New Heart Attack Treatment Discussed

Thrombolytic therapy is spreading rapidly, but no one knows whether it is safe or effective

Heart attack patients who come to any of a number of major medical centers within a few hours after their chest pains begin are being offered an extremely aggressive experimental treatment called thrombolytic therapy. If the patient agrees to this treatment, a cardiologist will thread a catheter into the blocked coronary artery and inject an enzyme, usually streptokinase, to dissolve the clot obstructing the artery and causing the heart attack. In most cases, blood will begin flowing again through the artery and, cardiologists hope, the heart attack will be halted before irreversible damage is done.

The method sounds so logical and looks so promising that some cardiologists are already real enthusiasts. Garrett Lee of the University of California at Davis, for example, says he could not participate in a randomized controlled trial of thrombolytic therapy because he would not want to deny his patients the treatment. Alphonso Jordan of Albert Einstein College of Medicine says, "If I were having a heart attack, there is no place in the world that I would rather be than in my cath lab with streptokinase being infused into my artery."

Yet, as even the enthusiasts readily admit, there are serious questions about thrombolytic therapy. No one knows whether patients given this treatment live longer or do better than patients given conventional therapies. No one knows to what extent streptokinase might have adverse side effects. No one is even sure when after thrombolytic therapy to assess the effectiveness of the treatment. But because thrombolytic therapy is spreading so rapidly, investigators at a National Institutes of Health workshop* called for a clinical trial of the treatment to begin as soon as possible.

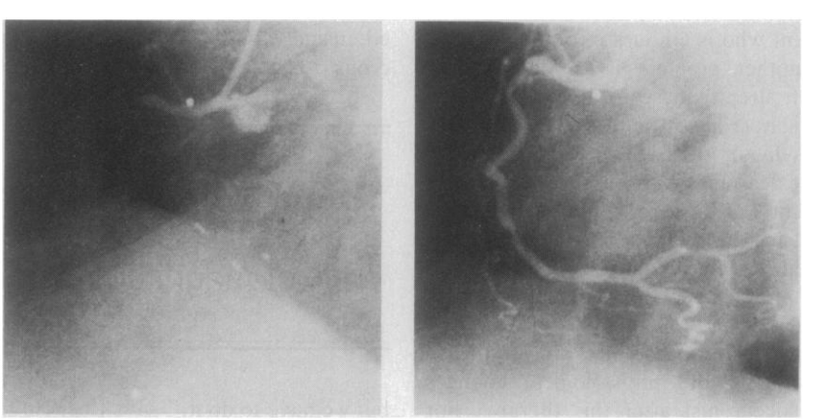
Thrombolytic therapy came quickly into use after it was discovered, by accident, just a few years ago by Peter Rentrop and Karl Karsch. (Rentrop and Karsch were at the University of Göttingen when they made their discovery but they have recently moved to New York's Mount Sinai Medical Center.) A patient with a severely narrowed right coronary artery began having a heart attack in the catheterization laboratory at a Göttingen hospital. A physician had already threaded a catheter into the man's artery and had injected a radiopaque dye so that the artery would show up in x-rays. Suddenly, the artery became completely blocked. Rentrop was called in to help and, out of desperation, he poked a thin wire through the obstruction to restore blood flow. Within 2 minutes, the patient's electrocardiogram began looking normal and his heart attack, apparently, ceased.

This experience made Rentrop and Karsch realize that it is possible, and perhaps even desirable, to insert a catheter into a blocked artery during a heart attack. They then decided to try injecting streptokinase through the catheter rather than breaking up clots mechanically with a wire. Streptokinase was already being used in Europe to break up blood clots during heart attacks, but patients were being given the enzyme intravenously. There was some evidence that intravenous streptokinase might cause bleeding, including cerebral hemorrhages. By injecting streptokinase directly into the clot, Rentrop and Karsch could use less of the enzyme.

From that beginning, thrombolytic therapy spread rapidly. Last year at the American Heart Association's annual meeting a standing-room-only crowd heard a handful of papers on it. This year, more than 20 papers were presented.

As they gain more experience, investigators are becoming bolder. Some are inserting balloons into the just-opened arteries to squash atherosclerotic plaques that might trigger future heart attacks. Others are using thrombolytic therapy as a way station before doing coronary artery bypass surgery. Even very sick patients are being treated with thrombolytic therapy. Lee, for example, has treated three patients in cardiogenic shock—they were on respirators, their hearts were barely beating, and their kidneys were barely functioning. Of the total of 30 patients he has treated so far with thrombolytic therapy, the only death was an 82-year-old man in shock. The man had lung and kidney disease as well as heart disease, Lee recalls, but after the thrombolytic therapy, "he woke up. Unfortunately, 2 weeks later he was on a respirator because his lungs were so bad. He died of pneumonia."

Thrombolytic therapy fits a pattern in which heart attack patients have been treated ever more intensively. Twenty years ago the rule was to barely touch a heart attack patient. Doctors prescribed 30 days or more of bed rest. Then came coronary care units where patients are carefully monitored and given drugs to control their blood pressure, heart rate, and heart rhythms. Next was the radical idea that heart attack patients could get out of bed after 2 or 3 days. Finally,



Successful thrombolytic therapy

Angiogram shows blocked coronary artery at left. On the right, the artery is opened and blood is flowing again. [Source: Garrett Lee, University of California at Davis]

*The workshop on "Limitation of Infarct Size With Thrombolytic Agents," was held on 9 and 10 November and was sponsored by the National Heart, Lung, and Blood Institute and the Bureau of Biologies of the Food and Drug Administration.

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many cardiologists became interested in thrombolytic therapy, although many still resisted—at least when the idea was very new. "I got a lot of resistance from other doctors at my hospital," says Lee. "They said that when a patient is infarcting [having a heart attack] you should leave him alone."

So far, because thrombolytic therapy is so new, no one has treated more than 30 or 40 patients and many have treated far fewer. For this reason, even basic details of the method are still being worked out. For example, most cardiologists are using thrombolytic therapy only on patients who are no more than 3 hours into their heart attack. Heart attacks generally last from 12 to 24 hours although half the heart cells that are destined to die in an attack die within the first few hours. But, as was pointed out at the NIH workshop, it frequently is very difficult to determine just when a heart attack began. One patient who is, apparently, 3 hours into his attack may be the medical equivalent of another patient who is 6 hours into his.

Another problem is to decide how much streptokinase to give. So far, investigators have tried dosages that vary by a factor of 2. Says Rentrop, "The most learning is in assessing what a patient will tolerate. When do you stop [infusing the enzyme]? You walk a tightrope between the danger of re-occlusion and the danger of significant hemorrhage."

Investigators also are still trying to understand the physiological changes that occur just after this therapy. For example, most patients have arrhythmias that would be interpreted as a bad sign in a more conventional context. Usually, arrhythmias are viewed as a symptom that the heart is receiving insufficient oxygen or that heart tissue is damaged. But researchers at the workshop proposed that arrhythmias following thrombolytic therapy might be a good sign; they might indicate that the oxygen-deprived heart cells in the area affected by the heart attack are starting to function again. This interpretation of arrhythmias, said Eugene Braunwald of Peter Bent Brigham Hospital, "never occurred to me before this meeting."

Another immediate result of thrombolytic therapy is that creatine kinase (CK), an enzyme found in heart cells, surges into the bloodstream. Cardiologists commonly monitor the presence of CK in heart attack patients, reasoning that it is released when heart cells die and that the more CK in the blood, the greater the area of heart muscle killed by a heart attack. The discovery that huge amounts of CK enter the blood following thrombolytic therapy was quite a surprise to doctors. One participant at the workshop said that physicians at his hospital pointed to the arrhythmias and high CK levels in patients given thrombolytic therapy and argued that the therapy was actually causing heart attacks.

Burton Sobel of Washington University theorizes that excess CK in the blood following thrombolytic therapy may be a good sign. The gush of blood to the heart when the clogged artery opens up may wash CK off of dead or dying heart cells. Normally, only 15 percent of the CK in dead cells enters the bloodstream following a heart attack and cardiologists had always wondered where the rest of it was. Thrombolytic therapy, says Sobel, "may be our Rosetta stone."

Because thrombolytic therapy is still an experimental treatment, investigators must obtain written informed consent from their patients. This is a difficult task because the patients are in the middle of a heart attack, are in pain, and are sedated, usually with morphine. "It's ludicrous [to try to obtain informed consent] but we have to do it," says Lee. He tells of carefully explaining the procedure and drawing diagrams for patients who really are in no condition to rationally decide whether they want the treatment. Frequently, he says, the patients ask their families to decide. John Markis of Beth Israel Hospital in Boston has had similar experiences in his attempts to obtain informed consent. He says that patients' families often telephone a relative or their family doctor and ask him to decide. Both Markis and Lee report that virtually all of their patients agree to thrombolytic therapy.

If thrombolytic therapy really catches on, physicians will be faced with a touchy issue. There are not enough trained cardiologists to treat all the heart attack patients. Thomas W. Smith of Harvard Medical School, who did not attend the workshop but who was interviewed after the meeting by *Science*, explains that even though coronary catheterization is a 20-year-old technique, it is not always available in hospitals that do not do heart surgery. For that reason, small hospitals often do not have catheterization laboratories or physicians on duty with experience in coronary catheterization. Because thrombolytic therapy must be performed immediately, it is not practical to think of transporting heart attack patients to hospitals with proper facilities. But, says Smith, "As I've thought about it, it seems to me that the facilities needed are not that great. What is lacking is experienced, expert personnel."

Smith explains that it takes at least 2 years of full-time training in a busy catheterization laboratory before a physician is proficient enough to attempt thrombolytic therapy. "It's terribly tricky. You have to push the catheter through the aorta and find the tiny openings to the coronary arteries. Then you have to thread the catheter through the coronary artery. There are all sorts of hazards. Without experience, the chances of doing more harm than good are considerable."

But for the time being, at least, these problems of access to the treatment are in the future. Many participants at the workshop were not at all certain that thrombolytic therapy is benefiting patients. And even if it is beneficial, the far simpler treatment of simply infusing streptokinase intravenously might do equally well. For these reasons, the workshop concluded with an impassioned plea from Braunwald for a randomized controlled clinical trial comparing thrombolytic therapy, intravenous infusions of streptokinase, and usual care in coronary care units.

Said Braunwald, "We are dealing with a technology that is diffusing very rapidly throughout the country and throughout the world and I think it is not being properly assessed. I would characterize the studies up to now as pilot studies. I think it's very likely that community hospitals are adopting this approach. I think it will become progressively more difficult to do a trial. I think we're dealing with something that is one order of magnitude bigger than bypass surgery. There are some very critical questions that can be framed now."

—GINA KOLATA

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