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Impairment of Fibrinolysis by Streptokinase, Urokinase and Recombinant Tissue-Type Plasminogen Activator in the Presence of Radiographic Contrast Agents

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Objectives. **The purpose of this study was to determine whether an adverse interaction exists between radiographic contrast agents and thrombolytic drugs.**

Background. **Coronary thrombosis may occur in the setting of unstable angina and after coronary angioplasty. However, the use of thrombolytic drugs in the setting of unstable angina has not been beneficial and, in one large trial of angioplasty in patients with unstable angina, was associated with an increased incidence of ischemic complications and abrupt closure. The reasons for these results are not clear. Coronary arteriography was performed in many of these trials, and it is known that fibrin structure and assembly are altered by radiographic contrast agents.**

Methods. **Blood samples were obtained from patients before (n = 25) and after (n = 20) angiography using iohexol. Blood samples obtained before angiography were tested for response to streptokinase (10 and 100 IU/ml), urokinase (100, 200 and 500 IU/ml) and recombinant tissue-type plasminogen activator (rt-PA) (100 and 1,000 IU/ml) and the results measured. Iohexol, diatrizoate or ioxaglate (4% by volume) was added to separate aliquots of the baseline sample, and the test was repeated. Blood samples obtained after angiography were tested in a similar manner.**

Results. **The onset of lysis at baseline by rt-PA at 1,000 IU/ml occurred at 72 ± 8.2 s (mean ± SD) and was markedly delayed in the presence of diatrizoate (527 ± 181.7 s, $p < 0.001$) or iohexol (460 ± 197.0 s, $p < 0.001$) but not ioxaglate. At 100 IU/ml, there was no lysis detected with rt-PA after the addition of any contrast agent. The addition of a contrast agent caused similar delays in the onset of lysis by urokinase and streptokinase; similar to rt-PA, the effect was smaller at higher concentrations of drug. In vivo blood samples obtained from the patient after angiography showed delays in the onset of lysis by rt-PA and urokinase but not streptokinase.**

Conclusions. **These data demonstrate that radiographic contrast agents impede fibrinolysis. This previously undescribed interaction was demonstrated using an in vitro test system, but these findings may have clinical relevance when thrombolytic drugs are used at the time of angiography.**

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Thrombotic complications during cardiac catheterization are uncommon but serious events (1,2). During coronary angioplasty, the potential for coronary thrombosis is higher and contributes to abrupt closure. Although several reports have raised concerns about thrombosis specifically related to nonionic contrast agents, large studies have not confirmed this observation (3–6). When thrombotic complications occur during cardiac catheterization, it has been noted incidentally that thrombolytic drugs are not particularly useful for dissolving clots embolized into the coronary circulation (5). One of several possible explanations for failure of clot lysis is that contrast agents alter the assembly and structure of fibrin, thereby making clots more resistant to the action of thrombolytic drugs. Support for this explanation comes from in vitro data showing that both diatrizoate and iopamidol cause the formation of long, thin fibrin fibrils having a lower mass/length ratio than normal (7). In certain disease states, fibrin assembled from thin fibrils is more resistant to fibrinolysis (8). The occurrence of an alteration in fibrin structure by diatrizoate or iohexol was confirmed in vivo using blood samples obtained during the course of cardiac catheterization (9). Thus, contrast agents as such do not impair the action of the drugs; rather, they cause an alteration in fibrin that renders it inherently more resistant to fibrinolysis.

The alteration in fibrin caused by contrast agents could have importance when thrombolytic drugs are used during coronary interventions or when serial coronary angiography is used to

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evaluate thrombolytic therapy. Several trials using serial angiography to evaluate the results of thrombolytic therapy in unstable angina have not shown a beneficial effect, and in one large randomized trial, it was concluded that the prophylactic use of urokinase before coronary angioplasty in the setting of unstable angina was detrimental (10–12). In the Thrombolysis and Angioplasty in Unstable Angina (TAUSA) trial (12), coronary filling defects were not decreased, and the occurrence of abrupt closure, ischemia and bypass surgery ranged from 2.5 to 4 times higher in patients receiving urokinase. Because coronary angiography was used before drug therapy, one explanation for these findings might be that the radiographic contrast altered the structure of fibrin, which, in turn, adversely affected the action of urokinase. Although there is both in vivo and in vitro evidence for an alteration in fibrin structure by contrast media, to our knowledge there has not been a direct demonstration of an impairment in the action of thrombolytic drugs by contrast agents. Recently, a new method to evaluate the action of thrombolytic drugs has been developed and tested clinically (13,14). The purpose of the present study was to use this new method to test the hypothesis that radiographic contrast agents cause an impairment in the action of thrombolytic drugs.

Methods

Patients. The study group included 25 patients randomly selected from those referred for diagnostic cardiac catheterization. Patients fasted for at least 8 h before collection of the baseline blood sample but continued to receive their regular medications. Also, most patients received diazepam (5 to 10 mg) and diphenhydramine (25 to 50 mg) orally 30 to 60 min before the procedure. Cardiac catheterization and angiography were performed from the femoral approach using standard techniques. The study was approved by the Human Studies Committee of the institution, and all subjects gave written informed consent for the procedure.

Sample collection and preparation. After vascular access was obtained, a baseline 10-ml blood sample was collected from the femoral vein or artery before heparin or radiographic contrast administration. The blood was placed in a collection tube (Vacutainer no. 367705, Becton Dickinson), where 4.5 ml of blood mixed with 0.5 ml of buffered sodium citrate. Samples were kept at room temperature until testing, which was completed within 6 h. This sample was tested to establish the baseline responses to the fibrinolytic drugs.

Radiographic contrast medium was then added to an aliquot of the baseline blood sample, and it was tested again. The amount of radiographic contrast medium within the vasculature during and after angiography is constantly changing as contrast agent is injected and simultaneously excreted. When contrast agent is injected into a coronary artery, the concentration is very high within the artery for ~5 to 10 s. However, this rapidly decreases after each injection to some ambient level that slowly increases during the procedure and then decreases. We modeled this low level of circulating contrast medium by mixing 40 μl of contrast agent with 960 μl of blood to yield a mixture that was 4% contrast medium by volume. This was based on an estimated contrast medium administration of 200 ml/procedure and a blood volume of 5 liters. Separate evaluations were performed using the ionic contrast agent diatrizoate (Hypaque-76, Sanofi-Winthrop), the nonionic agent iohexol (Omnipaque, Sanofi-Winthrop) and ioxaglate (Hexabrix, Mallinckrodt), an ionic, low osmolar contrast agent. To confirm the effects of contrast, a second blood sample was obtained at the conclusion of the procedure in 20 of the patients. All had received iohexol (155 ± 36 ml) for their angiography. This in vivo sample was tested without added contrast medium using identical procedures.

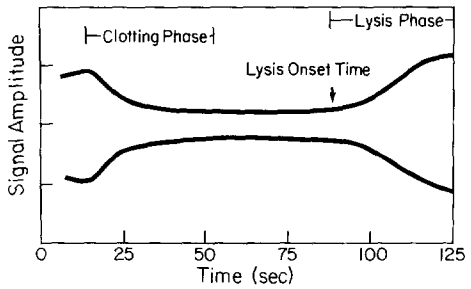

Figure 1. Signal amplitude of the paramagnetic particle oscillation plotted against time to determine lysis onset time. Signal amplitude reflects the motion of the paramagnetic particles in response to the oscillating magnetic field. As thrombin-stimulated clot formation occurs, oscillation of the paramagnetic particles is restricted, and the plotted lines converge. When the drug causes clot lysis, the paramagnetic particles are released from the confines of the polymerizing fibrin network, oscillation amplitude increases, and the plotted lines diverge. Lysis onset time is defined as the time in seconds from application of the blood drop into the sample well to the time that signal amplitude begins to increase during clot lysis.

Test procedures. The assessment of fibrinolysis was performed using the dry reagent method described by Oberhardt et al. (13). The test system consists of a microprocessor-based analyzer and individual disposable test cards that contain a known concentration of a drug. For each analysis, a new test card is placed in the analyzer and warmed to 37°C. An unmeasured drop of whole blood is placed in the sample well of the card and drawn into the reaction chamber by capillary action; this starts the timing sequence. In the reaction chamber, blood mixes with buffers and thrombin, which initiates clot formation. The reaction chamber also contains inert paramagnetic particles of iron oxide <1 μm in diameter. As the paramagnetic particles are freed from the dry reagent matrix, they are driven into oscillation by orthogonal magnetic fields, one of which is varied with time. The oscillation of the particles is monitored optically during clot formation and lysis and displayed graphically by the computer (Fig. 1). Optical detection of particle motion is performed in the infrared range (900 nm) and thus is unaffected by hemoglobin concentration. Lysis onset time is defined as the time, in seconds, from dissolution of the dry reagents to the onset of an increase in signal amplitude during clot lysis and was the variable moni-

tored as the test end point. Lysis onset time was determined automatically by the computer using a mathematical algorithm to detect the increase in signal amplitude at the onset of lysis. Separate test cards were used to test streptokinase (Astra, Inc.) at concentrations of 10 and 100 IU/ml, recombinant tissue-type plasminogen activator (rt-PA) (Genentech, Inc.) at concentrations of 100 and 1,000 IU/ml and urokinase (Abbott Laboratories) at concentrations of 100, 200 and 500 IU/ml.

Statistical analyses. Comparison of lysis onset times at baseline and with the contrast agents added was accomplished with a repeated-measures analysis of variance followed by a Neuman-Keuls test when a significant difference was detected among the variables (15). Comparison of the baseline and in vivo contrast samples was performed with a paired *t* test. All values are displayed as mean value ± SD, and $p \leq 0.05$ was considered significant.

Results

Study patients. There were 15 men and 10 women in the study group (mean age 64 ± 12 years). The diagnosis derived from the procedure was coronary artery disease in 20 and an infiltrative cardiomyopathy in 1; no definite pathologic abnormalities were found in four patients. None of the patients had previously received a thrombolytic drug. Other baseline characteristics of the study group are shown in Table 1.

In vitro test results. The baseline lysis onset time with streptokinase at 10 IU/ml was 97 ± 14.7 s. Diatrizoate and iohexol both prolonged lysis onset time to 144 ± 43.4 and 135 ± 61.1 s, respectively ($p < 0.001$). However, lysis onset time was not prolonged by ioxaglate (106 ± 20.8 s). A similar pattern was seen when streptokinase was tested at 100 IU/ml. As expected, the baseline lysis onset time was shorter (45 ± 6.9 s) at the higher concentration of streptokinase. With the addition of diatrizoate, lysis onset time increased to 64 ± 19.6 s ($p < 0.001$), and with iohexol it increased to 51 ± 9.3 s ($p < 0.05$), but with the addition of ioxaglate it was not increased (49 ± 7.5 s) compared with the baseline. These findings are summarized in Figure 2.

When rt-PA was tested at a concentration of 100 IU/ml, the baseline lysis onset time was 552 ± 114.1 s. When repeat testing was performed after the addition of any of the contrast agents, no lysis occurred up to 1,000 s, at which point the test was automatically terminated by the computer software (Fig. 3). At a concentration of 1,000 IU/ml of rt-PA, the baseline lysis onset time was 72 ± 8.2 s. With the addition of diatrizoate, lysis onset time increased over sixfold to 527 ± 181.7 s ($p < 0.001$), and with iohexol it increased to 460 ± 197.0 s ($p < 0.001$). However, with the addition of ioxaglate, there was no significant alteration of lysis onset time (118 ± 14.9 s).

At the lowest dose of urokinase tested (100 IU/ml), the baseline lysis onset time was 201 ± 64.4 s. Compared with the baseline value, the lysis onset time was significantly prolonged by diatrizoate (365 ± 151.0 s, $p < 0.001$), iohexol (341 ± 151.8 s, $p < 0.001$) and ioxaglate (323 ± 97.3 s, $p < 0.001$), with the prolongation by diatrizoate significantly greater than that by the other two contrast agents (Fig. 4). The baseline lysis onset time at 200 IU/ml of urokinase was 113 ± 26.7 s, and the addition of each contrast agent caused it to prolong significantly. Again, diatrizoate caused more prolongation than iohexol or ioxaglate. At the highest dose of urokinase tested, diatrizoate continued to prolong lysis onset time (134 ± 155.2 s). However, lysis onset time was not significantly altered by the addition of iohexol (96 ± 34.1 s) or ioxaglate (104 ± 96.4 s). As reflected by the larger standard deviations for all of the testing performed with urokinase, there was considerably more variability in the individual responses after the addition of the various contrast agents.

Table 1. Clinical Characteristics of 25 Study Patients

Age (yr)	63 ± 12
Gender	
Men	15 (60%)
Women	10 (40%)
Race	
Black	8 (32%)
White	17 (68%)
Smoker	5 (20%)
Diabetes mellitus	9 (36%)
Hypertension	16 (64%)
Medications	
Aspirin	16 (64%)
Angiotensin-converting enzyme inhibitor	3 (12%)
Calcium channel blockers	11 (44%)
Diuretic drugs	8 (32%)
Nitrates	12 (48%)
Digoxin	4 (16%)
Beta-blockers	5 (20%)

Data presented are mean value ± SD or number (%) of patients.

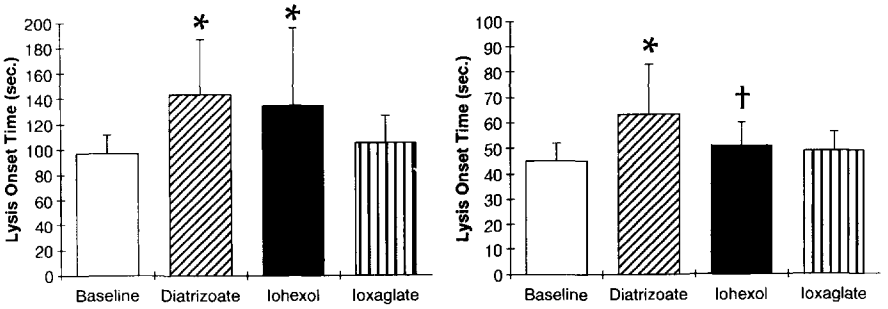

Figure 2. Lysis onset times with streptokinase before and after contrast agent administration. Mean lysis onset times in seconds are shown at baseline and after the addition of diatrizoate, iohexol or ioxaglate at 4% by volume (n = 25). Results for 10 IU/ml **(left)** and 100 IU/ml **(right)** of streptokinase are shown. *$p < 0.001$, †$p < 0.05$ versus baseline value. **Error bars** = 1 SD.

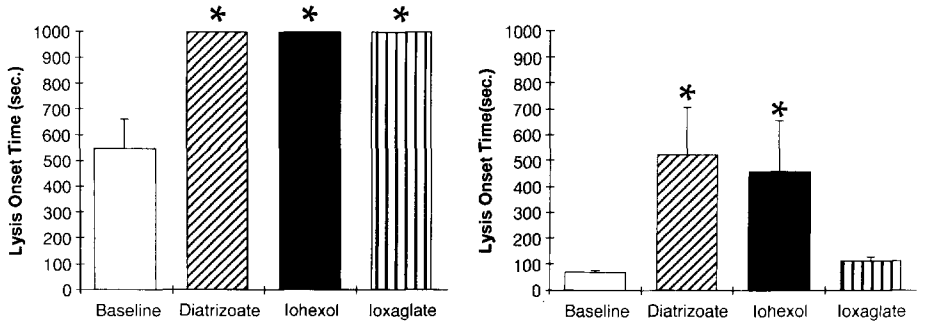

Figure 3. Lysis onset times with recombinant tissue-type plasminogen activator (rt-PA) before and after contrast agent administration. Lysis onset times in seconds are shown at baseline and after the addition of diatrizoate, iohexol or ioxaglate at 4% by volume (n = 25). Results for 100 IU/ml **(left)** and 1,000 IU/ml **(right)** of rt-PA are shown. *p < 0.001 versus baseline value. **Error bars** = 1 SD.

In vivo test results. No alteration in fibrinolysis by streptokinase at either concentration could be measured in the samples obtained after angiography with iohexol (Table 2). However, fibrinolysis by both rt-PA and urokinase was affected significantly. At 100 IU/ml of rt-PA, mean lysis onset time was increased by 37%, and at 1,000 IU/ml it increased by 18%. With urokinase, the mean lysis onset times increased 15%, 10% and 7% at 100, 200 and 500 IU/ml, respectively.

Discussion

The hemodynamic and electrophysiologic effects of contrast agents have been well characterized, but less is known about their effects on blood and coagulation. Many studies (16) have shown that contrast agents are weak anticoagulant agents, with ionic agents having a more potent effect than nonionic agents. In addition, both in vitro and in vivo studies (7,9) have shown that fibrin assembly in the presence of contrast agents is altered with the formation of thin fibrils having a low mass/length ratio compared with normal. Fibrin fibrils of a similar structure occur naturally in certain disease states, and blood clots formed in such cases are known to be resistant to the action of thrombolytic drugs (8). We therefore hypothesized that the action of fibrinolytic drugs would be impaired when tested on fibrin assembled in the presence of contrast agents. The results of the present study confirm this hypothesis. Our in vitro data show that diatrizoate and iohexol delayed the onset of lysis induced by all drugs tested. Ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase. With all of the drugs tested, increasing the concentration reduced the prolongation of onset of lysis induced by the contrast agents. To confirm that this was not simply an in vitro observation, a second blood sample was obtained from a subset of the study patients at the conclusion of angiography. This showed that iohexol delayed the onset of lysis by rt-PA and urokinase but not by streptokinase.

Drug concentrations tested. Because the impairment in fibrinolysis related to the contrast media was reduced by increasing concentrations of drug, it is important to relate the concentrations of drug that we tested to existing data about drug concentrations during therapy. Several studies have examined the concentrations of rt-PA during clinical use of the drug. Steady-state rt-PA concentrations were measured 60 min after the start of an infusion at 0.75 mg/kg body weight. At this dose, the mean plasma rt-PA level was 1.2 ± 0.6 μg/ml (696 IU/ml), and the euglobulin fibrinolytic activity was 910 ± 735 IU/ml (17). In another study (18), plasma levels of rt-PA measured 50 min after beginning a more conventional dosing schedule were 1,668 ± 966 ng/ml (967 IU/ml). Similar levels of rt-PA have been documented in other studies (19–22). Because we used whole blood instead of plasma for our measurements, the concentration of rt-PA that we tested should be clinically relevant. Unfortunately, similar information on in vivo concentrations of streptokinase after human administration are very limited (23,24). However, if a typical dose of 1.5 million IU of streptokinase were given as a bolus with a blood volume of 5 liters, the resulting concentration could be in the range of 300 IU/ml. Because the actual rate of administration is slower, and there will be some simultaneous elimination of the drug, the concentrations of streptokinase tested seem a

Figure 4. Lysis onset times with urokinase before and after contrast agent administration. Lysis onset times in seconds are shown at baseline and after addition of diatrizoate, iohexol or ioxaglate at 4% by volume (n = 25). Results for 100 IU/ml **(left)**, 200 IU/ml **(middle)** 500 IU/ml **(right)** of urokinase are shown. *p < 0.001, †p < 0.005, ‡p < 0.025 versus baseline value. **Error bars** = 1 SD.

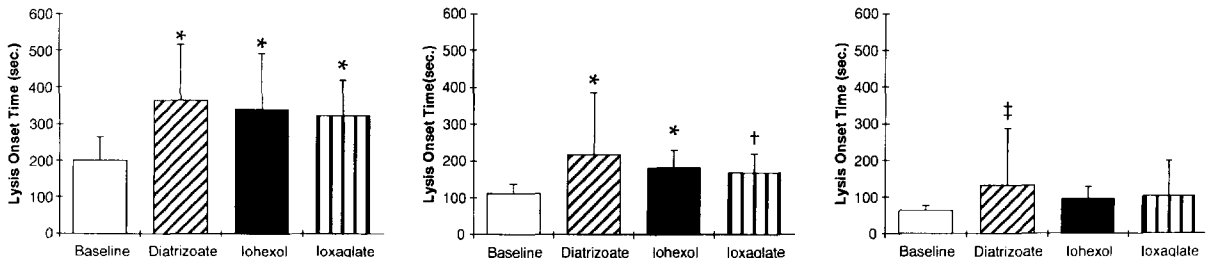

Table 2. Mean (±SD) Lysis Onset Times (in seconds) at Baseline and After Angiography With Iohexol in 20 Patients

	Baseline (before contrast agent)	After Contrast Agent
Streptokinase		
10 IU/ml	97 ± 16.0	101 ± 14.4
100 IU/ml	44 ± 5.2	43 ± 3.7
rt-PA		
100 IU/ml	541 ± 118.9	714 ± 168.4*
1,000 IU/ml	71 ± 7.3	84 ± 27.7†
Urokinase		
100 IU/ml	185 ± 30.3	213 ± 44.7*
200 IU/ml	106 ± 14.0	117 ± 23.3*
500 IU/ml	61 ± 8.9	65 ± 10.1‡

*$p < 0.001$. †$p < 0.04$. ‡$p < 0.02$. rt-PA = recombinant tissue-type plasminogen activator.

reasonable approximation of the clinical concentrations. To our knowledge, there are no clinical data on concentrations of urokinase during therapy, and these would be more difficult to estimate because the drug is often infused slowly directly into a coronary artery or occluded aortocoronary bypass graft (25,26).

Concentration of contrast media. The impairment in fibrinolysis demonstrated in this study occurred at low concentrations of contrast media. We tested a concentration of 4% by volume as an approximation of that circulating during a typical procedure. During the injection of contrast agent into a coronary artery, the local concentration is transiently very high, but between injections the arterial surface is exposed to a much lower concentration for a longer period of time. Although it was not measured directly, the amount of contrast in the in vivo blood samples obtained at the end of the procedure was most likely much lower than the 4% by volume used for the in vitro testing. In these samples, an impairment in thrombolysis by rt-PA and urokinase still was demonstrated, but of a smaller magnitude. Obviously, the most relevant concentration of dye to measure would be that occurring locally immediately adjacent to a forming thrombus, but this would be difficult to determine in a clinical study. Although the concentration of contrast agent is continuously changing during a procedure, the amounts that we used could occur clinically for more than a brief period of time.

Relevance to clinical situations. The implication of our results is that thrombus developing in the presence of circulating contrast agents is more resistant to thrombolysis. There are three clinical situations in which the possibility of coronary thrombus is greatest. First, in unstable angina, numerous studies have defined the pathophysiologic sequence leading to partial or complete thrombotic occlusion of a coronary artery (27). It is known that the surface of a fragmented or fresh thrombus is very active and a potent stimulus for further thrombus formation (28). Second, with coronary interventions there is a strong stimulus to thrombosis created by the mechanical trauma of the procedure. Finally, acute myocardial infarction is frequently the consequence of coronary thrombosis. In these clinical situations, performing angiography would expose existing or developing thrombus to contrast agent, and the characteristics of fibrin forming could be altered. It would be difficult to directly test the hypothesis that contrast agent administration impairs thrombolysis in a prospective clinical trial, but some insight can be gained by reviewing studies of thrombolytic therapy for unstable angina (29–36).

A recent meta-analysis by Moliterno et al. (37) on pooled data from 12 studies involving 2,368 patients with unstable angina showed no effect of thrombolytic therapy on the occurrence of major clinical events (death and myocardial infarction). In some of these trials, angiography was performed immediately before the administration of the thrombolytic drug and thus may have affected the results. However, in several of the smaller trials, angiography was not performed until after thrombolytic therapy, and a decrease in clinical ischemic events was found. However, other factors are likely to be involved, because the large Thrombolysis in Myocardial Infarction (TIMI)-IIIB (38) study did not show a favorable effect of thrombolytic drugs in unstable angina, and the patients did not receive radiographic contrast before thrombolytic drug was given.

Additional clinical data potentially supporting an adverse interaction between contrast agents and thrombolytic drugs come from the TAUSA trial (11,12). In that study, 469 patients with unstable angina were randomized to receive intracoronary urokinase or placebo after baseline angiography but before angioplasty of the culprit lesion. Those receiving urokinase had a significantly higher incidence of abrupt vessel closure and ischemic complications compared with the placebo group. The TAUSA investigators reported a higher incidence of angiographic dissections in their cohort and speculated that the increased ischemic complications in the urokinase group could be related to greater wall hemorrhage in the presence of urokinase. Our observations suggest an additional potential mechanism related to the impairment of fibrinolysis by contrast agents.

Study limitations. The test method we used to quantify the thrombolytic action of a drug has been shown to be reproducible with a low coefficient of variation for replicate measurements (13,14). However, there are some potential limitations. 1) Although this test quantifies the thrombolytic potential of a particular drug, the actual effectiveness in vivo may differ. Clots formed in the test system may differ from those formed in vivo. Arterial thrombi are often platelet rich, whereas clots formed in vitro tend to be platelet poor and thus may behave differently during lysis. Discrepancies between the behavior of a thrombolytic drug in vitro and in vivo and the effectiveness in clots of differing composition have been demonstrated in animal models (39,40). 2) In vitro testing with known concentrations of a thrombolytic drug may not correspond directly with the actual in vivo concentration achieved. Collen et al. (41) showed that after a standard dose of rt-PA, there was considerable variation in the plasma rt-PA level among patients. 3) Because it would be very difficult to measure the actual concentration of contrast within the coronary artery, it

was estimated, as was the duration of exposure. Although these estimations seem reasonable, their relation to actual clinical situations is unknown. 4) Blood samples were obtained from either an artery or a vein, and thus there could be some small variability in the results related to the source of the blood sample. 5) The exact relation between a delay in the onset of lysis, as measured here, and the clinical effectiveness of a drug is unknown. However, despite these limitations, when our observations are considered within the context of the available clinical data, they suggest that an important interaction exists between contrast agents and the action of fibrinolytic drugs. Of the drugs tested, streptokinase seemed to be slightly less affected by contrast agent than the other drugs, and ioxaglate appeared to cause the least interference in fibrinolysis.

Conclusions. Recently, there has been debate supported by in vivo and in vitro data suggesting that procedures using certain radiographic contrast media may facilitate thrombotic processes in vitro (42–46). Little attention has been given to the possible effects of contrast agents on fibrinolysis. This study demonstrates that contrast agents can alter the response of lytic drugs. Although demonstrated in an in vitro test system, these results may have considerable clinical relevance, and the possibility of this type of interaction has not been previously identified.

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