are unknown, but possibilities include angiotension II (8) and increased expression of endothelin, which have also been implicated in nitrate tolerance (11). If these prove to be the case, then blocking these mediators with angiotensin-converting enzyme inhibitors or endothelin receptor blockers might have significant effect on enhancing myocardial contractility that is independent of the changes in loading conditions induced by vasodilatation in patients with left heart failure (14). It is interesting to note that prostacyclin has been shown in all clinical studies of PPH to have a greater effect on raising cardiac output than on lowering pulmonary artery pressure (1–3). Whether the effect is a direct one on the myocardium or indirect via neurohormonal activation has not been determined. Although most patients with PPH have reduced cardiac output on presentation, the development of a chronic high output state could have long-term detrimental effects on underlying cardiac function (15).

**Prostacyclin and cardiac output.** Increasing the cardiac output to normal or elevated levels might be an effective way to reduce or eliminate neurohormonal activation in these patients, whether the activation was initiated by the heart failure or the prostacyclin therapy. In our series, every patient had an increased cardiac index from the medication, and reducing the cardiac index to a normal level by reducing the prostacyclin dose did not result in rebound pulmonary vasoconstriction. Rather, we speculate it was associated with less neurohormonal activation, allowing the prostacyclin to be effective at a lower dose. If the prostacyclin were reduced to a point where the cardiac output became low, we would expect neurohormonal activation would recur, which could lead to tolerance again.

The fact that a high cardiac output state was produced from chronic prostacyclin therapy is consistent with the drug having positive inotropic effects. Modest inotropic effects of prostacyclin have been reported in animal studies (12,13). Prostacyclin has also been demonstrated to have a significant effect on enhancing myocardial contractility that is independent of the changes in loading conditions induced by vasodilatation in patients with left heart failure (14). It is interesting to note that prostacyclin has been shown in all clinical studies of PPH to have a greater effect on raising cardiac output than on lowering pulmonary artery pressure (1–3). Whether the effect is a direct one on the myocardium or indirect via neurohormonal activation has not been determined. Although most patients with PPH have reduced cardiac output on presentation, the development of a chronic high output state could have long-term detrimental effects on underlying cardiac function (15).
Conclusions. These data support the argument that patients with PPH on prostacyclin therapy need to be closely monitored with periodic determination of the cardiac output to optimize the dose and avoid a chronic high output state. In addition to too low a dose, it is possible for patients with PPH to be on excessive doses. Combined therapy with agents that prevent tolerance or enhance the efficacy of prostacyclin need to be explored (16).

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REFERENCES