systemic responses including increased catecholamine output.[8] This, and the outpouring of catecholamines in exercising patients compared with the same patients resting, strongly suggests improved intraventricular and intra-Hisian conduction by catecholamines as a principal explanation for the marked differences between rate-related and exercise-induced left BBB.[9-13] (The exercise effect could also be partly due to withdrawal of vagal tone.[6-14]) Indeed, in 2 patients with rate-related left BBB isoproterenol increased the critical rate at which left BBB appeared.[10] Isoproterenol decreased the refractory period in the fascicle involved in rate-related BBB,[12] and in 2 patients with fixed BBB it normalized conduction.[11] Glucagon has also corrected prolonged intraventricular conduction.[15] In this context, our patients' exercise-induced left BBB did not disappear at the end of exercise, but only after heart rate dropped significantly (higher cycle length) and at a lower pressure-rate product (Figure 2).

"Rate-related" (rate *increase*-related) BBB is an effect of disturbance in phase 3 of the transmembrane cell action potential.[16,17] In phase 3 improvement of conduction by catecholamines seems related to reduction in tissue refractoriness.[11,12] Catecholamines also decrease the resting potential and hyperpolarize conducting tissues. Yet, the relation of catecholamines may be more complex; their effects on oxygen consumption may offset improved conduction at least in patients with myocardial ischemia. (Differences in exercise-induced left BBB in patients with chest pain and normal coronaries versus those with chest pain and coronary disease[5,18-22] do not pertain, because chest pain with normal large coronaries may occur through other mechanisms.) While rate-related and exercise-induced left BBB should be clearly distinguished, they may have a common basis in induction at particular rate thresholds, that for exercise-induced left BBB being markedly raised by factors favoring conduction peculiar to exercise, notably catecholamines.

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Sustained Hemodynamic Effects with Therapeutic Doses of Intravenous Nitroglycerin in Congestive Heart Failure

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Having been used in the treatment of angina for more than 100 years,[1] nitrates are now being extensively used as vasodilators in the management of patients with congestive heart failure (CHF).[2,3] In controlled trials, isosorbide dinitrate has been demonstrated to provide prolonged symptomatic and functional improvement in CHF.[4,5] A randomized study using a nitrate-hydralazine combination has documented a significant reduction in mortality in men with severe CHF.[6] However, rapidly developing tolerance to oral and topical nitrates has also been reported.[7,8] Despite the widespread use of nitrates in CHF, there are limited data available on the circulatory effects of intravenous nitroglycerin. This study was therefore undertaken to (1) evaluate the hemodynamic re-

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TABLE I Comparison of Hemodynamic Responses at Peak Infusion of Nitroglycerin and After 48 Hours in 15 Patients with Congestive Heart Failure

Parameters	Control (mean + SE)	Peak Dose (mean + SE)	Mean % Change	p Value	After 48 Hours (mean + SE)	Mean % Change	p Value
Pulmonary capillary wedge pressure (mm Hg)	28 ± 1	17 ± 0.8	−39	<0.01	17.6 ± 0.5	−37	<0.01
Right atrial pressure (mm Hg)	13 ± 0.5	8 ± 0.4	−42	<0.01	7.8 ± 0.4	−40	<0.01
Mean pulmonary artery pressure (mm Hg)	38 ± 1	26 ± 1.2	−31	<0.01	28.4 ± 0.4	−25	<0.01
Cardiac index (liter/min/m^2)	2	2.5 ± 0.1	32	<0.01	2.4 ± 0.1	26	<0.01
Stroke volume index (ml/beats/m^2)	24 ± 0.5	34 ± 1.0	38	<0.01	33 ± 0.6	33	<0.01
Pulmonary vascular resistance (dyne/s/cm^{-5})	249 ± 18	161 ± 19	−35	<0.01	168 ± 20	−32	<0.01
Mean arterial pressure (mm Hg)	98 ± 6	83 ± 5	−15	<0.01	84 ± 4	−13	<0.01
Systemic vascular resistance (dyne/s/cm^{-5})	2,145 ± 86	1,376 ± 51	−36	<0.01	1,386 ± 38	−36	<0.01
Heart rate (beats/min)	88 ± 3	86 ± 4.2	−2	NS	86 ± 3.8	−2	NS

The hemodynamic measurements between peak dose and at 48 hours were not significant.
NS = not significant; SE = standard error.

sponses to a therapeutic dose and to 48 hours of continuous intravenous nitroglycerin infusion at that rate, and (2) determine whether circulatory tolerance develops with continuous nitroglycerin after a therapeutic response was achieved.

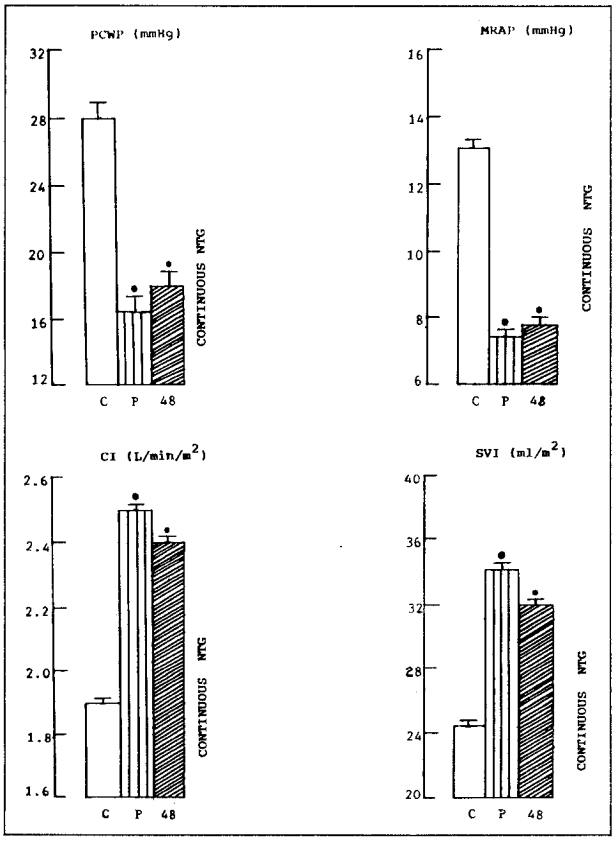

FIGURE 1. Changes in pulmonary capillary wedge pressure (PCWP), mean right atrial pressure (MRAP), cardiac index (CI) and stroke volume index (SVI) at control (C), peak effect (P) and after 48 hours of continuous intravenous nitroglycerin. The *dots* indicate significance ($p < 0.01$) from control values. Values are mean ± standard error of the mean.

Twelve men and 3 women, ages 28 to 66 years (mean 52) were studied. All patients had chronic CHF—New York Heart Association functional class III (10 patients) and IV (5 patients)—of at least 6-month duration. Eight patients had ischemic cardiomyopathy and 7 had dilated cardiomyopathy. Patients were excluded if they had angina pectoris, frequent ventricular ectopic beats, recent myocardial infarction or a systolic blood pressure <95 mm Hg. All vasodilators were discontinued 72 hours before evaluation. Digitalis and diuretics were continued throughout the study.

After written informed consent was obtained a 7Fr thermodilution Swan-Ganz catheter was introduced via femoral vein percutaneous puncture and positioned in the pulmonary artery under fluoroscopic guidance. Balloon inflation allowed recording of the pulmonary capillary wedge pressure, which was used to indicate left ventricular filling pressure. Pressures were measured using Gould Statham P23 transducers and recorded on a San-ei Rectigraph recorder. Cardiac output was determined by the thermodilution technique using a bedside computer (Hoyer Bremen HMV 7905), and averaging 3 consecutive values with <10% variation. At any given time interval, the averages of 5 consecutive readings were used for mean right atrial pressure, mean pulmonary artery pressure and pulmonary capillary wedge pressure. Derived hemodynamic variables were calculated as follows: cardiac index (liter/min/m^2) = cardiac output/body surface area; stroke volume index (ml/beats/min^2) = cardiac index/heart rate; systemic vascular resistance (dyne-s-cm^{-5}) = mean arterial pressure − mean right atrial pressure × 80/cardiac output; pulmonary vascular resistance (dyne-s-cm^{-5}) = mean pulmonary artery pressure − pulmonary capillary wedge pressure × 80/cardiac output. All pressures were recorded with the patient supine and the transducers placed at midchest level along the fourth intercostal space. All patients were studied in the morning in a fasting state without any premedication. Nitroglycerin was prepared for intravenous infusion by diluting the drug in 540 ml of 5%

dextrose in glass bottles. Baseline hemodynamic measurements were repeated at 15-minute intervals until a steady state was ensured. After the baseline pressures were recorded, the nitroglycerin infusion was begun at a rate of 10 μg/minute with 5-minute increments until a hemodynamic response appeared with a decline of at least 5 mm Hg in the right or left ventricular filling pressures or a ≥20% decrease in systemic vascular resistance, a decrease of systolic blood pressure to ≤90 mm Hg, or a significant untoward effect. Once a significant hemodynamic response was achieved, the nitroglycerin infusion was maintained at this rate for a total study period of 48 hours. Hemodynamic measurements were repeated every 15 minutes until maximal response was obtained, and also after completion of the protocol. Data are expressed as mean ± standard error of the mean. Student t test is used to compare changes in hemodynamic variables.

All 15 patients were hemodynamically monitored and responded to intravenous nitroglycerin. At peak effect there were significant decreases in filling pressures of the left and right ventricles, and an increase in the cardiac index and stroke volume index ($p < 0.01$) (Figure 1 and Table I). The onset of hemodynamic effects was invariably seen within 30 minutes of onset of infusion, with peak effects occurring between 60 and 90 minutes. The peak infusion rate of nitroglycerin averaged 78 ± 22 μg/minute. These beneficial effects were sustained for 48 hours and were statistically significant ($p < 0.01$) versus control values, but not versus measurements made at peak dose (Figure 1 and Table I).

This study demonstrates that continuous intravenous nitroglycerin for 48 hours results in signficant sustained hemodynamic improvement in patients with severe CHF. There was no evidence of nitrate tolerance in any of our patients. These results contrast with a recent report by Packer et al[9] indicating development of early tolerance in patients with CHF during continuous infusion of nitroglycerin. Packer, however, had evaluated only high, fixed doses of nitroglycerin and not lower doses titrated to achieve a maximal therapeutic response, as done in the present study.

Tolerance to hemodynamic response and antianginal effect has been observed after continuous exposure to organic nitrates. The mechanism of nitrate tolerance is still ambiguous;[10,11] it is postulated that prolonged administration of nitrates results in depletion of sulfhydryl groups in the vascular smooth muscle. The sulfhydryl groups help generate the production of cyclic guanosine monophosphate after interacting with organic nitrates and cyclic guanosine monophosphate, in turn, brings about vasodilation. Nitrate tolerance develops rapidly in patients with angina pectoris.[7] Tolerance to the clinical effects of isosorbide dinitrate developed when the drug was given at 30 mg 4 times daily for 7 days. Drug efficacy was, however, maintained when the dosage interval was increased to 30 mg administered 3 times in 24 hours—a reduction of only 30 mg of isosorbide dinitrate in a day. The clinical effects of a 20-mg dose of isosorbide dinitrate given 4 times daily remain to be studied. Rapid attenuation of antanginal effects have been demonstrated with transdermal nitrates.[12] However, when used in CHF as opposed to angina, transdermal nitroglycerin has been shown to provide sustained efficacy for 24 hours.[13,14] Olivari et al[15] also found salulatory acute hemodynamic benefits of transdermal nitroglycerin in CHF, with a decline in mean pulmonary artery pressure maintained for 24 hours.

Vasodilators not only improve the quality of life but also significantly increase survival in patients with severe CHF.[6,16] This study clearly indicates substantial hemodynamic benefits with optimal therapeutic doses of intravenous nitroglycerin. Hence, before we lay too much emphasis on tolerance, more controlled trials need to be conducted using different dosage schedules of intravenous nitroglycerin in CHF.

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