Determinants of Drug Response in Severe Chronic Heart Failure. 1. Activation of Vasconstrictor Forces During Vasodilator Therapy

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SUMMARY Vasodilator drugs activate neurohumoral forces that produce peripheral vasoconstriction and tachycardia and probably cause the rebound events observed upon abrupt withdrawal of therapy. To determine their role in limiting therapeutic vasodilator responses, these reactive forces were measured in 40 patients with severe chronic heart failure by quantifying the magnitude of rebound change (MRC) after nitroprusside withdrawal. Group 1 patients (n = 22), who had minimal reactive vasoconstriction (MRC ≤ 27%), showed marked hemodynamic effects with nitroprusside (4.5 μg/kg/min) and isosorbide dinitrate (40 mg orally), associated with significant decreases in heart rate with both drugs (p < 0.001). Despite administration of the same doses of both drugs, group 2 patients (n = 18), who had marked rebound changes (MRC > 27%), showed significantly smaller changes in cardiac index, systemic vascular resistance and mean arterial pressure (p < 0.001), associated with no change or increases in heart rate. Rebound events were attenuated and the responses to nitroprusside and nitrates were enhanced in four patients in whom these drugs were readministered after pretreatment with i.v. phentolamine (0.3 mg/min). We conclude that activation of neurohumoral forces can limit the hemodynamic responses to vasodilator administration; this supports the use of combination therapy of direct-acting vasodilators and neurohumoral antagonists in selected patients with severe chronic heart failure.

ADMINISTRATION of peripheral vasodilator agents is of established value in the management of patients with severe chronic heart failure. However, recent studies have indicated that the response to vasodilator therapy varies. Although cardiac performance often improves substantially, many patients show little objective hemodynamic benefit, and some may have adverse cardiovascular reactions. These varied results may occasionally be due to differences in the doses of drugs but factors in addition to direct drug-mediated vasodilation are probably important.

In normal and hypertensive subjects not in heart failure, nitroprusside not only produces direct peripheral vasodilation, but also activates counterpoising mechanisms that cause peripheral vasoconstriction and tachycardia. These counterpoising forces become evident as rebound phenomena when, upon the abrupt cessation of nitroprusside, direct drug-mediated vasodilation rapidly disappears, leaving the reactive forces unopposed. The rebound hemodynamic changes after the abrupt withdrawal of nitroprusside in patients with congestive heart failure suggest that similar reactive mechanisms underlie the responses to vasodilator therapy in such patients as well.

Given similar degrees of peripheral vasodilation, left ventricular chamber size is an important factor in the response to vasodilator therapy in patients with severe chronic heart failure. However, what determines the magnitude of peripheral vasodilation in patients given similar doses of vasodilator drugs is not known. Marked activation of reactive vasoconstrictor forces can greatly limit the therapeutic hypotensive responses to vasodilator administration in hypertensive patients, so it is likely that these forces can also limit the magnitude of drug-induced peripheral vasodilation in patients with heart failure. To explore this question, we evaluated the degree of activation of vasoconstrictor forces by quantitative analysis of rebound hemodynamic changes after the abrupt withdrawal of nitroprusside in a large series of patients with severe heart failure who manifested differing responses to similar doses of vasodilator drugs.

Methods

We evaluated 45 patients, 35 men and 10 women, ages 40-83 years (mean 64 years). All had severe chronic congestive heart failure refractory to optimal conventional therapy with digitalis and diuretics. The etiology of heart failure was ischemic cardiomyopathy in 32 patients, idiopathic cardiomyopathy in five and advanced rheumatic valvular regurgitation in five (two with mitral regurgitation and three with aortic regurgitation); three patients had undergone aortic and/or mitral valve replacement more than 1 year before study. Diagnosis was based on clinical, electrocardiographic, echocardiographic and radioisotopic criteria and was confirmed by cardiac catheterization in 25 patients. The duration of heart failure ranged from 6 months to 8 years. Thirty-three patients were in normal sinus rhythm, seven had atrial fibrillation and five had ventricular pacemaker rhythm.
All patients were studied during a period of relative clinical stability. No patient had sustained a myocardial infarction within 3 months or an episode of acute heart failure within 3 weeks before this study; no patient had received any vasodilator drug within 7 days. Bed rest was maintained and all medications were withheld for 12–24 hours before evaluation. Doses of digoxin and diuretics were continued unchanged throughout the period of study but were separated from the administration of vasodilator drugs by at least 12 hours.

Hemodynamic Measurements

After written, informed consent, right-heart catheterization was performed with a triple-lumen, flow-directed catheter to measure right atrial, pulmonary arterial and pulmonary capillary wedge pressures. Arterial cannulae were inserted into the radial artery in all patients to measure systemic pressures. Measurements were made with zero reference level at the midaxillary line with the patient supine. Left ventricular filling pressures (LVFPs) were measured as mean pulmonary capillary wedge pressure or pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Thermodilution cardiac outputs (COs) were determined in triplicate with a bedside CO computer (Instrumentation Laboratories) using iced injectate. Heart rates (HRs) were derived from a continuously recorded ECG. Patients with LVFPs less than 20 mm Hg were excluded from the present study.

Drug Administration

The following hemodynamic variables were determined for at least 3 hours to ensure stability of the baseline hemodynamic state before drug administration: mean arterial pressure (MAP), HR, LVFP, mean right atrial pressure (MRAP) and CO. The variation between repeated measurements for all variables during this control period was less than 10%. Fifty milligrams of sodium nitroprusside (Nipride, Roche Laboratories) were reconstituted in 250 ml of 5% dextrose in water and infused by peripheral vein at controlled rates determined by an IVAC 530 infusion pump. The drug was initially infused at 0.25 μg/kg/min and the dosage was increased to 0.50, 1.00, 1.50, 3.00 and 4.50 μg/kg/min every 20–30 minutes; all hemodynamic variables were redetermined at the highest dose of nitroprusside. The duration of the nitroprusside infusion was approximately 3 hours, and during the treatment period no patient received more than 350 ml of fluid. When the final infusion rate was achieved, nitroprusside was abruptly discontinued, and the hemodynamic variables were redetermined every 5 minutes for 30 minutes and every 15–30 minutes until the pretreatment hemodynamic state was reestablished. Patients were carefully observed for adverse effects of nitroprusside withdrawal, and nitroprusside was reinstituted in five patients who had severe rebound symptoms (pulmonary edema and rest angina).

Three to 24 hours after nitroprusside therapy, all hemodynamic variables were again determined for a 3-hour control period to reestablish a stable predrug state. At this time, 32 patients received a 40-mg dose of isosorbide dinitrate orally and all hemodynamic variables were redetermined every 15 minutes for 90 minutes.

Twenty-four hours thereafter, the responses to nitroprusside and nitrates therapy were reevaluated in four patients, who were pretreated with a continuous infusion of phenolamine (0.3 mg/min). The infusion of phenolamine was begun 1 hour before and continued through the period of readministration of nitroprusside and isosorbide dinitrate, which were performed in a manner identical to the initial evaluation.

Statistical Analysis

Mean systemic and pulmonary arterial pressures were determined by electronic filtration. When analyzing changes in HR, the five patients with a permanent ventricular pacemaker rhythm were excluded; the seven patients with atrial fibrillation were included, however, and the HRs were determined as the average of three 20-second rate determinations. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated as follows: CI = CO/body surface area (1/min/m²); and SVR = 80 × (MAP – MRAP)/CO (dyn-sec-cm⁻²).

Quantitative analysis of rebound events observed after nitroprusside withdrawal was performed as previously described. Peak rebound was defined as the time when the maximal increase in SVR was observed after discontinuation of the drug. The magnitude of hemodynamic rebound changes was defined as the percentage increase in SVR at peak rebound (SVR₂) above the pretreatment value (SVR₁), where the magnitude of rebound change (MRC) = (SVR₂ – SVR₁)/SVR₁ × 100. Quantification of MRC was taken to represent the degree of activation of arterial vasoconstrictor forces during vasodilator administration. Peak rebound could not be defined in the five patients who required reinstitution of nitroprusside because of severe rebound symptoms, so they were excluded from further analysis.

The responses to nitroprusside therapy were evaluated in the remaining 40 patients by comparing the hemodynamic variables at the maximal infusion rate of the drug (4.5 μg/kg/min) with their control values. The responses to nitrate therapy were evaluated by comparing the variables at the time of peak effect of isosorbide dinitrate on SVR (30–60 minutes after oral administration) to their control values. Both comparisons were performed by the t test for paired data. Patients were then divided into two groups, based on whether the observed MRC was 27% or less (group 1) or more than 27% (group 2); this point of division was chosen based on the MRC that had previously predicted a zero change in HR during nitroprusside administration (see Appendix). The control hemodynamic variables and the hemodynamic responses in the two groups were compared.
by the t test for independent variables. The changes in hemodynamic variables during therapy were then tested for possible relation to the values for MRC by least-squares linear regression analysis. Group data are expressed as mean ± SD.

**Results**

The hemodynamic changes during the administration of nitroprusside (40 patients) and nitrate therapy (32 patients) are listed in table 1.

**Nitroprusside Therapy**

With nitroprusside, there was a great variation in the hemodynamic changes, although the same dose was administered to all 40 patients. CI rose by 0.13–1.98 l/min/m², and SVR decreased by 10–75% of the control values, associated with variable changes in LVFP, MAP and HR. After the withdrawal of nitroprusside, SVR rose to levels from 13% below to 82% above (mean 27 ± 23%) the control SVR.

In the 22 patients in group 1, SVR decreased 1169 dyn-sec-cm⁻² (56%) with nitroprusside (4.5 µg/kg/min). CI increased 1.19 l/min/m² (76%) and MAP decreased 19.1 mm Hg, as HR slowed significantly (from 88 to 81 beats/min). LVFP and MRAP decreased 12.0 mm Hg and 5.7 mm Hg, respectively. All changes were significant (p < 0.001). The mean MRC after nitroprusside withdrawal in this group was 10%.

In contrast, in the 18 patients in group 2, the same dose of nitroprusside produced only modest arterial vasodilation. SVR decreased only 590 dyn-sec-cm⁻² (36%), CI increased only 0.64 l/min/m² (31%) and MAP decreased only 12.9 mm Hg, associated with significant increases HR (88 to 94 beats/min). LVFP and MRAP decreased in group 2 patients, 9.6 mm Hg and 4.2 mm Hg, respectively. All changes were significant (p < 0.001) except for the changes in HR (p < 0.05). The mean MRC in this group was 47%.

The hemodynamic responses to nitroprusside in groups 1 and 2 differed significantly from each other with respect to changes in SVR (p < 0.001), CI (p < 0.001), MAP (p < 0.01) and HR (p < 0.001), but the changes in LVFP and MRAP in the two groups were

**Table 1. Hemodynamic Changes During Nitroprusside and Nitrate Administration in Groups 1 and 2**

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The p values below each set of variables indicate significance of the differences between the groups in magnitude of drug-induced changes.  
* p < 0.001, drug vs control.  
† p < 0.05, drug vs control.  
‡ p < 0.001, group 1 control vs group 2 control.  
§ p < 0.05, group 1 control vs group 2 control.  
Abbreviations: CI = cardiac index; LVFP = left ventricular filling pressure; MAP = mean arterial pressure; MRAP = mean right atrial pressure; HR = heart rate; SVR = systemic vascular resistance.
similar. Patients in groups 1 and 2 were similar with respect to age and sex, the etiology of underlying heart disease and the number of patients with auscultatory evidence of mitral regurgitation. The echocardiographic end-diastolic dimension\(^7\) was similar in the two groups (67 ± 10 mm in group 1 and 62 ± 9 mm in group 2), as were the pretreatment LVFP, MRAP and MAP. Only the control CI (1.57 in group 1 vs 2.04 \(1/\text{min}/\text{m}^2\) in group 2, \(p < 0.001\)) and the control SRV (2082 in group 1 vs 1618 dyn-sec-cm\(^{-6}\) in group 2, \(p < 0.05\)) differed significantly between the two groups (fig. 1).

Nitrate Therapy

Although the same dose of isosorbide dinitrate was administered to all 32 patients, the hemodynamic responses were highly variable. In 30 patients, SRV decreased 4–53% as CI rose by 0.17–1.20 \(1/\text{min}/\text{m}^2\) above the control values. In two patients, CI decreased (0.12 and 0.54 \(1/\text{min}/\text{m}^2\), associated with increases in SRV of 5% and 6%, respectively) with nitrate therapy. There were variable changes in LVFP and HR.

In the 15 patients in group 1 who received nitrates, SRV decreased 725 dyn-sec-cm\(^{-4}\) (37%), CI increased 0.73 \(1/\text{min}/\text{m}^2\) (46%) and MAP decreased 10.5 mm Hg, associated with a decrease in HR (from 82 to 78 beats/min). LVFP decreased 7.3 mm Hg and MRAP decreased 5.8 mm Hg. All changes were significant (\(p < 0.001\)).

In the 17 patients in group 2 who received nitrates, SVR decreased only 302 dyn-sec-cm\(^{-4}\) (18%), CI increased only 0.27 \(1/\text{min}/\text{m}^2\) (13%) and MAP decreased only 5.9 mm Hg. HR did not change significantly. LVFP decreased 8.9 mm Hg and MRAP decreased 4.0 mm Hg. All changes were significant (\(p < 0.001\)).

The hemodynamic responses to nitrates in groups 1 and 2 differed significantly with respect to changes in SVR (\(p < 0.001\)), CI (\(p < 0.001\), MAP (\(p < 0.01\)) and HR (\(p < 0.01\)), but the changes in LVFP and MRAP were similar. The MRC after withdrawal of nitroprusside predicted the changes in SVR (\(r = 0.91\), see 6.1, \(p < 0.001\)) (fig. 2A), CI (\(r = -0.86\), see 0.19, \(p < 0.001\)) (fig. 3A) and HR (\(r = 0.74\), see 3.6, \(p < 0.001\)) during subsequent nitrate therapy. The MRC was superior to the prenitrate SVR (\(r = -0.48\), see 13.0, \(p < 0.01\)) in predicting changes in SVR with nitrates (fig. 2B) and was superior to the prenitrate CI (\(r = -0.46\), see 0.32, \(p < 0.01\)) in predicting the subsequent changes in CI (fig. 3B).

Effects of Pretreatment with Phentolamine

When the control hemodynamic state was reevaluated, the effects of nitroprusside and nitrate therapy were reevaluated in four patients after pretreatment with a continuous infusion of phentolamine (0.3 mg/min) (table 2).

Phentolamine increased CI and HR and decreased MAP, LVFP and SVR in all four patients. Using the values after phentolamine as the new control hemodynamic state, nitroprusside and nitrates further increased CI and decreased ventricular filling pressures and systemic pressures and resistance. The magnitude of the changes in CI, MAP and SVR with nitroprusside and nitrates was greater and the MRC was smaller during treatment with phentolamine than that observed during the first administration of both drugs. This was true despite the higher pretreatment CI and lower pretreatment SVR during phentolamine therapy, in which case more marked MRCs and less pronounced hemodynamic benefit from drug readministration would have been expected (fig. 1). Two of the four patients had previously been treated with 40 mg of oral isosorbide dinitrate every 4 hours without clinical benefit; both patients improved significantly when 60 mg of oral phenoxybenzamine daily was added to the therapeutic regimen.

Discussion

The present study supports the concept that in patients with chronic heart failure, the hemodynamic responses observed during vasodilator therapy are the result of two interacting forces: the direct peripheral vasodilating effects of the drug and the secondary activation of counterposing mechanisms, which cause peripheral vasoconstriction and tachycardia and are responsible for the rebound hemodynamic changes upon the withdrawal of therapy.\(^8\) The magnitude of peripheral vasodilation achieved during vasodilator administration correlates inversely with the degree of
activation of these vasoconstrictor forces, which is largely determined by the severity of the heart failure state. In patients with minimal vasoconstrictor responses to drug administration (those with a severely decreased CI and elevated SVR), vasodilator therapy produces marked hemodynamic changes without an increase in HR; in contrast, in patients with marked activation of vasoconstrictor forces (those with a mildly abnormal CI and SVR), these same doses produce reflex tachycardia and minimal hemodynamic effects. Quantitative analysis of rebound events can therefore predict the magnitude of peripheral vasodilation during the subsequent administration of oral vasodilator agents.

It is likely that these vasoconstrictor forces are at least in part the result of vasodilator-induced activation of the sympathetic nervous and renin-angiotension systems. In normal and in hypertensive subjects, vasodilator drugs markedly stimulate these neurohumoral mechanisms, which limit the hypotensive response, produce tachycardia during therapy and result in marked rebound changes after abrupt discontinuation of treatment. In congestive heart failure, however, there is a variable attenuation of circulatory reflexes, the greatest attenuation being in patients with the most left ventricular impairment. Whether this attenuation is due to depletion of myocardial stores of catecholamines or the limited responsiveness of neurohumoral systems greatly stimulated in an attempt to support a failing state.
circuit is unclear.13, 25-29 In either case, in patients with severe left ventricular failure, plasma catecholamines fall to increase and may even decrease with vasodilators;13, 30 this is consistent with our observations that patients with a markedly reduced CI manifested little change or even decreases in HR despite significant decreases in systemic pressures during therapy and demonstrated mild rebound changes. Patients in our study with a mildly reduced CI, however, manifested reactions similar to those of normal and hypertensive subjects, which is consistent with experimental evidence that baroreceptor reflexes are only mildly attenuated in subjects in whom ventricular function is only mildly impaired.29 In such patients, enhancement of vasodilator responses and attenuation of rebound changes by α-sympathetic or reninangiotensin blockade confirm the important role of neurohumoral mechanisms in limiting the direct pharmacologic effects of vasodilator drugs.31, 32

The relative preservation of neurohumoral circulatory responses may explain the limited effectiveness of vasodilator therapy in patients with only mild left ventricular failure reported by previous investigators. The administration of nitroprusside and nitrates to patients with only a mildly decreased CI or stroke work or only a modestly elevated LVFP or SVR results in little improvement in forward output and is often accompanied by significant increases in HR.3-6, 12, 33-39 This has been attributed to an excessive reduction in ventricular filling pressure beyond that required to preserve stroke volume or to an excessive reduction in peripheral resistance beyond that needed to maintain systemic arterial pressure. However, the two groups in our study with different MRCs had similar control values for LVFP and MAP and had similar values for LVFP and SVR during treatment. Furthermore, the patients with marked rebound changes manifested smaller decreases in MAP and SVR than did patients with mild rebound phenomena. Therefore, although preservation of LVFP and systemic blood pressure is undoubtedly important in many patients, an excessive lowering of these pressures did not explain the different hemodynamic responses seen in our two groups or the variable responses observed by others.3, 6, 20-41

Table 2. Responses to Nitroprusside and Nitrates Before and After Phentolamine

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Responses to nitroprusside (NP), 4.5 g/kg/min i.v., and isosorbide dinitrate (ISDN), 40 mg orally, were evaluated during initial administration and in an identical fashion 24 hours later during a continuous infusion of phenolamine, 0.3 mg/min. Rebound refers to hemodynamic variables at peak rebound after withdrawal of nitroprusside; values in parentheses represent the maximum of rebound change in systemic vascular resistance expressed in terms of control values. *Control values 2 days before initiation of the phenolamine infusion.

Abbreviations: See table 1.

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Alternatively, to explain the limited response to vasodilator drugs in patients with near-normal levels of SVR, other investigators have hypothesized that the ability to dilate vascular beds must be proportional to the degree of basal vasoconstriction.\(^5\)\(^{12}\) Although this concept of vascular sensitivity may account for the varied effects of agents with specific sites of action (i.e., the pronounced effects of angiotensin converting-enzyme inhibition in high-renin states),\(^45\) it does not explain the differing responses in patients treated with direct-acting vasodilator drugs. Zelis et al. reported that despite the high levels of peripheral resistance, the peripheral vessels in patients with severe congestive heart failure are less responsive to vasodilator stimuli than they are in patients with compensated heart failure or in normal subjects.\(^64\) Furthermore, the concept of vascular sensitivity does not explain the occurrence of rebound withdrawal phenomena in patients treated with direct-acting agents. Instead, our present observations suggest that when similar quantities of such drugs are administered, differences in the degree of peripheral vasodilation are due to differences in the magnitude of the circulatory reaction to drug administration rather than different sensitivity to the direct vascular effects of these agents. This is consistent with our finding that the MRC was a better predictor of the magnitude of peripheral vasodilation achieved during drug administration than was the calculated SVR before treatment.

Our observations must be interpreted cautiously. We quantified only the rebound changes in SVR and thus examined only the arterial component of drug-induced vasoconstrictor forces. It is likely, however, that during vasodilator administration, vasoconstriction occurs as well and may accordingly influence the magnitude of changes in venous return and ventricular filling pressures observed during therapy. Our observation that the reduction in ventricular filling pressures with nitroprusside and nitrates was similar in patients with marked differences in the magnitude of rebound arterial vasoconstriction suggests that vasoconstrictor forces may operate independently; we did not, however, perform peripheral plethysmographic studies during nitroprusside withdrawal in an attempt to quantify rebound vasoconstrictor phenomena. More important, the degree of activation of arterial vasoconstrictor forces determines only the magnitude of the decrease in SVR that is achieved with a given dose of a vasodilator drug and not necessarily the manner in which the reduction in SVR is translated into an improvement in cardiac performance. We have shown that whether peripheral vasodilation results in a drop in blood pressure with minimal changes in CO or produces marked increases in stroke work with minimal hypotension is likely to be determined by myocardial factors (ventricular chamber size or systolic wall stress) rather than peripheral mechanisms.\(^7\) If such myocardial factors are to be evaluated independently, drug doses need to be titrated to achieve comparable decreases in peripheral resistance in the patients being studied. This would require smaller doses of a vasodilator drug in patients with minimal reactive forces than in patients with intact neurohumoral responses.

Finally, although our observations demonstrate the importance of vasoconstrictor forces in limiting acute vasodilator responses, their role in modifying the effects of long-term vasodilator therapy is not known. Several studies, however, suggest a role of major importance. Pagani et al. showed that delayed peripheral vasoconstriction is responsible for the rapid attenuation of acute responses to nitroprusside.\(^11\) Similarly, activation of the sympathetic and renin-angiotensin systems may explain the attenuated responses to repeated doses of captopril, nitrates and prazosin.\(^44\)\(^{45}\) Whether, with time, these counterposing forces remained unchanged, increase in magnitude and result in complete loss of drug effect, or whether the mechanisms themselves are attenuated and permit restoration of drug action remains to be determined.\(^55\) Nevertheless, the concept of delayed activation of counterposing vasoconstrictor forces may explain why the acute responses to a vasodilator agent may not necessarily predict its long-term hemodynamic or clinical benefits.\(^46\)\(^{51}\)\(^{54}\)\(^{55}\) Similarly, phenomena may account in part for the lack of correlation of plasma drug levels and hemodynamic effects.\(^47\)\(^{48}\)\(^{56}\) Of potentially greater importance, however, the preliminary data in the present study indicate that blockade of these forces may enhance the acute responses to vasodilator drugs and thus could prevent drug tolerance or restore the effectiveness of drugs to which tolerance has developed; further work, however, is needed to confirm and expand these findings. Combination therapy of direct-acting vasodilators with drugs that interfere with the activity of the sympathetic nervous or renin-angiotensin systems may therefore be a more effective approach to the treatment of heart failure than the use of single-agent therapy.\(^55\) The superiority of this approach has already been established in selected patient populations in the treatment of systemic hypertension.\(^16\)\(^17\)

In conclusion, the present study indicates that many of the reported differences in the responses to vasodilator therapy are due to varying degrees of activation of counterposing vasoconstrictor forces, which can limit and modify the hemodynamic benefit. Such mechanisms may be responsible for the limited effectiveness of vasodilators in patients with milder degrees of heart failure, for the tachycardia in some treated subjects, for the rapid attenuation of initial beneficial responses and for the rebound changes which occur upon the abrupt withdrawal of therapy. Concomitant use of drugs that block the sympathetic nervous or renin-angiotensin systems may enhance the effects of direct-acting vasodilator agents and reduce the potential for drug tolerance and rebound clinical events.

**Acknowledgment**

We are greatly indebted to the nurses of the Ames and Rose Cardiac Care Units of the Mount Sinai Medical Center for their invaluable help in this study. We also thank Irma Rosenblatt for her assistance in the preparation of the manuscript.
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Appendix

We have shown that the magnitude of rebound change (MRC) after nitroprusside withdrawal varies over a continuum of values. Therefore, any point of division selected (for purposes of analysis) in an effort to separate those patients with marked from those with minimal reactive vasoconstriction is arbitrary. In the present analysis, we divided patients into two groups based on the MRC that had previously predicted a zero change in heart rate during nitroprusside administration (27%). This is based on the hypothesis that activation of the sympathetic nervous system in response to vasodilator administration is generalized and produces peripheral vasoconstriction and tachycardia to similar degrees. The absence of reflex tachycardia would thus imply minimal sympathetically mediated vasoconstriction; such an analysis necessarily disregards peripheral vasoconstrictor forces that may be unassociated with changes in heart rate. Of note, the 27% value for MRC coincides with the mean value for MRC in our 40 patients.

The MRC in the present study was determined in terms of the percentage increase rather than the absolute increase in systemic vascular resistance above control values (SVR); this was done in an effort to relate the observed rebound changes to the basal level of vasoconstriction. Since SVR differed to a small but significant degree in our two groups of patients, by dividing the absolute changes observed by SVR, we may have enhanced the MRCs in patients with a low SVR and minimized the rebound events in patients with an elevated SVR.

However, even if we had expressed the rebound increases in systemic vascular resistance in absolute terms and had used the mean increase in our 40 patients (406 dyn-sec-cm⁻²) as the point of division in the present analysis, our results would not have differed significantly. All 18 patients in group 2 had a rebound increase in systemic vascular resistance greater than 406 dyn-sec-cm⁻², and all but one of the 22 patients in group 2 (with a MRC of 24%) had a rebound increase in systemic vascular resistance less than this value.
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_Circulation_. 1981;64:506-514
doi: 10.1161/01.CIR.64.3.506

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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