The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction

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ABSTRACT We studied the hypotensive effect of a rapid intravenous infusion of high-dose streptokinase in 98 patients with an acute myocardial infarction. The systolic blood pressure fell from 132 ± 20 (range 90 to 174) to 97 ± 21 mm Hg (range 58 to 152) at 15 ± 8 min (range 4 to 40) after the commencement of the streptokinase infusion (p < .001). A fall in diastolic blood pressure from 80 ± 16 (range 51 to 105) to 61 ± 15 mm Hg (range 32 to 92) accompanied the fall in systolic pressure (p < .001). The fall in blood pressure was associated with an increase in heart rate (73 ± 14 to 78 ± 17 beats/min, p < .001), preceded the appearance of clinical signs of reperfusion by 37 ± 38 min and was similar in magnitude and timing in patients with anterior and inferior infarction. There were direct relationships between the rate of infusion of streptokinase and both the magnitude (r = .49, p < .001) and the rate of fall of systolic blood pressure (r = .67, p < .001) as well as both the magnitude and rate of fall of diastolic blood pressure. In most patients, the fall in blood pressure was transient (9 ± 6 min, range = 2 to 30) and easily managed by slowing or stopping the infusion, placing the patient in the Trendelenburg position, or by administering an infusion of low-dose norepinephrine or dopamine. However, in four patients with severe left ventricular dysfunction, severe hypotension persisted for more than 60 min. Our data indicate that in patients with either anterior or inferior myocardial infarction, a rapid infusion of high-dose intravenous streptokinase may frequently cause transient and sometimes severe hypotension, the magnitude of which is directly related to the rate of infusion of streptokinase.


SHORT-TERM INTRAVENOUS INFUSION of high-dose streptokinase is an effective method of coronary thrombolysis and coronary artery reperfusion during an acute myocardial infarction.1–9 In most recent studies, intravenous streptokinase has been administered rapidly so as to achieve a high concentration of streptokinase in proximity to the coronary thrombus and thereby accelerate thrombolysis.10–13 One limitation of the administration of a rapid intravenous infusion of streptokinase is that it can cause a significant fall in systemic blood pressure.4, 5, 9 This study investigates the frequency and severity of the hypotensive effect of intravenous infusion of streptokinase in patients with acute myocardial infarction and its relationship to the rate of the infusion.

Methods

Patient population. The patient population consisted of 101 consecutive patients who were entered into a prospective study of intravenous streptokinase in acute myocardial infarction and in whom the systemic blood pressure was continuously monitored during the infusion of streptokinase. The study inclusion criteria were (1) chest pain of 3 hr or less duration, (2) ST segment elevation indicative of transmural ischemia, (3) unresponsiveness of both the chest pain and the electrocardiographic changes to sublingual nitroglycerin, (4) no contraindication to thrombolytic or anticoagulant therapy, and (5) consent of both the patient and his or her physician. The diagnosis of acute myocardial infarction was subsequently confirmed by a rise in serum levels of the creatine kinase MB isoenzyme in all patients.

Three patients were excluded from analysis. Two patients were receiving intravenous nitrates to control hypertension and their baseline blood pressures had already been reduced by more than 30 mm Hg before streptokinase and in one patient the fall in blood pressure coincided with the onset of ventricular tachycardia. The remaining 98 patients (76 men and 22 women, 63 ± 11 years old, range 40 to 86) constitute the study population.

Study protocol. An intravenous infusion of 750,000 U of streptokinase (Hoechst-Roussel) in 45 to 75 ml normal saline was administered into a peripheral vein over 30 ± 16 min (range 7 to 78). The rate of infusion of streptokinase (U streptokinase/kg body weight/min) was determined in 92 of the 98 patients by dividing the total dose of streptokinase by the weight.
of the patient and by the time interval over which the infusion was administered. Eighty-eight patients were given 100 mg iv hydrocortisone before streptokinase.

The brachial arterial blood pressure and the heart rate were monitored at 1 min intervals for at least 5 min before and during the entire streptokinase infusion with a Dinamap automatic oscillometric cuff blood pressure recorder. The blood pressure varied by less than 10% during the interval preceding the commencement of the streptokinase infusion and the lowest value recorded during this interval was accepted as the baseline blood pressure. The fall in blood pressure was defined as the difference between the baseline blood pressure and the minimum blood pressure recorded during the infusion of streptokinase. The rate of fall of blood pressure was defined as the fall in blood pressure (mm Hg) divided by the time interval from the commencement of streptokinase to the time of the minimum value (min). These variables were calculated separately for systolic and diastolic blood pressures.

Statistical methods. Continuous variables are described by their mean and standard deviation. The unpaired Student t test was used for comparisons between two groups and the paired Student t test was used to assess the significance of serial changes in blood pressure and heart rate. Proportional differences between groups were compared with the use of Fisher’s exact test. Correlations between the rate of infusion of intravenous streptokinase and the magnitude and rate of fall in systolic and diastolic blood pressures were calculated by the unweighted linear least squares method. All statistical analyses were performed with BMSP biostatistical programs and a p value of <.05 was considered to represent statistical significance.

Results

Fall in blood pressure. The mean systolic blood pressure before streptokinase for the entire study population was 132 ± 20 mm Hg (range 90 to 174). During the intravenous infusion of streptokinase, there was a mean fall of 35 ± 19 mm Hg (range 0 to 82) to a minimum value of 97 ± 21 mm Hg (range 58 to 152), which was recorded at 15 ± 8 min (range 4 to 40) after the commencement of the infusion (p < .001 for fall in systolic blood pressure). In most patients the duration of the fall was brief, lasting 9 ± 6 min (range 2 to 30). The mean diastolic blood pressure before streptokinase was 80 ± 16 mm Hg (range 51 to 105). A fall of 20 ± 14 mm Hg in diastolic pressure to a minimum value of 61 ± 15 mm Hg (range 32 to 92) accompanied the fall in systolic pressure (p < .001 for fall in diastolic blood pressure).

In 85 of the 98 patients (87%), there was a fall in systolic blood pressure of more than 10% of the baseline value (BP fall). In the remaining 13 patients, there was a lesser fall or no fall in blood pressure (no BP fall). In 18 patients the systolic blood pressure fell to a minimum value of 90 to 99 mm Hg, in 17 patients it fell to 80 to 89 mm Hg, in 10 patients it fell to 70 to 79 mm Hg, and in 10 patients the minimum systolic blood pressure was less than 70 mm Hg. Therefore, a fall to a systolic blood pressure of 90 mm Hg or less occurred in 37 of the 98 patients (38%).

Influence of rate of streptokinase infusion on blood pressure. Figure 1 illustrates that both (1) the magnitude and (2) the rate of fall in systolic blood pressure were each directly related to the rate of infusion of streptokinase in patients with either anterior or inferior infarction. There were also similar direct relationships between the rate of infusion of streptokinase and the magnitude of the fall of diastolic blood pressure (r = .38, p < .001) and the rate of fall of diastolic blood pressure (r = .53, p < .001) respectively.

Figure 1, A shows that a BP fall (points above broken line) was frequent at all rates of streptokinase infusion, but 12 of the 13 patients with no BP fall received an infusion of streptokinase at a rate slower
more than 500 U/kg/min (p < .001 for rates <500 vs ≥500 U/kg/min). The exception was a patient in whom streptokinase was completely inactivated by a high titer of neutralizing antibodies.15

**Relationship between heart rate and fall in blood pressure.** The mean heart rate increased from 73 ± 14 beats/min before streptokinase to 78 ± 17 beats/min at the time of maximum fall in blood pressure (p < .001). In only eight patients (five with inferior and three with anterior infarction) did the heart rate fall by 10 beats/min or more (or ≥10%) from the baseline value. The increase in heart rate was similar in patients with and without a significant fall in blood pressure. Two patients with inferior infarction who had a fall in systolic blood pressure that was initially associated with an increase in heart rate developed transient third-degree atrioventricular block when the systolic blood pressure fell below 85 mm Hg. In one of these two patients, the onset of atrioventricular block occurred 22 min before the appearance of any of the clinical signs of reperfusion and in the other patient, reperfusion was not achieved.

**Relationship between site of infarction and fall in blood pressure (table 1).** There were 45 patients with anterior infarction and 53 patients with inferior infarction. There were no significant differences in blood pressure before streptokinase, the magnitude of the fall in blood pressure, or the rate of fall of blood pressure between patients with anterior or inferior infarction. Both groups of patients also had a similar increase in mean heart rate during the streptokinase infusion.

**Relationship between time of reperfusion and time of fall in blood pressure.** The onset of the fall in blood pressure always preceded the appearance of any of the clinical signs of reperfusion. The time of maximum blood pressure fall preceded the appearance of clinical signs of reperfusion in 74 of the 78 patients in whom the timing of both events could be determined (mean 37 ± 38 min, range 5 to 216). In the remaining four patients, all with anterior infarction, the minimum blood pressure was recorded up to 10 min after the appearance of clinical signs of reperfusion.

**Clinical characteristics of patients with a fall in blood pressure.** The most important determinant of the fall in blood pressure was the rate of infusion of streptokinase. Therefore, the clinical characteristics of the BP fall group and the no BP fall group were compared after controlling for infusion rate by restricting the analysis to the 33 patients in the former group and the 12 patients in the latter group receiving infusions at a rate of 400 or less U/kg/min (the fastest effective rate in the no BP fall group). Patients in the BP fall group had evidence of more extensive myocardial damage, as suggested by a higher incidence of prior myocardial infarction (30% vs 8%) and a higher peak serum level of creatine kinase MB (161 ± 82 vs 121 ± 98 IU/liter). There was no difference in (1) age (62 ± 12 vs 57 ± 11 years), (2) sex distribution (85% vs 92% males), (3) location of infarction (58% vs 50% anterior), or (4) baseline blood pressure (130 ± 20 vs 124 ± 16 mm Hg). There was also no difference between these two groups with respect to the frequency of par- tency of the artery of infarction at delayed angiography or the incidence of hemorrhagic complications.

**Recovery of blood pressure.** The fall in blood pressure was generally, but not always, transient and easily managed. In 81 of the 85 patients with a fall in systolic blood pressure, recovery to baseline values occurred within 9 ± 6 min (range = 2 to 30). In 28 of these 81 patients (33%) with a mean fall in systolic pressure of 31 ± 12 mm Hg to a minimum blood pressure of 111 ± 19 mm Hg, recovery of blood pressure occurred spontaneously, without any intervention, within 7 ± 4 min (range = 2 to 21). In 35 patients (41%) with a mean fall of 38 ± 16 mm Hg to a minimum systolic pressure of 91 ± 15 mm Hg, the blood pressure recovered in 9 ± 6 min (range = 2 to 30) after the infusion was slowed or stopped, with or without placing the patient in the Trendelenburg position. In the remaining 18 patients, with a mean fall of 51 ± 17 mm Hg to a minimum systolic pressure of 75 ± 11 mm Hg, an infusion of low-dose norepinephrine or dopamine was administered in addition to the other measures and the blood pressure recovered within 11 ± 7 min (range = 2 to 29).

In four patients with severe left ventricular failure
before administration of streptokinase, systolic hypotension of less than 85 mm Hg persisted for more than 60 min despite intravenous infusion of catecholamines.

Discussion

In this study, a transient fall in blood pressure was frequent during intravenous infusion of high-dose streptokinase in patients with acute myocardial infarction and both the magnitude and the rate of the fall in blood pressure were directly related to the rate of infusion of intravenous streptokinase. This hypotensive effect was similar in patients with anterior and inferior infarction and not infrequently resulted in significant hypotension. The fall in blood pressure was usually associated with an increase in heart rate and was not temporally related to clinical signs of reperfusion, suggesting that it was distinct from the Bezold-Jarisch reflex, which has been reported to occur at the time of reperfusion in some patients with inferior infarction.16, 17

Although the fall in blood pressure was generally of short duration and easily managed by slowing or interrupting the infusion of streptokinase, in some patients it was severe and prolonged and in about 20% of patients administration of vasopressors was required. Our data suggest that the risk of hypotension was related to the extent of damage to the myocardium; the most severe falls in blood pressure occurred in hemodynamically compromised patients. In such patients, the hemodynamic combination of hypotension and an increase in heart rate can further reduce perfusion to the acutely ischemic myocardium18-20 and thereby accelerate the rate of progression of myocardial necrosis and reduce the potential for myocardial salvage by reperfusion.21 Hypotension may also lead to hypoperfusion in the nonischemic myocardium, especially if it is supplied by stenotic coronary arteries or via collaterals.22

Because of the frequent prompt recovery of blood pressure after placement of the patients in the Trendelenburg position, patients are now treated in the supine position when possible, with one pillow under the head and another under the legs. Our data suggest that severe falls in blood pressure may be avoided by limiting the rate of infusion of intravenous streptokinase. Therefore, in hemodynamically compromised patients and in those with a baseline systolic blood pressure of less than 100 mm Hg, we now commence the infusion at a slow rate of about 200 to 250 U/kg/min or less and have an infusion of norepinephrine available “on standby.” Our findings underscore the importance of continuous monitoring of blood pressure during intravenous infusion of high-dose streptokinase and have important implications for the use of streptokinase in an out-of-hospital setting.

Despite the frequency of its occurrence, the pathophysiology of this hypotensive effect is not known. The symptomatic and visible cutaneous flushing that frequently heralds or accompanies the fall in blood pressure and the associated increase in heart rate are suggestive of a vasomotor effect, but this has not yet been documented. Invasive hemodynamic monitoring that would delay the initiation of treatment is not used in our clinical studies and in our experimental studies in anesthetized dogs, sheep, and monkeys, blood pressure has not been observed to fall during an intravenous bolus injection of high-dose streptokinase. In contrast, a marked fall in blood pressure occurred in dogs given rapid intravenous infusions of streptokinase-activated human plasminogen,23 streptokinase-plasmin activator complex,24 and trypsin,25 an enzyme with a broad spectrum of activity similar to plasmin. This hypotensive effect of the streptokinase-plasminogen complex has been attributed to a rapid increase in serum plasmin concentration24 and differs from the effect of streptokinase alone, probably because streptokinase is a weak activator of canine circulating plasminogen.26 In the study by Green et al.,24 the hypotensive effect in conscious dogs (mean fall of 56 mm Hg) had a time course and recovery similar to our clinical observations and was related to plasmin activation of kallikrein and production of bradykinin. Their conclusions regarding the role of bradykinin appear to be consistent with the clinical features of marked flushing and the known ability of plasmin to activate Hageman factor and generate bradykinin.27 Unfortunately, the systemic vascular resistance was not measured during that study.

In addition to the effect of bradykinin, there are several other mechanisms that could reduce systemic vascular resistance during the infusion of streptokinase. Vasodilation may be due to plasmin activation of the complement pathway28 or to endothelial prostacyclin secretion, which in experimental studies is stimulated by short chain, human fibrinogen degradation products.29 A direct vasodilative effect of streptokinase is reminiscent of vasoactive properties of many peptides. However, our observations that the effect is short-lived and that a closely timed second infusion of streptokinase may either have no effect or an attenuated effect on blood pressure and the observation in European studies that hypotensive reactions also occur after high-dose intravenous infusions of both urokinase30 and tissue-type plasminogen activator31 suggest

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that the fall in blood pressure is not due to a specific effect of streptokinase.

Allergy has also been postulated as the cause of the fall in blood pressure. Although low titers of antistreptokinase antibodies are almost ubiquitous in man, allergy seems unlikely because allergic reactions to streptokinase are very rare and do not accompany the fall in blood pressure. On the contrary, in our experience, in patients with high titers of neutralizing anti-streptokinase antibodies the fibrinolytic system is not activated and there is no fall in blood pressure during intravenous infusion of streptokinase. Furthermore, allergy could not explain the fall in blood pressure observed with intravenous urokinase or tissue-type plasminogen activator.

Since a depletion of serum fibrinogen lowers serum viscosity and therefore systemic vascular resistance, theoretically this could cause a fall in blood pressure. This mechanism is unlikely, however, because in our experience, hypotension can occur early in the development of plasminemia (a lytic state inducing elevated levels of fibrinogen degradation products) before serum fibrinogen has significantly decreased.

Finally, it was not possible to implicate the administration of opiates, nitroglycerin, antiarrhythmic agents, or any other medication as the cause for the fall in blood pressure.

**Clinical implications.** In patients with either anterior or inferior myocardial infarction, rapid infusion of high-dose intravenous streptokinase frequently causes a transient and sometimes severe fall in blood pressure, the magnitude of which is directly related to the rate of infusion of streptokinase. To avoid severe hypotensive reactions, the rate of infusion of streptokinase should probably not exceed about 500 U/kg/min in normotensive patients. In hemodynamically unstable patients with reduced myocardial reserve who are more likely to develop significant and sometimes resistant hypotension and in patients with low initial blood pressure, the rate of infusion should be much slower (200 to 250 U/kg/min or less) and a vasopressor infusion should be available “on standby.”

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