Intravenous Hyaluronidase Therapy for Myocardial Infarction in Man: Double-blind Trial to Assess Infarct Size Limitation

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SUMMARY Patients with their first myocardial infarction not initially complicated by severe atrio-ventricular block or power failure were given a skin test and then randomized to receive either hyaluronidase or placebo in double-blind fashion. Hyaluronidase, 500 IU/kg i.v., was given every 6 hours for 42 hours. Of the 48 eligible patients, 26 received hyaluronidase and 22 received placebo. The mean CK serum entry was 3140 ± 2111 mIU/ml (mean ± SD) in hyaluronidase patients and 3574 ± 1476 mIU/ml in placebo patients (p < 0.21). The mean infarct size was 54.6 ± 35.8 CK gram-equivalents in the hyaluronidase patients and 64.0 ± 31.4 CK gram-equivalents in the placebo patients (p < 0.20). Among the 21 patients treated within 6 hours of the onset of infarction, the difference in infarct size was greater (p < 0.15). There was no significant difference in the incidence of power failure, ventricular arrhythmias, recurrence of ischemic pain, infarct extension or mortality. No benefit of hyaluronidase was demonstrated in this study, which was designed to detect a 50% reduction of infarct size. However, to detect a 20% reduction in infarct size would require a much larger study population.

THE CONCEPT that the extent of myocardial necrosis developing during the course of a myocardial infarction can be influenced by many factors independent of the underlying coronary pathology and collateral blood supply has been the focus of extensive investigation. The importance of infarct size is attested to by evidence of positive correlations between infarct size and the incidence of cardiogenic shock, frequency of ventricular arrhythmias, the severity of hemodynamic abnormalities, and prognosis in the hospital and after discharge. It is presumed that a zone of ischemic tissue surrounds an area of necrosis, and that the fate of this border zone depends on various influences on the infarcted ventricle but this concept is controversial.

Attempts to limit human infarct size are based on evidence from animal studies that certain interventions may limit the extent of myocardial necrosis after experimental coronary artery occlusion. Although many interventions appear to limit infarct size in animals, only a few have been documented in humans, among them propranolol, practolol, nitroglycerin, trimethaphan and hyaluronidase. Quantitation of infarct size in the living patient is difficult. The two principal techniques are ECG mapping and the serial CK technique. Both have
been refined extensively since their introduction, but many problems persist and significant disparities between estimated and pathologic infarct size can occur in individual subjects.

Hyaluronidase is an enzyme that depolymerizes the mucopolysaccharide hyaluronic acid of the intracellular ground substance.\textsuperscript{22, 23} Hyaluronidase was first given intravenously to humans with acute myocardial infarction in 1955 by de Oliveira et al.\textsuperscript{24} on the presumption that the myocardial edema of acute myocardial infarction might be reduced. Subsequently, evidence has accumulated that hyaluronidase may limit the extent of myocardial necrosis during acute myocardial infarction in experimental animals.\textsuperscript{25-31} The reported effects of hyaluronidase include reduction of myocardial edema,\textsuperscript{26, 29} increased diffusion of nutrients inward and harmful metabolites outward through depolymerized mucopolysaccharides of the intracellular ground substance,\textsuperscript{28} preservation of myocardial blood flow,\textsuperscript{27, 30, 31} and direct protective effects on the microvasculature.\textsuperscript{28}

The single study in humans providing evidence of infarct size limitation by hyaluronidase is that of Maroko et al.\textsuperscript{19} In this study, the beneficial effects of hyaluronidase were expressed in terms of the extent of Q-wave development and R-wave loss in hyaluronidase-treated and control patients. Although the extent of abnormality was significantly less in the hyaluronidase-treated patients, the difference could not be expressed quantitatively.

The serial CK technique,\textsuperscript{31} as well as allowing comparisons between groups of patients, permits a quantitative expression of infarct size. Accordingly, we undertook a trial of i.v. hyaluronidase administration in patients with acute myocardial infarction to demonstrate efficacy in terms of limitation of infarct size expressed quantitatively.

**Methods**

We previously found CK release of 2686 ± 1530 mIU/ml (mean ± sd) during acute myocardial infarction in 25 patients of the type we planned to evaluate in the present study. We predicted a major infarct size reduction of 50% in the treated group, based on animal studies.\textsuperscript{28} Using conventional values for α (0.05) and β (0.10), we determined that a sample size of 46 patients was required to permit the relevant conclusions.\textsuperscript{28} With an allowance for drop-outs and ineligible patients, we planned to enter 52 subjects.

Eligible patients were those entering the coronary care units of three university hospitals in Hamilton, Ontario, with a diagnosis of acute myocardial infarction based on a history of characteristic pain and ECG abnormality (at least 1 mm of ST-segment elevation in at least two adjacent ECG leads). The following additional criteria had to be met: onset of acute pain within 12 hours, no previous myocardial infarction, age ≤ 72 years, no muscle trauma or intramuscular injections, absence of second- or third-degree atrioventricular (AV) block, systolic blood pressure ≥ 95 mm Hg, absence of pulmonary edema (wet rales at least one-third of the way up the posterior chest and interstitial edema on the x-ray). Eligible patients were asked for informed consent.

Intramuscular injections were prohibited for the remainder of the study and cardioversion was cause for rejection. A heparin lock was placed in a large freeflowing vein and serial 2-ml blood samples were obtained at 2-hour intervals for 72–96 hours. The samples were stored at 4°C and centrifuged; the serum was stored at −20°C. CK analysis was carried out in duplicate as a batch for each patient, using the SKI bulk reagent modification of the Rosalki method\textsuperscript{34} at 37°C in a single research laboratory.

Hyaluronidase of bovine testicular origin (Wyeth Ltd.) was obtained in a concentration of 7500 IU/vial and diluted with 2 ml of distilled water at the time of administration. Every eligible patient had a scratch test in which one drop of saline and one drop of hyaluronidase were applied to adjacent scratches on the forearm. If wheal and flare were absent after 5 minutes, 0.01 ml of saline and 0.01 ml of hyaluronidase were injected intradermally at adjacent sites. Absence of a wheal and flare after 10 minutes determined final eligibility for the study.

Lyophilized hyaluronidase and lactose placebo were prepared in identical vials and stored in boxes of 40 vials each. The boxes were block-randomized in groups of four using a random number sequence, and the boxes were then numbered consecutively. The identifying code was filed in the hospital pharmacy and in the Department of Epidemiology and Biostatistics, but was not available to the investigators or clinical personnel except in the event of an emergency. The code was not broken until all data were analyzed. Each patient was assigned a number from 1–60 and received the corresponding medication. The initial dose of hyaluronidase was 500 IU/kg lean body weight, administered as an i.v. bolus over 1–2 minutes. The dose was repeated seven times at 6-hour intervals.

**Infarct Size**

Infarct size was measured by the serial CK technique\textsuperscript{31} as modified by Norris et al.\textsuperscript{35} Each measured CK value was corrected by subtraction of 100 mIU/ml (mean normal) and was plotted on a log scale y-axis. Time was on the x-axis with 0 time as the onset of the characteristic pain of myocardial infarction. The curve was visually inspected for the point where the steep linear downslope began. The first point selected on this portion of the curve was always at least the third successive decreasing value in relation to the preceding two values. Subsequent points were included only down to a measured value of 250 mIU/ml (elevation of 150 mIU/ml) to minimize the deviations from the exponential regression model that often became apparent at these low levels. An exception was made for very small myocardial infarctions (peak CK value less than 600 mIU/ml) where these low CK values were significant proportions of the total downslope points available for analysis. The points were fitted to an exponential regression to yield Kd (exponential CK disappearance rate) and R² (correlation coefficient) for each patient. If on the downslope
three successive values were equal or rising, an extension of the infarct size was considered to have occurred and that portion of the downslope was considered to have ended at the first point of the sequence for the purpose of calculation of Kd.

The equations of Roberts et al.21 were used to determine the integrated appearance function of CK. Each 2-hour serum level of CK was corrected for CK disappearance to yield a value for cumulative serum CK to that time according to the following equations:

\[ \text{CK}_t = \frac{\sum_{0}^{1} \left( \frac{E_{t-x} + E_t}{2} \right) \cdot \Delta t}{\text{CK}_x + \text{Kd}} \]

where \( \text{CK}_x \) = cumulative CK serum entry/ml serum, \( E_t \) = serum CK at time t, \( \text{Kd} \) = exponential disappearance rate determined for each patient, \( \frac{E_{t-x} + E_t}{2} \) = average CK value during the preceding time interval x (generally 120 minutes), and \( \Delta t \) = exact time interval (generally 120 minutes).

A curve of cumulative serum entry of CK to each point in time after the onset of infarction was then developed from the curve of serial serum CK values.

A plateau of cumulative CK occurred in conjunction with the onset of the linear downslope of the serum CK values. All cumulative CK values clustering about this plateau were averaged to obtain a mean value for CK serum entry. Myocardial CK release was expressed in terms of the cumulative entry of CK into 1 ml of plasma (\( \text{CK}_x \)), as suggested by Norris et al.,38 and also as infarct size49 according to the following equation:

\[ \text{IS} = \frac{\text{CK}_x \cdot \text{DV}}{P_{\text{CK}} (\text{CK}_N - \text{CK}_t)} \]

where IS = infarct size in CK-g equivalents, DV = distribution volume (0.044 body weight), \( P_{\text{CK}} \) = proportion of CK depleted from the heart which enters serum (0.15), \( \text{CK}_N \) = concentration of CK in normal myocardium (1700 IU/g), \( \text{CK}_t \) = concentration of CK in center of homogeneously infarcted myocardium (425 IU/g).

**Clinical Evaluation**

Patients were evaluated twice daily for the occurrence of power failure according to the following criteria: absent — jugular venous distention \( \leq 1 \) cm with the patient at 45°, normal pulmonary venous pattern on the chest x-ray; mild — jugular venous distention \( > 1 \) cm or pulmonary venous hypertension on the chest x-ray; moderate — S3 gallop or interstitial pulmonary edema on the chest x-ray; severe — airspace pulmonary edema or cardiogenic shock.

Patients underwent arrhythmia monitoring with bedside and central monitoring facilities for at least 96 hours after admission. Arrhythmia computer facilities were available in only one of the three units, and therefore arrhythmia monitoring was subjective and incomplete. Conventional lidocaine bolus and infusion regimens were used to treat ventricular ar-

Ventricular arrhythmias and conduction disorders were classified as follows: absent; mild — five or fewer unifocal premature ventricular complexes (PVCs)/min or first-degree AV block; moderate — more than five unifocal PVCs/min, complex PVCs (R-on-T, pairs or runs, multifocal), accelerated idioventricular rhythm or Mobitz I AV block; and severe — ventricular tachycardia, ventricular fibrillation, asystole, Mobitz II or third-degree AV block.

Patients were interviewed twice daily for the recurrence of chest pain by nursing and study personnel. A recurrence of ischemic pain after the first 24 hours of hospitalization was considered to have occurred if the patient experienced pain in the chest or characteristic referral areas, similar in character to that precipitating admission, and lasting at least 10 minutes. The pain of pericarditis was specifically looked for and ruled out.

Myocardial infarction extension was defined as recurrence of ischemic pain in the chest or characteristic referral areas, accompanied by a further increase of CK to at least 200 mIU/ml.

**Statistical Methods**

Separate comparisons of \( \text{CK}_x \), peak serum CK, and CK infarct size were made between the 26 hyaluronidase-treated patients and the 22 control patients using unpaired t tests. \( \text{CK}_x \), of the 12 hyaluronidase-treated patients and the nine control patients who began therapy less than 6 hours after the onset of infarction was also evaluated using an unpaired t test.

**Results**

Between July 1977 and April 1979, 55 patients were judged to have met the entry criteria and underwent skin testing. Three patients had a wheal and flare reaction at least 5 mm in diameter and were excluded. Fifty-two patients began i.v. therapy, but two of them had no ST-segment elevation and therapy was discontinued before all doses were given; no increase in CK or change in ECG occurred. One patients received all doses of medication, but was then found to have entered the trial 19.5 hours after the onset of pain. Therefore, 49 patients were appropriate entrants to the trial; however, one died within 7 hours after intiation of therapy. The autopsy revealed external cardiac rupture through an acute anterior wall infarction. Infarct size could not be calculated because only three CK samples had been obtained by the time of death. The three ineligible patients and the patient who died were excluded from analysis without knowledge of whether they had received hyaluronidase or placebo. Therefore, 48 patients constitute the study group. Table 1 is a summary of clinical data.

The mean CKs was 3140 ± 2111 mIU/ml (± sd) in the hyaluronidase-treated patients, and 3574 ± 1476 mIU/ml in the control patients (p < 0.21) (fig. 1). The mean peak serum CK level was 1749 ± 941 mIU/ml in the hyaluronidase-treated patients, and 1947 ± 771 mIU/ml in the control patients (p < 0.25). The mean infarct size was 54.6 ± 35.8 CK gram-equivalents (g-
Eq) in the hyaluronidase-treated patients and 64.0 ± 31.1 CK g-Eq in the control patients (p < 0.20).

Among the 21 patients who began therapy less than 6 hours after the onset of myocardial infarction, the mean CK, was 3151 ± 2181 mIU/ml in the hyaluronidase-treated group and 4055 ± 1509 mIU/ml in the placebo group (p < 0.15).

There was no significant difference in the incidence of moderate-to-severe power failure, moderate-to-severe ventricular arrhythmias and conduction disorders, the incidence of ischemic pain recurrence or the incidence of infarct extension between the hyaluronidase-treated and the placebo groups (table 1).

The patient ruled nonanalyzable because of early death from anterior myocardial rupture had been receiving placebo. Patient 14 in the hyaluronidase group died suddenly on day 13 with ventricular fibrillation; permission for autopsy was refused. The mean follow-up in the hyaluronidase patients was 12 months (range 3–26 months), with one additional death at 10 months. The mean follow-up in the placebo patients was 13 months (range 6–25 months), with one death at 2.5 months.

None of the 26 hyaluronidase-treated patients had an allergic reaction during their hospital stay. Sixteen of these patients had skin tests 3–6 months after treatment and none had a positive reaction.

**Discussion**

Administration of hyaluronidase at a mean of 6.9 hours after the onset of acute infarction did not result in reduction of infarct size compared with placebo-treated patients. The likelihood that a true difference as great as 50% in infarct size would have been missed is 0.006. The less sensitive clinical variables (moderate-to-severe power failure, moderate-to-severe ventricular arrhythmia, ischemic pain, myocardial infarct extension, death) did not differ significantly between the hyaluronidase-treated and placebo groups. The outcomes in this study require further examination in relation to the data from other studies of the limitation of myocardial infarct size by hyaluronidase.

Bovine testicular hyaluronidase (molecular weight 60,000) catalyzes the degradation of hyaluronic acid, an important constituent of the intracellular ground substance. Evidence of increased intracellular diffusional transport prompted the studies of de Oliveira et al., who reported that the ST-segment elevation produced by left anterior descending coronary artery ligation in six dogs was markedly reduced by the i.v. administration of 100,000 IU of hyaluronidase. There was no quantitation of infarct size nor control data. Maroko et al. found decreased ST-segment elevation and CK depletion in dogs given i.v. hyaluronidase before or shortly after left anterior descending coronary artery occlusion. They subsequently demonstrated decreasing efficacy with increasing time intervals from occlusion to hyaluronidase administration: no benefit occurred when the interval was 9 hours. They also found that hyaluronidase resulted in higher transmural, endocardial and epicardial blood flows, and higher endocardial/epicardial flow ratios than in control dogs. For a given flow reduction, CK loss was significantly less than in hyaluronidase-treated dogs.

Using light and electron microscopy, Kloner et al. found reduced myocardial cell and microvascular endothelial damage in rats given hyaluronidase after left main coronary artery occlusion. McClean et al. demonstrated a 50% reduction of total myocardial CK loss in rats given hyaluronidase 5 minutes and 24 hours after left main coronary artery ligation. Rotello et al. showed a less marked increase in coronary vascular resistance, less CK depletion and less lactate accumulation in isolated perfused rat hearts treated with hyaluronidase.

Maroko and co-workers casually allocated 111 patients to hyaluronidase or control therapy. A 35-lead precordial unipolar ECG was recorded on admission and 7 days later. The extent of change during this time was expressed in terms of an arbitrary Q-wave score and a quantitative assessment of reduction of R-wave voltages. In the 91 patients suitable for analysis, the changes were significantly less in hyaluronidase-treated patients than in controls.

The differences between the study of Maroko et al. and the present study require emphasis. Their study was not double-blind or placebo-controlled, although the ECG readers did not have knowledge of the therapy. Patients who had a persistent intraventricular conduction defect or died between recording of the first and second electrode maps were excluded from analysis. Because inferior or subendocardial infarctions cannot be assessed by precordial electrode map-
### Table 1. Summary of Clinical Data

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<th>CK&lt;sub&gt;i&lt;/sub&gt; (mU/ml)</th>
<th>Peak CK (mU/ml)</th>
<th>IS (CK g-Eq)</th>
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**Abbreviations:** CK<sub>i</sub> = cumulative CK serum entry; IS = infarct size; mod = moderate; I = inferior; A = anterior.
ping, only patients with transmural anterior of anterolateral infarction entered the study. The difference in ECG evolution between the hyaluronidase-treated and the control patients cannot be quantitatively related to the extent of myocardial necrosis.

All patients entered the study of Maroko et al.\(^\text{19}\) within 8 hours (mean 4.6 hours) after the onset of acute myocardial infarction. In the present study, the mean time from the onset of myocardial infarction to hyaluronidase therapy was 6.9 hours, similar to that in several other studies of infarct size, but the upper limit of 12 hours may have been excessive. Peter et al.\(^\text{18}\) demonstrated decreased infarct size in propranolol patients only when therapy was started within 4 hours after the onset of myocardial infarction. The likely importance of early therapy is suggested by the more marked difference of CK release and the approach to statistical significance for the difference between hyaluronidase-treated and control patients entering the present study within 6 hours after pain began.

The serial CK method of estimating infarct size is problematic. The constants that relate serum appearance of CK to myocardial release were developed in dogs, and most have been assumed to be similar in humans. However, rather wide standard deviations exist for the constants in dogs;\(^\text{36}\) the ratio of CK serum entry to myocardial CK loss varies inversely with infarct size;\(^\text{37}\) there may be ongoing CK release beyond the plateau of the cumulative release curve;\(^\text{38}\) and there is evidence of biexponential disappearance and two-compartment distribution of CK.\(^\text{39}\) The divergences from the original theoretical model may reduce the likelihood of sensitive comparisons of infarct size, and may have obscured a real, though modest, difference in infarct size between hyaluronidase-treated and control patients in the present study.

The possibility that a given intervention might systematically alter certain of the constants relating the peripheral appearance of CK to the myocardial loss must also be considered. Because hyaluronidase increases intracellular diffusional transport, the rate of CK serum entry to myocardial CK loss might be higher in patients receiving hyaluronidase, which would result in spuriously large calculated infarct sizes. If this were so, one would predict that peak and plateau CK levels in the serum would be achieved more quickly in hyaluronidase-treated than in control patients. In the present series, there was no significant difference between hyaluronidase- and placebo-treated patients in mean time to peak CK (21.1 vs 21.8 hours) or in mean time to plateau CK (31.2 vs 34.3 hours). We previously observed a linear relationship between infarct size and plateau CK.\(^\text{40}\) This relationship was calculated for the hyaluronidase- and placebo-treated patients and the slopes were not significantly different. The present data do not suggest more rapid and complete CK release as a result of hyaluronidase therapy. A firm conclusion about the possible effect of hyaluronidase upon the rate of CK serum entry to myocardial CK loss awaits evaluation in animals.

Our initial choice of a target of 50% reduction of infarct size was based upon consideration of what might be a clinically significant difference in addition to a statistically significant difference. Whereas major reduction of infarct size might lessen the risk of power failure\(^\text{50}\) and acute arrhythmias,\(^\text{5}\) we considered the possibility that a minor reduction of infarct size might not reduce the risk of these complications and might even be harmful if ischemic areas were salvaged and the risk of subsequent arrhythmia were increased.\(^\text{11}\) Infarct size reduction of about 50% has been observed in rats treated with hyaluronidase.\(^\text{28}\) The extent of myocardial salvage during the course of myocardial infarction in humans is likely to be much less than 50%.

The only quantitative data in humans come from studies using the serial CK technique. Peter et al.\(^\text{18}\) found a 25% reduction of CK, in patients treated with propranolol within 4 hours after infarction. Shell and Sobel\(^\text{17}\) found a measured infarct size 24% less than predicted in hypertensive patients treated with trimethaphan. A more realistic estimate of the infarct size limitation to be anticipated as a result of interventions in humans might therefore be 20%. In the
present study, there is a suggestion of smaller infarct size of this degree in the hyaluronidase-treated patients, although the difference is not statistically significant. A true difference of infarct size as great as 50% would not have been missed by the present study ($p = 0.006$). However, if a true difference as small as 20% exists, the probability that it could have been missed in a study of this size is 0.30. The necessary sample size to detect a 20% reduction of infarct size with conventional levels of $\alpha$ and $\beta$ errors would be 264 patients\(^8\) (using the mean CK, of 3574 ± 1476 mIU/ml in the placebo patients of the present study). The clinical significance of a 20% reduction in infarct size is not known.

Acknowledgment

The authors warmly acknowledge the cooperation and participation of the residents and the head nurses and their staffs in the coronary care units of the Hamilton General Hospital, St. Joseph's Hospital and McMaster University Medical Centre. We are grateful to Dr. A. L. Johnson for assistance with the study design and maintenance of the medication codes, to Dr. W. R. Porter of Wyeth Ltd. for providing hyaluronidase and placebo, and to Anne Glover for typing the manuscript.

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Intravenous Isosorbide Dinitrate in Patients with Refractory Pump Failure and Acute Myocardial Infarction

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SUMMARY We studied the hemodynamic effects of isosorbide dinitrate administered by continuous i.v. infusion to 22 patients with chronic refractory pump failure and 18 with pump failure due to acute myocardial infarction. In patients with severe pump failure, i.v. ISDN markedly decreased pulmonary capillary wedge pressure (p < 0.001), moderately increased cardiac output (p < 0.01), and decreased systemic vascular resistance (SVR) (p < 0.001). There were no deleterious effects on arterial pressure and heart rate. The effects obtained in acute and chronic left ventricular failure were similar. Patients with initial SVR levels lower than 1500 dyn-sec-cm⁻¹ did not significantly increase their cardiac output (p < 0.005). Cardiac output increased more than 25% only in patients with initial high SVR levels (> 2000 dyn-sec-cm⁻¹). Positive correlations were found between high SVR and elevated plasma catecholamines (r = 0.53, p < 0.05) and between the initial SVR and initial heart rate (r = 0.70, p < 0.01). The i.v. administration of isosorbide dinitrate appears to be an efficient therapy, particularly in selected patients with ischemic pump failure.

NITRATE PREPARATIONS and other vasodilators have been used to treat acute and chronic pump failure,¹⁻⁴ but few data have been reported on the effects of i.v. isosorbide dinitrate (ISDN).⁵⁻⁸ Although nitrates are predominantly venodilators,⁶⁻¹¹ decreases in systemic vascular resistance and increases in cardiac output have been reported.⁷⁻¹²⁻¹⁶ Nitrates are helpful in many patients with coronary heart disease, although a sudden, sharp decrease in the diastolic arterial pressure may enhance myocardial ischemia, particularly in the acute cases.¹⁷⁻¹⁹

The present study was performed to evaluate the hemodynamic effects of i.v. ISDN in 40 patients with acute and chronic pump failure. Serial determinations of plasma catecholamines were also made to assess their relation to hemodynamic status and response to therapy.

Patients and Methods
Forty patients with pump failure received i.v. ISDN (Isoket) in a dose range of 2–8 mg/hour, based on the hemodynamic and clinical response. We studied 22 consecutive patients with chronic refractory pump failure (group A) and 18 patients with acute myocardial infarction and pump failure (group B) (table 1). Refractory pump failure (group A) was manifest by persistent left-heart failure despite intensive conventional therapy. All patients in this category had dyspnea and hypoxia, wet rales and radiographic evidence of pulmonary venous congestion and cardiomegaly. Medical therapy in these patients included large i.v. doses of potent diuretics, digitalis, and bed rest in hospital. Other therapy included correction of electrolyte imbalance and treatment of arrhythmias.

The patients with chronic ischemic failure (group A, subgroup 1) all had recurrent myocardial infarction. These patients were not considered for surgery either because of their poor left ventricular function or because their coronary anatomy did not appear amenable to bypass grafting. Poor left ventricular function was demonstrated noninvasively or by complete cardiac catheterization and angiography. The left ventricular ejection fraction was less than 25% with diffuse hypokinesis and areas of akinesis or dyskinesis on nuclear ventriculography and, when measured, left ventricular end-diastolic pressure was greater than 20 mm Hg. Five of the coronary patients had significant mitral regurgitation and systolic regurgitant murmurs. Mitral regurgitation was diagnosed in three patients as 3+ on contrast ventriculography and was docu-
Intravenous hyaluronidase therapy for myocardial infarction in man: double-blind trial to assess infarct size limitation.
J A Cairns, D A Holder, P Tanser and E Missirlis

Circulation. 1982;65:764-771
doi: 10.1161/01.CIR.65.4.764

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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