A randomized prospective trial of intravenous nitroglycerin in patients with acute myocardial infarction

JOHN T. FLAHERTY, M.D., LEWIS C. BECKER, M.D., BERNADINE H. BULKLEY, M.D., JAMES L. WEISS, M.D., GARY GERSTENBLITH, M.D., CLAYTON H. KALLMAN, SC.M., KENNETH J. SILVERMAN, M.D.,* JEANNE Y. WEI, M.D.,* BERTRAM PITT, M.D.,** AND MYRON L. WEISFELDT, M.D.

ABSTRACT A prospective randomized study of intravenous nitroglycerin (TNG) administered for 48 hr after acute infarction was undertaken to determine whether clinical improvement and/or evidence of preservation of ischemic myocardium could be demonstrated. One hundred four patients were randomly assigned to TNG (n = 56) and placebo groups (n = 48). TNG was infused at a rate sufficient to lower mean arterial pressure 10%, monitored noninvasively. When all TNG- and placebo-treated patients were compared, no significant differences in clinical or laboratory outcomes could be demonstrated. TNG- and placebo-treated patients were retrospectively subdivided into early and late treatment groups (treatment begun <10 hr vs ≥10 hr after onset of symptoms). Early TNG treatment was associated with a lower incidence of infarct complications within the first 10 days, defined by new congestive heart failure, infarct extension, or cardiac death (15% in early TNG compared with a mean of 39% in the other three subgroups; p = .003). Mortality at 3 months was lower in the group treated early with TNG (15%) compared with a mean of 25% in the other three subgroups (p = NS). No significant differences were found in peak creatine kinase (CK) blood levels, creatine kinase infarct size, or preservation of precordial R waves by serial electrocardiographic mapping. Among 49 patients with pretreatment and day 7 to 14 posttreatment left ventricular ejection fraction measurements, improvement of ≥10% occurred in 35% of TNG patients treated early compared with 6% of those treated late with TNG, 11% of those treated early with placebo, and 0% of those treated late with placebo (p = .004). Similarly, in 68 patients in whom paired thallium scintigrams were taken, a decrease of ≥75% in the computer-determined thallium defect score was seen in 48% of TNG patients treated early, compared with 14% of TNG patients treated late, 33% of placebo patients treated early and 0% of placebo patients treated late (p = .039). Patients demonstrating significant scintigraphic improvement were treated earlier, tended to have less severe initial scintigraphic abnormalities, inferior rather than anterior infarctions, a longer history of angina, and no prior history of heart failure. Thus intravenous TNG could not be shown to result in significant improvement in clinical or scintigraphic outcomes when the patient population was analyzed as a whole. After retrospective subgroup analysis, intravenous TNG could be shown to protect ischemic myocardium in the subset of patients with small-to-moderate sized myocardial infarctions when treatment was begun within 10 hr of the onset of symptoms. The results of this trial also suggest that future clinical trials designed to show a reduction in infarct size might limit patient entry to those admitted early after symptom onset and those with significant abnormalities in their admission scintigraphic studies. Larger-scale studies are needed to determine whether TNG therapy can significantly reduce mortality and to further define the population of patients who may profit most from this treatment.


From the Department of Medicine, Division of Cardiology, The Johns Hopkins University School of Medicine, Baltimore.
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Address for correspondence: John T. Flaherty, M.D., Johns Hopkins Hospital, Division of Cardiology, 600 North Wolfe St., Baltimore, MD 21205.
Received Nov. 2, 1982; revision accepted May 19, 1983.
*Present address: Beth Israel Hospital, Boston, MA.
**Present address: University of Michigan Medical Center, Ann Arbor, MI.

SHORT-TERM administration of intravenous nitroglycerin (TNG) to patients with acute myocardial infarction has been shown to improve left ventricular function in patients with congestive heart failure and to reduce electrocardiographic evidence of ischemia in patients with or without failure.1-2 Numerous experimental studies in dogs have also shown reduction in ischemia associated with increased collateral flow when TNG is given after coronary artery occlusion,
except when perfusion pressure is allowed to fall exces-
sively or significant reflex tachycardia occurs. In a re-
cent study in conscious dogs with coronary artery occlusion, a 6 hr infusion of intravenous TNG, given in a dose to reduce mean arterial pressure 10%, produced an increase in collateral flow and a reduction of approximately 50% in the extent of necrosis. In view of the favorable effects of short-term therapy, we undertook a prospective randomized study to test the hypothesis that intravenous TNG therapy given continuously for 48 hr after the onset of acute myocardial infarction would have lasting beneficial effects.

The study used both clinical and laboratory end points. It was recognized at the outset that with the anticipated sample size of 100 patients, mortality alone would not be an adequate end point for the trial. The emphasis was therefore on other clinical variables (infarct extension, new heart failure, ventricular arrhythmias) and on laboratory parameters which might indicate that ischemic myocardium had been salvaged: thallium-201 perfusion studies, gated cardiac blood pool scans, two-dimensional echocardiograms, precordial electrocardiographic mapping, and serial creatine kinase (CK) determinations. Myocardial perfusion and gated blood pool scintigrams were obtained on admission and compared with studies performed 7 to 14 days later in both TNG- and placebo-treated patients to assess pretreatment and posttreatment left ventricular function and myocardial perfusion and to allow separation of the effects of therapy from those occurring spontaneously over time.

Methods

Patients. One hundred four patients admitted to the Coronary Care Unit of the Johns Hopkins Hospital within 12 hr of the onset of symptoms were entered into this single-blinded randomized prospective study. Candidates included patients with a high probability of acute myocardial infarction, as defined by a history of prolonged chest pain typical of acute infarction and by electrocardiographic changes compatible with acute ischemia. The diagnosis of acute infarction was subsequently confirmed by elevation of serum CK in 97 of 104 (93%) patients and in 96 (92%) by evolution of electrocardiographic characteristics of acute infarction. The seven patients in whom acute infarction was excluded by cardiac enzyme criteria did not have follow-up scintigraphic studies but continued to receive routine clinical follow-up. Excluded from the study population were patients with age greater than 75 years, systolic blood pressure less than 90 mm Hg, heart rate less than 55 beats/min, and severe hypertension requiring administration of an intravenous vasodilator (defined by a persistently elevated systolic blood pressure greater than 200 mm Hg and/or diastolic blood pressure greater than 120 mm Hg after relief of chest pain).

Experimental protocol

Baseline studies. After informed consent was obtained, a card was drawn to randomize patients to either TNG or placebo treatment. Arterial pressure was monitored by a Doppler ultrasound blood pressure cuff (Arteriosonde) at 10 min intervals for 60 min while the admission studies were being obtained, and a 24 hr Holter electrocardiographic recording was begun. Baseline thallium-201 myocardial perfusion scintigrams were obtained in the anterior, 40 degree left anterior oblique (LAO) and 60 degree LAO views, followed immediately by a two-dimensional echocardiogram or gated blood pool scintigrams in the anterior and 40 degree LAO views. In patients with anterior infarctions, a 48-lead precordial QRS and ST segment map was obtained early and at least 1 hr later, before drug infusion. Swan-Ganz pulmonary artery catheters and radial artery cannulas were inserted only when clinically indicated and were not part of the experimental protocol.

Drug infusion protocol. Intravenous infusion of TNG was begun at 5 μg/min and the rate was increased stepwise at 3 to 5 min intervals with monitoring of arterial blood pressure. TNG infusion rate was adjusted by an infusion pump (IMED) to lower mean arterial pressure 10% from the control level. Mean arterial pressure was calculated by the formula: mean arterial pressure = diastolic pressure + (systolic pressure - diastolic pressure)/3. Systolic pressure was not allowed to fall below 90 mm Hg or heart rate to fall below 50 beats/min. Titration of the placebo infusion was carried out in a manner similar to the titration of TNG, to a flow rate of 20 to 30 ml/hr, which was a similar volume flow rate to that required for TNG. The study drugs were mixed in glass bottles and covered with aluminum foil. TNG was prepared by adding 100 ml of stock TNG solution (500 μg/ml; courtesy of Eli Lilly and Co.) to a 500 ml bottle of 5% dextrose in water from which approximately 100 ml had been removed. The placebo solution consisted of 0.9 ml of 95% ethanol added to each 500 ml bottle of 5% dextrose in water to match the composition of the vehicle in which TNG was dissolved.

Fifteen to 30 min after the final infusion rate had been obtained, the precordial map was repeated. Blood pressure was then monitored every 15 min for 4 hr, every 30 min for the next 4 hr, every hour for the next 4 hr, and then every 2 hr until the infusion was terminated at 48 hr. All adjustments of infusion rate were made by the investigator while the nursing staff, housestaff, and patient remained blinded to which treatment was being given. Infusion rates were maintained constant except when a reduction or termination was necessitated by one of the following: (1) fall in systolic blood pressure to less than 90 mm Hg or fall in heart rate to less than 50 beats/min, (2) a continuing fall in blood pressure of lesser magnitude accompanied by signs of patient deterioration, or (3) severe side effects such as headache or nausea and vomiting that persisted despite usual symptomatic treatment.

Management of other drugs during TNG or placebo infusion. All Killip class I and II patients received lidocaine, 1 mg/kg bolus and 20 μg/kg/min for at least 24 hr. Killip class III patients received half this dose. The dose of lidocaine was increased as necessary if multifocal or coupled premature ventricular contractions (PVCs) or ventricular tachycardia were observed. Additional antiarrhythmic drugs were added as clinically indicated. Oral antihypertensive medications were continued if appropriate. Chest pain associated with the initial infarction was treated with morphine. Recurrent episodes of chest pain associated with new electrocardiographic (ECG) changes were treated with sublingual TNG. Propranolol and/or long acting nitrates were added only after a second recurrent ischemic episode with electrocardiographic changes. Diuretics, either oral or intravenous, were administered only if clinical and radiographic signs of congestive heart failure remained after the initiation of intravenous treatment with TNG or placebo. Patients previously taking digitalis preparations were continued on the medication but digitalis was not initiated except for persistent heart failure or arrhythmias. Oxygen was administered by

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nasal cannula at 4 l/min in all patients. If arterial desaturation was documented, additional oxygenation was provided by face mask or other appropriate means. Unless contraindicated, all patients received intravenous sodium heparin by constant infusion to maintain the clotting time at twice control values. Potassium chloride was administered to all patients with serum potassium concentration less than 3.0 mEq/l and to those with levels between 3.0 and 3.5 mEq/l demonstrating coexistent PVCs or receiving digitalis or diuretic therapy.

Follow-up studies. Infusion of TNG or placebo was continued for 48 hr and then abruptly terminated. For those patients in the TNG group, 1 inch of TNG ointment (2%) was applied 1 hr later and the dose was increased every 4 hr at 1/2 inch increments until mean arterial pressure was lowered to the level previously achieved with intravenous TNG. This final dose was maintained for 72 hr unless significant side effects necessitated that the dose be reduced or the drug discontinued earlier. Placebo-treated patients received 1 inch of placebo ointment every 4 hr for 72 hr. All study medications were discontinued on the sixth day after Coronary Care Unit admission.

Seven to 14 days after admission, at least 2 days after discontinuation of TNG or placebo therapy, repeat thallium and gated blood pool scintigrams, two-dimensional echocardiograms, precordial QRS and ST segment maps, and 24 hr Holter ECG recordings were repeated. Long-term clinical follow-up was obtained by telephone interview. For discharged patients, the mean duration of follow-up was 15 months (range 4 to 44).

Methods of data acquisition and analysis

CK blood levels. Total serum CK blood levels were measured by a modified Rosalki technique on admission, every 4 hr for 24 hr, every 6 hr for the next 24 hr, and every 12 hr until hospital discharge. The upper limits of normal were 50 IU/l for men and 40 IU/l for women.

Precordial mapping studies. Patients with electrocardiographic changes in anterior or lateral leads underwent serial 48-lead precordial QRS and ST segment mapping. Details of the methods have been described previously. Recordings were made at 20 mm = 1 mV calibration, and ST segment voltages were measured 80 msec after the termination of the QRS complex. All records were read without knowledge of therapy, and any patients developing intraventricular conduction defects (QRS duration >100 msec) were excluded. Preservation of R wave voltage, expressed as percent of control, was analyzed in contiguous leads showing ST elevation of >1 mm on the initial map.

Twenty-four hour Holter electrocardiographic recording.

The Holter monitor recordings were read blindly by a trained technician using an electroscanner (Avionics Model 650) at a scanning speed 60 times normal. Arrhythmias were printed at a paper speed of 25 mm/sec and analyzed without knowledge of patient assignment. Ventricular arrhythmias were classified according to the modified criteria of Lown: class 0, no PVCs; class I, uniform PVCs, <30/hr; class II, uniform PVCs ≥30/hr during at least 1 hr of monitoring; class III, multiformed PVCs; class IV, PVCs in couplets or greater (including ventricular tachycardia). Evaluation of the Holter monitor recordings included the total PVC count as well as the maximum Lown classification noted during the 24 hr.

Scintigraphic studies. Thallium-201 and gated blood pool scintigrams were acquired with a gamma camera (Technicare 420 and 120) fitted with a medium-sensitivity or general all-purpose low-energy parallel-hole collimator, and interfaced to a dedicated computer (Medical Data Systems). For the thallium studies, 1.5 to 2.0 mCi thallium-201 chloride was injected intravenously and 400 K count images were acquired 10 min later in anterior, 40 degree LAO, and 60 degree LAO views in 128 × 128 matrix format on magnetic disc. Immediately after the thallium study was completed, a gated cardiac blood pool scintigram was acquired in anterior and approximately 40 degree LAO views (to best define the interventricular septum) without caudal angulation in 32 × 32 format, interpolated to 64 × 64, with 2 × software zoom. For the first 68 patients, technetium-99m human serum albumin (20 to 30 mCi) was used, while the remaining 36 patients were studied with in vivo labeled erythrocytes. A cardiac shield was used to improve image quality for both thallium and blood pool studies beginning with the sixtieth patient.

For 21 patients who did not undergo gated blood pool scintigraphic studies on admission because of arrhythmias, technical problems, or unavailability of equipment, two-dimensional echocardiographic studies were obtained and area ejection fractions were calculated as the mean of ejection fractions obtained from the cross-sectional and sagittal views of the left ventricle. This approach was validated in seven additional patients who had ejection fractions measured both by gated blood pool and two-dimensional echocardiographic methods. Since correlation of these two values revealed a parallel shift of 6% in the best-fit linear regression line from the line of identity, all echocardiographic ejection fractions were augmented by 6% to allow comparison with the scintigraphic ejection fractions.

Initial and posttreatment thallium perfusion scintigrams were analyzed by the "circumferential profiles" computer-assisted technique. A defect score was obtained for each study, reflecting both the extent and intensity of perfusion deficit. A curve of normalized thallium activity vs angular location was generated and superimposed on empirically determined normal limits with alignment of the apex. The defect score was calculated by integrating the area of the patient’s curve below normal, equivalent to the total reduction in activity divided by the total number of radii, or average reduction per radius. This method of computer scoring has been shown to have acceptably high intraobserver and interobserver reproducibility.

Gated cardiac blood pool scintigrams were analyzed with a commercial computer program (MUGE). Semiautomatic regions of interest were generated over the left ventricle for each frame in the cardiac cycle with a combined second-derivative and count threshold algorithm. A background region was automatically generated lateral and inferior to the left ventricle in the end-systolic frame, five pixels wide and two pixels removed from the computer-generated left ventricular edge. From these regions of interest, a background-corrected left ventricular time-activity curve was obtained and left ventricular ejection fraction was calculated as (end-diastolic counts - end-systolic counts)/end-diastolic counts. The lower limit of normal for ejection fraction in our laboratory is 50%. Regional wall motion was assessed visually in each view in each of five equal left ventricular segments by two observers who were unaware of patient identity and therapy. Segments were judged to be normal, hypokinetic, akinetic, or dyskinetic, and the total number of akinetic and dyskinetic segments was determined.

Statistical analysis. All results are expressed as mean ± 1 SD. The two tailed Student’s t test, chi square, Fisher’s exact, one-way analysis of variance, linear regression, stepwise logistic regression, and repeated measures analysis of variance were used for statistical analysis.

Results

Of the 104 patients entered into the study, 56 received TNG and 48 received placebo. There were no significant differences in clinical and laboratory parameters at admission between TNG- and placebo-treated patient groups (table 1).
Initial hemodynamic effects of drug infusion. The mean infusion rate of TNG required to obtain the desired 10% lowering of mean arterial pressure was 90 ± 74 μg/min (range 12 to 250). The mean duration of the TNG titration period was 81 ± 63 min (range 9 to 425). Mean arterial pressure was lowered from a control level of 107 ± 18 to 95 ± 15 mm Hg after final titration, systolic arterial pressure from 142 ± 27 to 123 ± 21 mm Hg, and diastolic pressure from 90 ± 1 to 81 ± 15 mm Hg (all p < .001 vs control). Mean heart rate was 81 ± 25 beats/min before and 79 ± 15 beats/min after institution of TNG therapy (NS).

In patients receiving placebo, mean arterial pressure declined slightly from 114 ± 19 to 110 ± 20 mm Hg during the titration period (NS). The mean duration of placebo titration was 27 ± 23 min (range 0 to 115). Pretitration and posttitration systolic pressures were 150 ± 29 and 146 ± 29 mm Hg, diastolic pressures 96 ± 18 and 93 ± 19 mm Hg, and heart rates 81 ± 25 and 79 ± 15 beats/min, respectively (all changes NS).

Retrospective subgrouping of patients into early and late treatment. When all 56 TNG-treated patients were compared with all 48 placebo-treated patients, no statistically significant differences in the major clinical or laboratory end points could be demonstrated. Specifically, there were no differences in the incidences of the clinical outcomes of early death, new congestive heart failure, or infarct extension nor in the laboratory parameters of ejection fraction or thallium-201 defect score. Since many previous studies of interventions designed to reduce infarct size have emphasized the importance of early treatment,9-11 we subdivided patients retrospectively into two subgroups, those treated <10 hr and ≥10 hr from the onset of symptoms. This arbitrary cut-off divided the TNG treatment group into subgroups of equal number (group 1, early; group 2, late; both n = 28). The placebo-treated group was divided into subgroups of 27 (group 3, early) and 21 patients (group 4, late). Admission clinical and laboratory parameters continued to show no statistically significant differences among all subgroups (table 1). By chance, however, group 4 contained more patients with normal ejection fraction and/or low thallium defect score. In this subgroup, 11 of 16 patients (69%) had normal initial ejection fractions (≥50%) compared with 54%, 40%, and 52% in the other three subgroups. Ten of 21 patients (48%) had an initial thallium defect score <1.0, compared with 25%, 24%, and 17% in the other three subgroups. This relative excess of patients with smaller infarctions in group 4 was not believed to represent a critical problem, since the most clinically relevant comparison is between early TNG and early placebo treatment, and secondarily between early and late TNG treatment.

Clinical end points. Of the 97 patients with enzymatic evidence of myocardial infarction, 32 (33%) developed one or more of the following infarct-related complications: (1) new congestive heart failure, defined by the presence of one or more of the following criteria 7 to 10 days after admission in the absence of a prior history of failure: (a) clinical signs of pulmonary congestion, basilar rales and ventricular gallop, or diffuse rales with expiratory wheezes (pulmonary edema), (b) pharmacologic therapy consisting of furosemide with or without digoxin, or (c) signs of pulmonary venous congestion on a chest radiograph obtained 7 to 10 days

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after admission; (2) infarct extension, defined by a secondary rise in CK of >200 IU/l with new electrocardiographic changes more than 24 hr after admission; or (3) cardiac death. The frequency of these complications, taken singly or in combination, did not differ significantly between the overall TNG- and placebo-treated groups.

However, when these data were analyzed for the four subgroups, a benefit of early TNG treatment was evident. Only one (6%) group 1 patient developed new congestive failure compared with seven (32%) group 2 patients, six (30%) group 3 patients, and two (11%) group 4 patients (p = .105). Myocardial infarct extension occurred in three (12%) group 1 patients compared with seven (27%) group 2 patients, seven (26%) group 3 patients, and two (11%) group 4 patients (NS). Death occurred within the first 10 days in only one (4%) group 1 patient compared with three (12%) group 2 patients, five (19%) group 3 patients, and one (6%) group 4 patient (NS). Nine of 10 deaths were a consequence of severe left ventricular pump failure. The remaining death was caused by arrhythmia on day 10 after admission.

When examined individually, differences in the incidence of these three infarct-related complications among the four treatment subgroups did not reach statistical significance. However, it should be noted that none of 10 early cardiac deaths were secondary to cardiogenic shock (class IV congestive failure). In addition, seven of these 10 deaths occurred within 24 hr of an infarct extension, with nine additional patients developing new congestive heart failure after an extension. Although we were aware of the difficulty in the interpretation of composite clinical end points, but because of the above-mentioned interrelation among these three unfavorable outcomes, we examined the incidence of any one of these complications within each of the four treatment subgroups. One or more of these complications was seen in four (15%) group 1 patients compared with 13 (50%) group 2 patients and 13 (48%) group 3 patients (p = .003). The higher percentage of smaller infarctions in group 4 was again reflected in a lower incidence of infarct-related complications during the first 10 days (two patients, 11%).

Twenty-four hour Holter electrocardiographic recordings. On the day of admission, primary ventricular fibrillation was observed in one placebo-treated patient, sustained ventricular tachycardia was seen in three TNG-treated patients and one placebo-treated patient, and complete heart block was seen in one TNG-treated and two placebo-treated patients (NS).

No significant differences were seen between TNG and placebo groups or among the four subgroups in the number of PVCs per 24 hr on the day of admission or on a follow-up recording made 7 to 14 days later. In the TNG group the mean number of PVCs decreased from 320 ± 192 to 194 ± 92, while in the placebo group it increased from 481 ± 980, 663 ± 2434, but these changes were not statistically significant. The incidence of late in-hospital complex PVCs (Lown class IV on days 7 to 14) was 18% for TNG-treated patients vs 30% for placebo-treated patients, but again this difference was not statistically significant.

Late clinical follow-up. Of the 93 patients surviving hospitalization, follow-up was complete at 3 months in 90; two of the three patients lost to follow-up had not had an acute myocardial infarction. There were 11 (11%) deaths within the first 10 days of infarction (four in the TNG subgroups [one group 1 and three group 2] and seven in the placebo subgroups [five group 3 and two group 4]). There were 11 (11%) additional deaths between 10 days and 3 months (seven TNG-treated and four placebo-treated patients). Overall 3 month mortality was distributed as follows: four (15%) in group 1, seven (27%) in group 2, seven (26%) in group 3, and four (22%) in group 4 (p = NS).

Laboratory end points

Ejection fraction by gated blood pool scintigraphy or twodimensional echocardiography. Left ventricular ejection fractions were compared before treatment and at least 2 days after its completion (days 7 to 14) to determine the effect of therapy on left ventricular function. Sixty-five patients were available for this analysis; in the remainder, death, technical problems, or patient refusal prevented acquisition of paired studies. Mean ejection fraction decreased from 51 ± 18% to 50 ± 16% for the entire TNG-treated group and from 54 ± 14% to 50 ± 16% for the entire placebo-treated group (NS). As shown in figure 1, when patients were divided into early and late treatment subgroups, the mean changes in ejection fraction were +2.4% in 20 group 1 patients, −0.4% in 18 group 2 patients, −3.3% in 18 group 3 patients, and −6.1% in nine group 4 patients (NS). However, the response of ejection fraction to treatment also appeared to depend on whether the initial ejection fraction was normal or abnormal (≥50% or <50%). Among patients with abnormal initial ejection fractions (<50%), group 1 demonstrated a significant mean increase in ejection fraction of 11 ± 4% (figure 2). In contrast, the mean changes were +1 ± 2% in group 2, −2 ± 1% in group 3, and 0 ± 7% in group 4 patients with abnormal ejection fractions on admission (p = .058). Among patients with initial ejection fraction ≥50%, all subgroups demonstrated
FIGURE 1. Mean ejection fraction responses in the four treatment subgroups for 65 patients who underwent determination of ejection fraction on admission and 7 to 14 days later. TNG < 10 hr, group 1; TNG ≥10 hr, group 2; placebo < 10 hr, group 3; placebo ≥10 hr, group 4.

The admission and follow-up gated blood pool scintigrams were also analyzed for the number of akinetic or dyskinetic left ventricular segments. Included in this analysis of segmental dysfunction were 35 patients with paired data and at least one akinetic or dyskinetic segment on the admission scintigram. Seven of 11 (64%) group 1 patients had a decrease in the number of akinetic or dyskinetic segments. In contrast, only four of 12 (33%) group 2 patients, three of eight (38%) group 3 patients, and one of four (25%) group 4 patients showed improved segmental motion (p = .068).

Analysis of mean data, however, obscured a marked heterogeneity in admission scintigraphic abnormalities and response to treatment. Certain individual patients showed marked scintigraphic improvement, while a smaller number demonstrated worsening. The data were therefore analyzed to determine the percentage of individuals in each subgroup with favorable or unfavorable scintigraphic responses. A “responder” was defined as a patient demonstrating an increase in ejection fraction of 10% or more (EF units), which is greater than the known variability involved in measuring this variable.11 A “nonresponder” was defined as a patient with initial ejection fraction in the abnormal range (<50%) who failed to improve by 10% or more. In addition, two patients with normal initial ejection fraction (≥50%) who demonstrated an especially large decrease in ejection fraction of >25% were also defined as “nonresponders.” Patients with a normal initial ejection fraction who did not demonstrate an increase of ≥10% or a decrease of <25% were considered to have shown “neutral” responses, since therapy would not be expected to increase fraction in these patients.

As shown in figure 3, by these definitions, group 1 patients had a significantly higher percentage of responders (35%) compared with 6% for group 2, 11% for group 3, and 0% for group 4 (p = .004). If patients dying early were included as nonresponders, the difference between group 1 and the other three subgroups was statistically even greater (p < .001).

Thallium-201 myocardial perfusion scintigraphy. Thallium defect scores were compared for the pretreatment and the days 7 to 14 follow-up studies. Sixty-eight patients were available for this analysis: in addition to early deaths and technical problems, patients with absent or very small initial defects (score <1.0) were excluded. This was necessary because of the inability to demonstrate significant scintigraphic improvement in these patients by the methods described. Mean defect score decreased from 5.5 ± 7.2 to 2.2 ± 3.3 (40%) in the TNG group (54 patients) and from 5.4 ± 6.3 to 2.3 ± 3.4 (42%) in the placebo group (44 patients). Analysis of responses in the four subgroups revealed mean decreases of 56% in 23 group 1 patients, 16% in 14 group 2 patients, 48% in 18 group 3 patients, and 33% in 13 group 4 patients (NS).

As with ejection fraction, individual patient responses were analyzed to determine the percentage demonstrating significant improvement in thallium defect score. On the basis of the previously defined variability in computer scoring,4 we defined a “responder” as having a significant initial perfusion defect (score ≥1.0) and a decrease in posttreatment score of 75% or more. This definition was thought to represent a stringent criterion for improvement. A “nonre-
sponder" was defined as having an initial defect score of $\geq 1.0$ but a posttreatment score that either increased or failed to decrease by 75% or more. Responses of patients with small or nonexistent initial perfusion defects (scores $< 1.0$) were defined as "neutral."

As shown in figure 4, by these definitions, group 1 patients had a significantly higher percentage of responders (48%) compared with 14% in group 2, 33% in group 3, and 0% in group 4 ($p = .039$). If patients dying early after infarction were included as nonresponders, the difference between group 1 and the other three subgroups became even more significant ($p < .001$).

Characteristics of responders and nonresponders. Among patients receiving TNG, certain admission clinical and scintigraphic parameters characterized individuals who responded scintigraphically (table 2). For this analysis, patients who were thallium and/or ejection fraction responders were combined and thallium and/or ejection fraction nonresponders were combined with those who suffered early death. The single most differentiating parameter was the interval between the onset of chest pain and the initiation of therapy. Eighty-four percent of responders had been treated within 10 hr of the onset of symptoms, compared with only 24% of nonresponders ($p < .001$, figure 5).

The magnitude of the initial thallium defect score and/or the admission ejection fraction was also important. Of 17 group 1 patients with initial thallium defect scores less than 6.0, 15 (88%) were responders compared with only two of 10 similar group 2 patients, suggesting that early treatment was important in patients with smaller perfusion defects. In contrast, of 12 TNG-treated patients with initial thallium defect scores greater than 6.0, only two responded (one treated early and one late). Stepwise logistic regression analysis indicated that the timing of TNG therapy over and above the magnitude of the initial thallium defect score affected the proportion of responders and nonresponders ($p = .001$). That both early treatment and a thallium score $< 6.0$ were required for a patient to be a responder was suggested by the interaction of timing of treatment and thallium score, which approached but did not reach statistical significance ($p = .123$).

FIGURE 3. Percentage of patients in each treatment subgroup meeting responder (R), nonresponder (NR), and neutral response (N) criteria for ejection fraction.

FIGURE 4. Percentage of patients in each treatment subgroup meeting responder (R), nonresponder (NR), and neutral response (N) criteria for thallium-201 perfusion defect score.
A similar relationship could be demonstrated for ejection fraction. Of 11 group 1 patients with admission ejection fraction ≥45%, 10 (91%) were responders compared with only three to nine (33%) of similar group 2 patients. Likewise, of eight group 1 patients with lower ejection fractions (<45%), four (50%) were responders compared with 0 of eight similar group 2 patients. Thus the timing of therapy appeared to affect the likelihood of a patient responding over and above the magnitude of the admission ejection fraction (p = .005). However, in contrast to the effect of thallium score, a higher ejection fraction (≥45%) did appear to increase the likelihood of a patient responding, even when the patient was treated late. Thus the beneficial effects of TNG treatment appear to be a function of both early vs late treatment and the size of the initial thallium defect score or the degree of left ventricular dysfunction, with the greatest benefit being obtained in patients treated early who had small perfusion defects and/or higher ejection fractions.

In general, placebo-treated responders (only six patients) demonstrated clinical and laboratory parameters similar to those of the TNG responders. Likewise, placebo-treated nonresponders (22 patients) had clinical and laboratory parameters similar to those of TNG nonresponders.

**CK blood levels.** No significant differences were seen in mean peak serum CK between TNG and placebo groups or among the four subgroups (1140 ± 884 IU/l for group 1, 971 ± 885 IU/l for group 2, 1122 ± 911 IU/l for group 3, and 838 ± 788 IU/l for group 4; NS).

Infarct size was estimated by the method of Shell et al. for 68 patients with sufficient CK data to permit this calculation. Mean infarct size for group 1 patients was 95 ± 97 gEq compared with 64 ± 63, 88 ± 100, and 96 ± 102 gEq for groups 2, 3, and 4, respectively (NS).

The time between onset of chest pain to peak CK blood level was shortest for group 1 patients (19.1 ± 6.9 hr vs 28.6 ± 19.5 hr for group 2 patients, p < .05). The mean rate of rise of the CK curve also appeared steeper (95 ± 137 IU/h/l/hr) in group 1 patients compared with that in group 2 patients (81 ± 111 IU/h/l/hr), group 3 patients (66 ± 64 IU/h/l/hr), and group 4 patients (47 ± 39 IU/l/hr) (NS). These findings suggest more rapid washout of myocardial CK with early initiation of TNG treatment.

**Precordial ST and QRS mapping studies.** Of 26 patients with anterior or lateral myocardial infarctions who underwent serial precordial mapping, 15 received TNG and 11 received placebo. During the control period, before initiation of therapy, the sum of ST segment

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**FIGURE 5.** Time (hr) between onset of symptoms and initiation of intravenous TNG therapy in responders (R) and nonresponders (NR) (see text).

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**TABLE 2**

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<th>Responders (n = 19)</th>
<th>Nonresponders (n = 21)</th>
<th>p value</th>
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<td>Time from symptoms to treatment (hr)</td>
<td>8.7 ± 1.8</td>
<td>11.5 ± 3.6</td>
<td>.003</td>
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<td>Time &lt;10 hr</td>
<td>84%</td>
<td>24%</td>
<td>&lt;.001</td>
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<td>Admission thallium score (U)</td>
<td>3.3 ± 2.8</td>
<td>9.6 ± 9.9</td>
<td>.012</td>
</tr>
<tr>
<td>Score &lt;6</td>
<td>89%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Admission ejection fraction (%)</td>
<td>55 ± 15</td>
<td>40 ± 15</td>
<td>.006</td>
</tr>
<tr>
<td>Ejection fraction ≥45%</td>
<td>79%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Peak CK (IU/l)</td>
<td>1056 ± 661</td>
<td>1473 ± 1072</td>
<td>.144</td>
</tr>
<tr>
<td>Previous angina</td>
<td>61%</td>
<td>37%</td>
<td>.158</td>
</tr>
<tr>
<td>Duration of angina (mo)</td>
<td>36 ± 68</td>
<td>21 ± 56</td>
<td>.215</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treated with digoxin</td>
<td>5%</td>
<td>40%</td>
<td>.020</td>
</tr>
<tr>
<td>Location and type of infarct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior transmural</td>
<td>53%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Anterior transmural</td>
<td>26%</td>
<td>53%</td>
<td>.132</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>21%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
elevations in all 48 precordial leads (ΣST) decreased 25% in both early treatment subgroups and 2% to 3% in both late treatment subgroups. During the hour after initiation of therapy, ΣST decreased 15% and 17% in groups 1 and 2, respectively. In contrast, during the same period in patients receiving placebo, ΣST increased in both early and late treatment subgroups (+5% and +27%, respectively; p < .05, TNG-treated vs placebo-treated patients).

Preservation of R wave voltage in leads with initial ST segment elevation (≥1 mV) was not significantly different among the four treatment subgroups. All groups showed decreases in mean ΣR over the first 10 days after infarction: −35% in group 1, −44% in group 2, −39% in group 3, and −57% in group 4 (NS). This failure to demonstrate improved preservation of R waves in patients with anterior infarctions would appear to correlate with the high incidence of nonresponders among patients with anterior transmural infarctions.

**Adverse effects.** Arterial hypotension necessitated discontinuation of the infusion in five patients (9%) receiving TNG and in five patients (10%) receiving placebo. In two of the TNG-treated patients and one placebo-treated patient, hypotension was associated with significant bradycardia. Reduction of the infusion rate was required in six TNG-treated (11%) and one (2%) placebo-treated patient. Four patients with significant right ventricular infarction complicating an inferior transmural infarction received TNG therapy. Hypotension necessitated discontinuation of the infusion in one and reduction of the infusion rate in another.

Sinus tachycardia was encountered in one patient (2%) during TNG infusion and in three patients (6%) during placebo infusion, with two of these placebo-treated patients also demonstrating hypotension. Sinus bradycardia occurred only in association with hypotension, as noted above. Headache was noted in two (4%) TNG-treated patients and in no placebo-treated patients. In one case it was necessary to reduce the rate of TNG infusion. Nausea and/or vomiting occurred in three (5%) TNG-treated patients but in no placebo-treated patients. In one of the three patients it was necessary to reduce the rate of TNG infusion.

**Discussion**

The results of our prospective randomized clinical trial of intravenous TNG failed to demonstrate significant benefit when the time interval between symptom onset and the initiation of therapy was not taken into account. Infusion of TNG begun within 10 hr of the onset of symptoms and continued for 48 hr to patients with acute myocardial infarction was associated with a lower incidence of early infarct complications. A significant reduction in the combined frequency of new congestive heart failure, infarct extension, or early cardiac death was demonstrated, although reductions in individual complications were not significant when tested separately. Noninvasive scintigraphic studies suggested that improvement in left ventricular ejection fraction and myocardial perfusion may have been responsible for the clinical beneficial effects observed in patients treated early.

Previous studies from this institution employed invasive monitoring techniques to measure the hemodynamic effects of short-term infusion of TNG in patients with acute myocardial infarction. This experience suggested that at lower infusion rates, TNG reduces pulmonary capillary wedge pressure while having only a mild effect on arterial pressure. Further increase in TNG infusion rate resulted in little further reduction in left ventricular filling pressure but did result in arterial vasodilatation, with progressive lowering of mean arterial pressure. Patients with severe left ventricular failure obtained the greatest hemodynamic benefit, while patients in all hemodynamic subgroups demonstrated equal anti-ischemic effects. In the present study arterial pressure was monitored noninvasively with an ultrasonic blood pressure cuff. Invasive monitoring was not used unless patients developed clinical indications. The infusion rate of TNG was titrated to obtain a 10% lowering of mean arterial pressure as the predetermined hemodynamic end point. Since in previous studies lowering of filling pressure had reproducibly preceded lowering of arterial pressure, a 10% lowering of mean arterial pressure was believed to provide evidence of a significant hemodynamic effect without requiring routine insertion of a Swan-Ganz catheter.

It was important to document the safety of long-term infusion of a potent vasodilator such as TNG in patients with acute myocardial infarction. Hypotension necessitated discontinuation of the infusion in only five of 56 patients (9%). In all cases, mean arterial pressure returned rapidly to baseline levels within 2 to 3 min of stopping the infusion. Reduction in infusion rate was required to reverse side effects in an additional six patients (11%). In the remaining 45 patients (80%) the infusion of TNG did not require adjustment during the entire 48 hr intravenous treatment period. Thus it would appear that by noninvasive monitoring, intravenous TNG can be safely administered to patients with acute myocardial infarction for prolonged periods.

Several recent studies have demonstrated beneficial...
effects of intravenous TNG on certain clinical and noninvasive laboratory end points in patients with acute myocardial infarction. Bussman et al.\textsuperscript{13} reported a reduction in CK infarct size with 48 hr infusion of intravenous TNG in a controlled but nonrandomized study in patients with elevated pulmonary artery diastolic pressure. In a preliminary report of a randomized clinical trial, Jaffee et al.\textsuperscript{14} also found a reduction in CK infarct size, but only in the subgroup of patients with inferior transmural myocardial infarctions. The present study also found that scintigraphic responders were twice as likely to have had inferior than anterior transmural infarctions. A possible explanation for this differential effect could be the greater effectiveness of anterior-to-inferior circulation intercoronary collateral channels demonstrated by Fuster et al.\textsuperscript{15} Derrida et al.\textsuperscript{16} in a randomized prospective study, demonstrated a significant reduction in in-hospital mortality and improved preservation of precordial R waves in patients with anterior transmural infarctions. In Derrida's study only those precordial leads with initial ST elevations without Q waves were examined, in contrast to the present study in which all contiguous leads with initial ST elevations were included in the analysis. Since these investigators analyzed only the small subset of precordial leads without initial Q waves, one might predict a greater sensitivity for detecting a beneficial effect of therapy. The method of analysis used in the present study was chosen to be comparable to that employed by Muller and Maroko\textsuperscript{9, 10} in their clinical studies of myocardial preservation.

Whether TNG is beneficial in patients with acute myocardial infarction and normal left ventricular filling pressure has been controversial. Borer et al.\textsuperscript{17} observed an increase in heart rate, which could be prevented by simultaneous administration of the \(\alpha\)-adrenergic agonist, phenylephrine, when TNG was given as a large sublingual dose to patients with normal filling pressures. In contrast, in a study performed at our institution, when TNG was administered by the intravenous route, reflex tachycardia was not observed, even in patients with normal filling pressures. Addition of phenylephrine, instead of providing added benefit, tended to reverse the beneficial hemodynamic and anti-ischemic effects obtained with TNG alone.\textsuperscript{18}

In a recent study that used a conscious, previously instrumented canine preparation of acute myocardial infarction, intravenous TNG reduced pathologic infarct size by increasing intercoronary collateral flow to the infarct zone.\textsuperscript{3} The addition of another \(\alpha\)-adrenergic agonist, methoxamine, to restore coronary perfusion pressure resulted in no further increase in collateral flow and no further reduction in infarct size compared with TNG alone. Similarly, regional ischemia induced by atrial pacing distal to a critical coronary stenosis was not improved when coronary perfusion pressure was restored in the presence of TNG.\textsuperscript{19} Thus it would appear that when arterial pressure is reduced slowly with intravenous infusion of TNG and reflex tachycardia is avoided, addition of an \(\alpha\)-adrenergic agonist to raise arterial pressure is unnecessary.

Paired scintigraphic studies were used to determine whether TNG treatment could result in measurable salvage of ischemic myocardium. Abnormalities in the initial study were taken to reflect the extent of myocardium that was ischemic and therefore still at jeopardy, in addition to the extent of myocardium that was already infarcted; abnormalities in the later study were believed to represent the extent of myocardium that ultimately underwent necrosis. With each patient serving as his own control, comparison of the paired scintigrams provided a measure of the amount of myocardium that was reversibly ischemic and therefore "salvaged" either by treatment with TNG or in the natural course of events. Comparison of TNG- and placebo-treated subgroups allowed separation of changes due to TNG therapy from changes due to spontaneous or purely time-related effects. Large thallium defect scores and/or low ejection fractions on admission scintigraphic studies have been shown to correlate with high in-hospital and early post-discharge mortality in patients with acute myocardial infarction.\textsuperscript{20-22} A second important reason, therefore, for obtaining pretreatment scintigraphic studies was to provide a more complete admission profile, which could ensure comparability of TNG- and placebo-treated subgroups.

The mechanisms by which early TNG treatment reduced thallium defect score remain speculative. Possible mechanisms include an increase in collateral blood flow to borderline ischemic myocardium due to (1) direct dilatation of intercoronary collateral channels, (2) reduction in left ventricular filling pressure with a decrease in subendocardial compressive forces, and/or (3) reversal of coronary artery spasm with an increase in antegrade flow to the infarct zone. Myocardial ischemia may have also been improved by the reduction in oxygen demands associated with reduction of both left ventricular filling pressure and systemic arterial pressure.

Although sodium nitroprusside may possess preload- and afterload-lowering qualities similar to those of TNG, several recent studies have suggested that TNG may be preferable for use in patients with acute myocardial infarction.
myocardial ischemia or infarction. Chiariello et al. showed that TNG decreased while nitroprusside increased the sum of precordial ST segment voltages in patients with acute anterior infarction. These authors also demonstrated opposite effects on ST elevations and opposite effects on intercoronary collateral flow in open-chest dogs with acute coronary occlusion. In a clinical study by Mann et al. using the xenon washout technique, TNG increased while nitroprusside decreased ischemic zone coronary flow in patients with angiographically visible collaterals. Thus the more favorable effect of TNG on intercoronary collateral flow would favor its use over nitroprusside in patients with acute ischemia or infarction.

Two randomized clinical trials of nitroprusside in acute myocardial infarction have recently been reported. Cohn et al. reported the results of the Veterans Administration Cooperative Trial, which included 812 patients with acute transmural infarction and elevated left ventricular filling pressure treated a mean of 17 hr after symptom onset. Forty-eight hour infusion of nitroprusside begun less than 9 hr after symptom onset resulted in a significantly higher short-term mortality as compared with placebo (24% vs 13%, respectively). In contrast, late treatment, initiated 9 hr or more after symptom onset, resulted in improved mortality (14% vs 22%). In another randomized clinical trial that compared 24 hr infusion of nitroprusside with placebo, Durrer et al. found a reduction in short-term mortality (3% vs 11%) in 328 patients treated a mean of 5 hr after symptom onset. These authors also demonstrated a reduction in peak MB CK isoenzyme blood levels, but only in patients with anterior infarctions. The population of patients entered into Durrer’s study were not restricted to those transmural infarctions or with elevated left ventricular filling pressures. The positive results of the Durrer study, however, must be interpreted in light of their failure to exclude patients with elevated blood pressure at the time of admission. The higher-than-expected incidence of free wall, septal, or papillary muscle rupture among placebo-treated patients might be at least in part a complication of untreated hypertension. The deleterious results of early nitroprusside therapy in the study of Cohn et al. might be a result of the “coronary steal” predicted in the above-mentioned animal preparation and clinical studies.

Early treatment with TNG appeared to improve perfusion and to reverse segmental wall motion abnormalities more often than could be accounted for by “spontaneous” or purely time-related changes. TNG might have acted to augment a tendency toward spontaneous improvement in patients with more highly developed intercoronary collateral channels. The finding that scintigraphic responders tended to have more frequent and longer histories of angina pectoris would fit with this hypothesis.

Further evidence for reversal of regional ischemia in noninfarcted myocardium was the improvement of segmental wall motion and overall ejection fraction noted with early TNG treatment. Improvement in segmental wall motion had previously been demonstrated by short-term administration of TNG to patients with myocardial infarction by Ramanathan et al. However, function of distant nonischemic left ventricular segments also improved, suggesting that the effect might have been caused by left ventricular unloading. In our study, since follow-up scintigrams had been obtained several days after termination of TNG treatment, effects on loading conditions could not explain the improvements in function noted.

The importance of early intervention has previously been demonstrated in both animal and clinical studies. In the animal preparation 3 to 6 hr after acute coronary occlusion seems to be the “cut-off” for reversibility. In contrast, clinical studies have suggested that this cut-off may be much later. Reasons for the longer time to the onset of irreversibility in man might include incomplete occlusion of the artery responsible for the infarct, the presence of collateral flow sufficient to maintain viability until therapy can be initiated, and/or differences in the nature of the infarction process in man compared with animals. In the present study the cut-off appeared to be approximately 14 hr, since all patients demonstrating significant improvement in their scintigraphic studies with TNG had been treated within 13.5 hr of the onset of their chest pain.

The interaction between the timing of intervention and the size of the admission perfusion defect or the level of left ventricular performance before treatment warrants further examination. It would appear that patients with extremely large risk regions were very unlikely to obtain significant benefit whether treated early or late. In contrast, patients with small-to-moderate sized risk regions showed a much higher incidence of significant benefit when treatment was initiated early. Limitations to the quantity of collateral flow relative to the number of grams of myocardium at risk may be responsible for this differential effect. This mechanism would be similar to that mentioned earlier to explain the higher percentage of responders among inferior transmural myocardial infarctions, which tend to have smaller risk regions, and the higher percentage of nonresponders among anterior transmural in-
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fractionts, which tend to have larger risk regions.

In summary, the results of our randomized prospective study failed to demonstrate benefits from intravenous TNG when patients treated early and late were studied together. However, when patients were subgrouped retrospectively according to early and late treatment, defined by treatment initiated less than 10 hr vs 10 hr or more after symptom onset, early treatment with intravenous TNG was associated with a reduction in the combined incidence of new congestive heart failure, infarct extension, or early cardiac death in patients with acute myocardial infarction. We were also able to demonstrate with early TNG treatment that there was a higher incidence of significant improvement in both myocardial perfusion and left ventricular function. Patients most likely to show significant scintigraphic improvement were those with small-to-moderate sized perfusion defects, better left ventricular function, and inferior rather than anterior transmural infarction.

However, the results of the present study must be interpreted cautiously, particularly in view of the retrospective data analysis required to delineate these beneficial effects. These results should be used to generate hypotheses to be tested in future clinical trials and to allow better design of future studies attempting to document a reduction in infarct size. Restricting study entry to patients admitted within 10 to 12 hr of onset of symptoms and to patients with significant perfusion abnormalities on their admission scintigraphic studies would seem particularly important. Intravenous TNG may also provide a valuable adjunct to more definitive interventions such as intracoronary streptokinase by maintaining viability of ischemic myocardium until more normal myocardial oxygen supply can be restored by thrombolysis. However, whether TNG should be given routinely to reduce ischemic injury in all patients with acute myocardial infarction awaits the performance of larger randomized clinical trials.

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References


23. Chiarello M, Gold HK, Leinbach RC, Davis MA, Maroko PR: Comparison between the effects of nitroprusside and nitroglycerin

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A randomized prospective trial of intravenous nitroglycerin in patients with acute myocardial infarction.

J T Flaherty, L C Becker, B H Bulkley, J L Weiss, G Gerstenblith, C H Kallman, K J Silverman, J Y Wei, B Pitt and M L Weisfeldt

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