A 49-Year-Old Woman With Hypertension Who Deteriorates After Acute Myocardial Infarction

Ward Cassells, MD; George Schroth, MD; L. Maximilian Buja, MD

Case History (George Schroth, MD)

The patient was a 49-year-old white woman with a history of essential hypertension and hypercholesterolemia and an unclear history of a stroke or aneurysm who presented after 2 days of intermittent, severe chest pressure associated with a severe headache. The symptoms had returned at 9:00 A.M. and were still present 2 hours later on presentation to the emergency department. No visual changes were reported. The patient complained of nausea but not dyspnea. She had no past history of chest pain, coronary artery disease, or myocardial infarction. Her risk factors for coronary atherosclerosis consisted of hypertension, hypercholesterolemia, obesity, and a 20-pack-year history of smoking. There was no family history of heart disease. The patient was taking her antihypertensive medication, which consisted of verapamil, triamterene, and hydrochlorothiazide, as prescribed.

The patient's previous history of cerebral aneurysm was unclear. It was associated with what the patient described as a "stroke" several years previously. A cholecystectomy had been performed 8 months previously. There was no history of alcohol or illicit drug use. She had no known allergies.

Physical Examination

The patient was an overweight, middle-aged white woman who was fully alert and oriented but in mild distress. She was afebrile with a blood pressure of 116/68 mm Hg; pulse, 80; and respirations, 16. Cardiac monitoring revealed intermittent complete atrioventricular (AV) dissociation. The patient's pupils were equal, round, and reactive to light; her extraocular muscles were intact; and conjunctivae were normal. Examination of the fundi revealed normal disc margins without hemorrhages, but arteriovenous nicking was apparent bilaterally. No Roth's spots were seen. Her oropharynx was without erythema, exudate, or petechiae. The patient's neck was supple and without adenopathy. Thyroid gland examination was normal. Carotid upstrokes were brisk bilaterally and without bruits. Jugular venous distention was not noted. The chest was clear to auscultation. On cardiovascular examination, there was no displacement of the apex beat, and the precordium was not hyperdynamic to inspection. There were no lifts or heaves. S1 and S2 were normal. An S4 was heard, but there was no S3. No murmurs or rubs were noted. Peripheral pulses were 2+ throughout. Abdominal examination revealed a soft and nontender abdomen with normal bowel sounds. No hepatosplenomegaly was noted, and no bruits were heard. The rectal examination was guaiac negative. The patient had no cyanosis, clubbing, or edema of her extremities. There was no evidence of Janeway lesions, Osler's nodes, or splinter hemorrhages. No femoral bruits were heard. The neurological examination demonstrated no focal abnormalities.

On admission, the ECG (Fig 1) showed normal sinus rhythm with first-degree AV block, ST segment elevation with Q-waves, and T-wave inversion in leads II, III, aVF, and V4, V5, and V6. Right-sided chest leads showed ST segment elevation in RV4, RV5, and RV6. ST depression was noted in leads V1-V3, I, and aVL. ECG monitoring revealed intermittent Mobitz type II and complete heart block.

Hospital Course

The patient was admitted with a diagnosis of acute inferolateral myocardial infarction with right ventricular involvement. An extensive workup generated comprehensive chemical analyses (Table 1). Because of her history of possible cerebral aneurysm, she was not treated with intravenous thrombolysis, and an emergency computed tomography (CT) scan of the head did not demonstrate any evidence of intracranial bleeding. Because of ongoing chest discomfort and AV dissociation, the patient was taken to the catheterization laboratory.

Left coronary angiography demonstrated a normal left main coronary artery. The left anterior descending coronary artery was noted to have severe diffuse distal disease. The circumflex artery demonstrated no significant narrowing. The right coronary artery was completely occluded just after the first acute marginal branch. The left ventricle was noted to have severe inferior hypokinesis. After primary percutaneous transluminal coronary angioplasty (PTCA) (performed at 3:00 P.M.) followed by 250,000 U urokinase (Fig 2), a second lesion was identified distally. This lesion was also dilated, and at the end of the procedure the patient had good right coronary flow. There was a dissection at the site of the first angioplasty as well as minimal residual...
stenosis. The left ventricular ejection fraction was 57%. The pulmonary capillary wedge pressure was 15 mm Hg; left ventricular pressure, 90/25 mm Hg; right atrial pressure, 14/12 mm Hg; pulmonary artery pressure, 26/20 mm Hg; and mean pulmonary artery pressure, 19 mm Hg. There was no gradient across the aortic valve.

During the procedure, the patient had persisting severe hypotension that required extensive volume resuscitation with intravenous saline, support with intravenous dopamine, insertion of a temporary pacemaker, and intra-aortic balloon pump counterpulsation. Hemodynamics at the end of the procedure were stable.

The patient was then taken to the coronary care unit. The heparin infusion that had been started in the catheterization laboratory was continued. By 8:30 p.m., the dopamine infusion was discontinued. By that time, the blood pressure was 130/80 mm Hg; pulse, 100; and pulmonary artery pressure, 37/22 mm Hg. Intra-aortic balloon pump support was continued, and the patient did well throughout the night.

TABLE 1. Laboratory Data and Studies

<table>
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<tr>
<th>Sodium, mEq/L</th>
<th>134</th>
<th>WBC, x10^3</th>
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<tr>
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<td>WBC differential</td>
<td>83P/13L/2M/1E/1B</td>
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<td>Hemoglobin, g/dL</td>
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<td>CO2, mEq/L</td>
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<td>Hematocrit, %</td>
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<td>RBC</td>
<td>Indices normal</td>
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<td>Creatinine, mg/dL</td>
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<td>PT, s</td>
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<td>Urea nitrogen, mg/dL</td>
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<td>Platelets, x10^3</td>
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<td>Phosphorus, mg/dL</td>
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<td>Arterial blood gases, 2 L/min O2</td>
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<td></td>
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<td></td>
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<td></td>
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<td>Albumin, g/dL</td>
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<td>Specific gravity</td>
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<td>pH</td>
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<td>ALT, U/L</td>
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<tr>
<td>Magnesium, mg/dL</td>
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<td>Bacteria</td>
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ALT indicates alanine transaminase (SGPT); AST, aspartate transaminase (SGOT); WBC, white blood cell count; PT, prothrombin time; PTT, partial thromboplastin time; and RBC, red blood cell count; P, polymorphonuclear neutrophil; L, lymphocyte; M, monocyte; E, eosinophil; and B, basophil.
The following day, there were no significant changes in the patient's symptoms or physical examination. Her hemodynamic studies showed a cardiac index of 2.5 L·min⁻¹·m⁻²; mean pulmonary artery pressure, 23 mm Hg; systemic vascular resistance, 1542; and pulmonary capillary wedge pressure, 16 mm Hg. At 1:00 P.M., the patient was noted to have an episode of AV dissociation with a junctional rate of 70 beats per minute. Her hemodynamic variables continued to be stable. The AV dissociation was treated with 0.5 mg atropine IV, and normal sinus rhythm returned. Later that day, the intra-aortic balloon pump, Swan-Ganz catheter, and temporary pacer were removed. At midnight, the patient developed chest discomfort that was graded 7/10 in severity. Her physical examination was unchanged from earlier in the day. The monitor demonstrated a Mobitz type I block. ECG was unchanged. The patient's blood pressure was 94/51 mm Hg; pulse, 70; and respirations, 18. She was given sublingual nitroglycerin three times with partial relief of her pain. Thirty minutes later, the patient again was noted to be in AV dissociation. The chest discomfort continued, and the patient was given 2 mg morphine IV. The partial thromboplastin time drawn before this episode suggested that the patient was not adequately anticoagulated; she therefore was given supplemental heparin, and her chest discomfort subsided shortly thereafter.

During the patient's third hospital day, the ECG was essentially unchanged from the previous day. New findings noted were a pericardial rub and a short I/VI systolic murmur at the left sternal border. An echocardiogram was performed, which revealed akinesis of the posterolateral, inferior, and distal right ventricular free walls. A small pericardial effusion was noted. No intraventricular thrombus was identified, and chamber dimensions and valve structure and function were within normal limits. The patient's cardiac enzymes are listed in Table 2.

The fourth hospital day was uneventful, and the patient was transferred to the intermediate care unit. At 1:48 A.M. on the fifth hospital day, the patient complained of acute shortness of breath while on the commode in her bathroom. She denied any chest discomfort at that time. The nurse described the patient as cool and clammy to touch. Her pulse was from 40 to 70 beats per minute with labored respirations of 35. Blood pressure was palpable at 70 mm Hg. On examination, the patient was noted to have crackles in both lung bases. A third heart sound was heard, and the first and second heart sounds were noted to be distant. Telemetry demonstrated complete heart block. Intravenous normal saline was begun. Oxygen was administered with a non-rebreather face-mask, and an external pacemaker was placed. The patient was also started on intravenous dopamine, and 0.5 mg atropine was given. The patient was transferred back to the coronary care unit. Shortly thereafter, the patient was intubated for acute respiratory failure and subsequently became asystolic. Resus-
citation was continued during which the patient had ventricular tachycardia, fibrillation, and electromechanical dissociation. After 45 minutes, the patient could not be resuscitated. She was pronounced dead at 3:05 A.M., and an autopsy was performed.

Case Discussion (Ward Casscells, MD)
This patient was a relatively young woman who appeared to be recovering from a large inferior infarct when she suddenly became short of breath and hypotensive, with complete heart block and a pulse ranging from 40 to 70 beats per minute. The first and second heart sounds were noted to be distant.

What Happened?
The presence of heart sounds and a palpable pressure rule out sudden electromechanical dissociation as the cause of death. Pulmonary embolism is rare in patients with myocardial infarction who have been treated with heparin and aspirin and brief bedrest. There was no indication of cerebral or femoral bleeding. No medications had been given. A diagnosis of myocardial rupture is suggested by the suddenness of the event, by the fact that the heart sounds became distant, and by the absence of chest discomfort. However, these features cannot confidently exclude (1) infarction in a new territory (that of the distal left anterior descending coronary artery, which was diseased) or (2) extension of the previous infarction by hemorrhage into the wall of the ventricle, by rethrombosis of the right coronary artery, or by hemorrhage into the wall of the artery. The recurrence of complete heart block is not a very helpful sign as this could occur from recurrent ischemia to the AV node or vagal discharge (the latter is well characterized in experimental acute pericardial tamponade and is consistent with the response to atropine). It is unlikely that reoclusion of the right coronary artery would by itself precipitate a nonarrhythmic fatality because that territory was already infarcted. The ejection fraction on day 1 (before therapy, when the right coronary artery was occluded proximally, the ST segments were elevated, and large Q-waves were present) was not very depressed (57%). Thus, reoclusion of the right coronary artery could not have caused sudden heart failure. Therefore, it is likely that this patient suffered myocardial rupture, with or without new myocardial necrosis due to hemorrhage or to occlusion of either the right or left anterior descending coronary artery.

Myocardial rupture occurs in only 2% to 3% of myocardial infarcts, but because it is an almost uniformly fatal event, it accounts for 10% to 30% of infarct fatalities. The patients at particularly high risk are those with a large, Q-wave anterior or apical infarct and no prior infarct,1,4 as previous infarction results in collaterals (which limit the size and transmural extent of the infarct)2 and in scar (which provides structural support). It is likely that rupture is preceded by infarct expansion (the acute stretching and thinning of the infarcted tissue that is due to transmural myocardial necrosis and lysis of collagen) and promoted by increased afterload. Expansion is distinguished from extension as the former does not involve new necrosis.6 Rupture may be made more likely by late (12 to 24 hours) thrombolytic therapy.7 This patient had chest discomfort for 2 days before admission, at which time she had Q-waves and an elevation in lactate dehydrogenase (Table 2). Rupture tends to occur between days 4 and 7, and this too applies to her case, as does the fact that women are at greater risk of rupture.8 Finally, inferior infarction with right ventricular involvement carries a threefold to fourfold greater risk of rupture than infarction restricted to the inferior wall.9 Thus, in this woman whose first infarct was large and transmural, involved the right ventricle, and was treated by late thrombolytic therapy, the sudden development of hypotension and heart block on the fourth hospital day (infarct day 5 or 6) is likely to be due to rupture of the heart.

Where Was the Rupture?
It could have involved the septum, causing an acute ventricular septal defect, but in general this would be accompanied by a new murmur and thrill, and these patients are likely to survive long enough to be diagnosed and have emergency surgery. Thus, this patient probably had a rupture of the apex or the inferior or posterior free wall.

Reperfusion by thrombolytic agents probably causes some oxidative injury and often converts an anemic infarct into a hemorrhagic infarct.1,10 Overall, the risk of rupture appears to be slightly increased by thrombolytic therapy3 (more so if begun after 12 hours), but the increased risk of extension or rupture is more than offset by the reduction in infarct size with its consequently reduced risks of arrhythmia and expansion or by other benefits of thrombolysis.11,12

### Table 2. Cardiac Enzyme Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Total CK, U/L</th>
<th>CK-MB, ng/mL</th>
<th>CK Index</th>
<th>Total LD, U/L</th>
<th>LD1, U/L</th>
<th>LD1/LD, %</th>
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<td>2518</td>
<td>290.5</td>
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<td>477</td>
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<td></td>
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<td>2914</td>
<td>368.5</td>
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<td>...</td>
<td>953</td>
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<td>...</td>
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<tr>
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<td>2.9</td>
<td>842</td>
<td>452</td>
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<td>12.0</td>
<td>3.0</td>
<td>794</td>
<td>397</td>
<td>50</td>
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CK indicates creatine kinase; and LD, lactate dehydrogenase.
What Can We Learn From This Patient's Story? In Retrospect, Should Anything Have Been Done Differently?

The diagnosis was made promptly. The differential diagnosis in a middle-aged hypertensive woman with no previous history of coronary symptoms who presents with chest discomfort and headache includes hypertensive crisis, aortic dissection, pulmonary embolus, myocarditis, pericarditis, and uncommon presentations of cervical spinal disease or cerebral hemorrhage with secondary myocardial ischemia. However, the ECG was diagnostic of an inferoapical and right ventricular infarction. The underlying problem is almost always rupture of, or hemorrhage into, an atherosclerotic coronary plaque followed by occlusive thrombosis. A minority of cases are precipitated by development of thrombosis on an ulcerated plaque or primary vasospasm. In general, vasoconstriction is a secondary complication of plaque hemorrhage and thrombosis.13,14

Rarely, such presentation is due to (1) dissection of a right coronary artery in a setting of a proximal aortic dissection, (2) arteritis or myocarditis, (3) a coronary anomaly or thromboembolism from the left atrium or from a patent foramen ovale, or (4) previously unsuspected aortic stenoses or hypertrophic cardiomyopathy. These unlikely possibilities can quickly be excluded in the catheterization laboratory.

What About the Headache and the History of a Prior Aneurysm or Stroke for Which a CT Scan Was Performed, Delaying Catheterization?

Although stroke can be a complication of myocardial infarction—particularly from thrombosis at the site of a transmural apical infarct and occasionally due to showers of emboli from the left atrium or ventricle, hypertensive crisis, or proximal aortic dissection—stroke complicates only 1% of myocardial infarctions.15 The diagnosis is more likely with a headache or history of aneurysms but usually present with a focal neurological sign (or, in the case of hemorrhage, with confusion, obtundation, or neck stiffness). Thus, the CT scan was unlikely to reveal a contraindication to thrombolytic therapy.

The CT scan delayed catheterization by 1 or 2 hours, a situation that might have resulted anyway had the catheterization laboratory not been immediately available. The delay was probably not a severe problem if the patient’s symptoms and ST segments had largely resolved in response to nitroglycerin, narcotic, oxygen, sedation, rest (for example, deferring the rectal examination, using stool softeners to prevent straining [note that she compensated on the commode], and testing stools for occult blood), aspirin, and reassurance.14 Moreover, the benefits of acute recanalization of the artery are much smaller both when therapy is begun late (in this case the infarct was at least 4 hours and perhaps 48 hours old with a stuttering course) and in inferior infarcts in general.11,12

Yet, there were several worrisome aspects about this patient’s presentation, even though she was not in a high Killip or Norris class. First, the history suggests that on the morning of presentation, she extended an infarct that began 1 or 2 days earlier. Second, the prognosis after infarct is worse for women than for men, even after correcting for other variables.16-18 Third, and most important, the ECG showed not only inferior ST elevations but also Q-waves and ST elevation in leads V3 and V4, an incomplete right bundle branch block with left anterior hemiblock, intermittent Mönitz type II and complete heart block, ST elevation in right ventricular lead 4,19 and widespread reciprocal changes. These features suggest a large inferior infarct involving the apex and right ventricle—and right ventricular involvement alone increases the mortality from 6% to 31%—as well as a likelihood of disease in the left anterior descending coronary artery.20-22 Moreover, no collaterals were seen, and this too is worrisome. The heart block, bradycardia, and hypotension limit the ability to treat the patient with nitroglycerin, morphine, and β-blockers. This is a major limitation: The benefits of nitrates have been proven in several randomized trials,23 and the duration of pain correlates with the size of the infarct. It is likely, but not proven, that prompt eradication of the patient’s discomfort not only comforts the patient but also reduces mortality. Pacing can allow the administration of morphine (or even β-blockers if sinus tachycardia is present). Patients with right ventricular infarction, especially when complicated by heart block, are very dependent on synchronous right atrial contraction to maintain cardiac output. Thus, it is important to place atrial and ventricular pacing wires as soon as possible.24

A pulmonary artery (Swan-Ganz) line was also placed. As demonstrated in this patient’s case, hypotension is common and requires volume supplementation. Conversely, volume overload that results in even a modest increase in pulmonary vascular resistance could cause decompensation of the impaired right ventricle. This patient’s pulmonary capillary wedge pressure was maintained at approximately 16 mm Hg, which was probably ideal, but of course this must be determined on an individual basis. The pulmonary artery line also helps assess right ventricular function when the neck veins are not elevated. Occlusion distal to the right atrial branch usually gives a W pattern. Ostial occlusion with right atrial ischemia can give an M wave (and usually a very sick patient with tamponade-like equalization of pressures).25

An intra-aortic balloon was also placed. This probably reduced ischemia of the septum, which contributes importantly to right ventricular function, maintained perfusion pressure to the right coronary artery (in the face of the patient’s recurrent hypotension), and helped correct her metabolic acidosis.26 As I will discuss, this patient also required primary angioplasty as opposed to intravenous thrombolytic treatment for her infarction. Thus, a case can be made (in retrospect, of course) for deferring the CT scan and going directly to the cardiac catheterization laboratory.

It is not mentioned whether the patient had been taking aspirin. If so, her aspirin trial was obviously unsuccessful. She may have developed a thrombus that was fibrin rich and platelet poor; however, the serial ECGs indicate a waxing and waning of the ST segments over the first day, consistent with cyclic flow variations caused by recurrent platelet aggregation and vasoconstriction.27 Thus, I believe she had the usual platelet-fibrin thrombus because she was on the wrong dose of aspirin28 or because her platelets responded to an agonist other than thromboxane A2 (eg, thrombin, serotonin,
collagen, platelet-activating factor, and others. In randomized trials of aspirin for acute myocardial infarction, 165 mg and 325 mg have shown benefit, whereas 75 mg has shown benefit in stable angina pectoris. If she had been taking 325 mg aspirin (or less), she should receive another 325 mg because patients' bleeding times have rather unpredictable dose-responses to aspirin. If a patient has been taking two aspirins daily yet presents with an acute myocardial infarction, it may be worth adding ticlopidine or dipyridamole or enrolling him or her into one of the trials of (1) newer antithrombin agents (eg, hirulog, hirudin, hirugen, or argatroban) (2) the inhibitors of IIb/IIIa receptors (such as the 7E3 antibody or integrin or argatroban), or (3) ciprostene (a long-acting prostacyclin) (for review, see Reference 29).

In theory, titration of bleeding times (which are shortened to 3 minutes in acute myocardial infarction) might be helpful, but no studies have addressed this. It is important to block the platelets and the coagulation enzymes before administering thrombolytic therapy because plasmin activates both systems and so is thrombogenic as well as thrombolytic.

Magnesium should be administered because of the patient's low (1.5 mg/dL) serum level. Even in patients with normal levels, magnesium decreases platelet aggregation, peripheral vascular resistance, heart rate, calcium entry, and ventricular arrhythmias. Only extremely high doses cause heart block or significant hypotension. Several trials have documented a 20% to 50% reduction in acute myocardial infarction mortality using 8 mmol MgSO4 IV over 5 minutes followed by 65 mmol over 24 hours. The ISIS-4 Trial will study the effects of magnesium in combination with thrombolytic therapy and captopril on both early and late mortality.

**Should This Patient Have Undergone Urgent Recanalization?**

Her symptoms began 2 days before admission, and her white blood cell count and levels of creatine kinase and lactate dehydrogenase were clearly elevated on the day of admission, which is consistent with 1 to 2 days of ongoing necrosis. It is clear that there is no benefit of thrombolytic therapy after 24 hours of infarct symptoms. However, the patient's symptoms were intermittent, and on presentation she had 2 more hours of pain and still had some R-wave and ST elevation in leads II, III, aVF, V1, and V6, suggesting that some myocardium could be salvaged. Treatment of acute myocardial infarction with thrombolytic therapy begun 2 to 6 hours after the onset of symptoms yields 30% and 20% reductions, respectively, in mortality. Furthermore, treatment begun as late as 12 hours after symptom onset prevents late ventricular dilation (“remodeling”) even though it does not reduce infarct size. This is associated with about a 15% reduction in mortality. These late net benefits are obtained despite a small increase in risk of death during the first 24 hours after late thrombolytic therapy. These deaths are the result of heart failure, ventricular rupture, or electromechanical dissociation (for review, see Reference 12).

The mechanism of late benefit of the open artery may relate to salvage of small amounts of epicardial or right ventricular myocardium, which typically infarct late. The open artery can also serve as a source of collaterals to protect a region jeopardized by occlusion of a different coronary artery. Moreover, despite the damage that can be caused by late reperfusion, the open artery may speed infarct healing by allowing for the delivery of the inflammatory cells, nutrients, and oxygen required for angiogenesis, fibroplasia, and scar formation. In patients with an open artery, the signal-averaged ECG is less likely to be abnormal.

The usefulness of late thrombolytic therapy in the subset of patients with inferior infarction extending to the right ventricle is not known. However, in a recent series of patients with inferior infarction, 54% of whom also had right ventricular infarction, thrombolytic therapy begun a mean of 6 hours after symptom onset was associated with a 71% lower mortality. It is noteworthy that even though right ventricular involvement in inferior myocardial infarction confers a fivefold increased risk of in-hospital mortality (compared with patients with inferior myocardial infarction without right ventricular involvement), late prognoses are almost identical. Right ventricular infarction is accompanied by profound hypokinesis with remarkable spontaneous improvement—to a near-normal range in most patients. Because the right ventricle is so thin, it seems to survive in a hibernating state, probably by diffusion of oxygen from the right ventricular cavity. Even late thrombolytic therapy is probably helpful for right ventricular function. Currently available databases may be able to suggest at least a retrospective answer to that question, particularly if information on right ventricular function is available. It is also conceivable that sustaining the right ventricle by diffusion of oxygen is the basis for the anecdotal reports of benefit from hyperbaric oxygen therapy of acute myocardial infarction.

**Thus, There Was a Sound Rationale for Attempting Recanalization. But How Should the Artery Have Been Opened?**

Three recent randomized trials have found that primary angioplasty saves more lives (and costs less) than t-PA, particularly for older patients and patients with large, complicated, or anterior infarcts. Primary PTCA is the best option in patients with a history of stroke, recent trauma or surgery, bleeding disorders, or severe systemic arterial hypertension.

The probable advantages of primary angioplasty include slightly faster, more certain recanalization; less residual stenosis; and less risk of infarct hemorrhage, of brain hemorrhage, and of dislodging a left ventricular thrombus. The relative benefits of PTCA versus lytic therapy in the subset of patients with inferior and right ventricular myocardial infarction are not known.

**What About the Subset of Female Patients?**

Several studies indicate that women have higher mortality than men with acute myocardial infarction, even though the extent of coronary disease and ventricular dysfunction is similar. Correction for the greater age and incidence of diabetes and hypertension in the female cohorts accounts for much but not all of the difference. Women also have a higher mortality from coronary bypass surgery and from elective or emergency angioplasty.

Few data are available on the benefits of thrombolytic therapy in women compared with men. Women are more susceptible to bleeding complications, but no
mortality difference was seen in the GISSI trial. In the recent PAMI trial, women with acute myocardial infarction randomized to PTCA had a 4% mortality rate versus a 14% mortality rate for treatment with t-PA. In this patient's case, the possibility that the CT scan had missed an aneurysm or stroke-in-evolution was another reason to choose primary PTCA rather than thrombolytic therapy.

**What Is the Rationale for Urokinase After Angioplasty?**

Major trials have indicated that the routine use of angioplasty following thrombolytic therapy results in higher mortality. There are some data justifying the widespread practice of using urokinase after angioplasty. In one small trial, the routine use of urokinase after elective angioplasty was associated with a nonsignificant 50% reduction in the risk of acute occlusion or Q-wave infarction. In a small retrospective study of the administration of urokinase following direct PTCA for patients who presented with acute myocardial infarction within 6 hours of symptom onset (or 24 hours with intermittent symptoms), there was a marked reduction in the rate of restenosis at 1 month.

In this patient's case, urokinase was obviously given because of the angiographic evidence of thrombosis. Indeed, after urokinase administration, the thrombus was lysed, and a more distal stenosis became apparent. However, the use of urokinase 6 to 48 hours after infarction probably has hazards as well. The conversion from bland to hemorrhagic infarct and the increased risk of rupture, as noted above, may have several mechanisms. Fibrin within the infarcted myocardium serves as a scaffold for fibroblast proliferation and for the elaboration of a collagen scar. In cases of severe necrosis, the cross-linked fibrin may be the only source of structural support. Moreover,
plasmin cleaves more than fibrin. It proteolytically acti-
vates collagenase and elastase and thus may actively
dergrade the infarct tissue.45 One approach to avoiding the
risks of post-PTCA lytic therapy would be to administer it
selectively to the arterial wall, via a perfusion catheter. In
the present case, however, urokinase was not given for
mural thrombus but rather for complete occlusion. Pres-
sumably the intracoronary infusion was discontinued as
soon as recanalization occurred so as not to irrigate the
infarct with more plasminogen activator. At any rate, the
urokinase and second PTCA achieved not only a patent
artery but also, more important, good flow—presumably
TIMI III flow, which confers a better prognosis than TIMI
II flow (a patent artery with slow flow, presumably due to
downstream emboli, aggregates of platelets or leukocytes,
and vasospasm; see Reference 12).

On the second hospital day, the patient experienced
recurrent chest discomfort. After angioplasty and
thrombolytic therapy, the recurrence of symptoms in the
patient on heparin and aspirin should at least raise the
question of hemorrhage into the wall of the coronary. In
this patient’s case, the partial thromboplastin time was
astutely checked and found to be low, and the symptoms
resolved with increased heparin. Had the partial throm-
boplastin time not been low, repeat catheterization and
possible repeat angioplasty or placement of an intracor-
ornary stent would have been indicated.

On day 3, the patient developed an apparent pericar-
dial rub and a soft systolic ejection murmur at the left
sternal border. The rub is expected with a Q-wave
infarction, but the location of the murmur suggests that
it could not be attributed to dysfunction of the posterior
papillary muscle. This would have raised some concern about the possibility of a ventricular septal defect. Presumably the echo, which noted inferoposterolateral and distal right ventricular akinesis and a small effusion, did not detect evidence of mitral regurgitation, ventricular septal defect, pseudoaneurysm, severe wall thinning, or left ventricular enlargement. In general, it is reasonable to start captopril at about this time (day 4 or 5 after infarction) to reduce the chance of late ventricular enlargement, heart failure, and death. However, the benefits of captopril can probably be obtained when it is begun several weeks after infarction and need not be started when the patient is hemodynamically unstable. There is in any case some question as to whether women benefit from captopril in this setting.

On day 4 when the patient suddenly developed dyspnea and shock, the chances of survival were extremely low. In such cases, if the catheterization laboratory is open, the patient should immediately undergo catheterization. Echocardiography can sometimes be helpful in the catheterization laboratory or at the patient’s bedside if the laboratory or operating room is not yet ready. If the diagnosis is confirmed at the bedside, pericardiocentesis may be helpful if accompanied by massive infusions of colloid, crystalloid, or blood.

From a broader perspective, it would of course have been better had this patient not been a smoker and had she been able to moderate her hypertension, hypercholesterolemia, and obesity by dietary means. It might also have saved her life had she sought medical attention during the first few hours of her chest discomfort. Finally, she probably would have benefited from taking aspirin and replacement estrogens, despite the history of hypertension, smoking, and questionable history of

Fig 7. Histologic section of distal right coronary artery exhibits plaque fissure and mural thrombus.

Fig 8. Cross sections of the cardiac ventricles reveals a transmural infarct extending from the apex (inferior aspect) to the base of the posterior wall. The infarct is pale at the apex but hemorrhagic elsewhere.
stroke.17 These continue to be important issues in patient and physician education.

Pathology Discussion (L. Maximilian Buja, MD)
A complete autopsy, including an examination of the brain, was performed on this patient. There was no evidence of a cerebral aneurysm. Although there was a history of cerebrovascular accident, no objective documentation was obtained.

The pericardial sac was tense and contained 200 mL of clotted and fluid blood, indicating that the patient had a clinically significant hemopericardium. The heart weighed 380 g. The coronary arteries were removed from the heart, and multiple cross sections were cut and examined. Severe atherosclerosis of the left and right coronary arterial systems was identified. There was 60% to 70% stenosis of the left main coronary artery, 50% to 70% stenosis of the left anterior descending coronary artery, 60% to 70% stenosis of the left circumflex coronary artery, and 50% to 70% stenosis of the proximal right coronary artery. The proximal PTCA site in the mid-right coronary artery showed occlusion by thrombus superimposed on an 80% residually stenotic plaque with plaque hemorrhage and medial dissection (Figs 3 through 7). The distal PTCA site in the distal right coronary artery showed 50% residually stenotic plaque with a plaque fissure and a small mural thrombus (Figs 3 through 7). There was 70% stenosis of the posterior descending branch and 60% stenosis of the left ventricular branch of the right coronary artery.

Histologically, the infarct contained degenerating neutrophils and a beginning granulation tissue formation consistent with a 5- to 7-day-old lesion.
There were no valvular or congenital lesions. Multiple cross sections of the cardiac ventricles showed significant alterations. The left ventricular wall was thickened indicating hypertrophy in response to chronic hypertension. There was a large recent hemorrhagic transmural myocardial infarct, approximately 5 to 7 days old, involving the inferoposterior free walls and septum of the left and right ventricles (Figs 8 through 10). There was a rupture in the paraseptal left ventricular free wall with hemorrhage in the epicardium. This lesion was responsible for the hemorrhage in the pericardial sac.

Cardiac rupture is the most dramatic complication of acute myocardial infarction, occurs in 1% to 5% of cases, and has been reported in up to 15% of fatal acute myocardial infarctions. It has the following characteristic features, almost all of which were seen in this patient: it most commonly involves the free wall of the left ventricle with a transmural infarct involving more than 20% of left ventricle, and it most frequently occurs in hypertensive patients, women, the elderly, and patients with their first episode of myocardial infarction. It occurs anytime during the first 10 days to 2 or 3 weeks following the acute myocardial infarction but most commonly between first and fifth day.

Factors thought to predispose to cardiac rupture include thinness of the apical wall, marked intensity of necrosis at the terminal end of the blood supply, poor collateral circulation, and shearing effect of muscular contraction against an inert and stiffened necrotic area.

This patient was treated with a combination of thrombolytic therapy (intracoronary urokinase) and PTCA in an effort to restore right coronary arterial patency to achieve reperfusion of ischemic tissue and salvage myocardium that had not yet undergone irreversible changes. Both of these treatment modalities have been shown to increase patient survival after acute myocardial infarction. Thrombolytic therapy has been shown to reduce patient mortality from acute myocardial infarction especially if administered early, and even if it is administered late after the so-called “window of opportunity,” which is traditionally up to 6 hours after onset of sign and symptoms of acute myocardial infarction. Despite this overall decrease in mortality, several studies have shown that there is an increased risk of cardiac rupture when thrombolytic therapy is administered late (more than 12 hours after onset of symptoms). This patient was brought to the catheterization laboratory 3 hours after admission to the emergency room. The exact time period after onset of her symptoms is not clear. However, the myocardial infarct was histologically 5 to 7 days old, which indicates that irreversible myocardial damage may have occurred several hours before starting thrombolytic therapy and coronary angioplasty.

PTCA per se does not appear to increase the risk of cardiac rupture. In one study, cardiac rupture was established as the cause of death in only 2 of 614 patients treated with coronary angioplasty for acute myocardial infarction, both with failed angioplasty. This rate is much lower than 1.5% to 8% estimates of cardiac rupture following fatal acute myocardial infarct where no prevention treatment was carried out.

The finding of a hemorrhagic infarct is consistent with reperfusion secondary to thrombolytic therapy and/or coronary angioplasty. Hemorrhagic infarcts occur almost exclusively in association with thrombolytic therapy or revascularization therapy. Patients with fatal acute myocardial infarcts without interventional therapy almost always have nonhemorrhagic (anemic) infarcts.

Based on the above clinical and pathological findings, the following sequence of events may have occurred, which can explain the patient’s clinical course. The right coronary artery, which was severely narrowed (80% stenosis) by atherosclerotic plaques, suddenly became completely occluded, probably by thrombus, resulting in acute myocardial infarction. The right coronary artery was later opened by PTCA and thrombolytic therapy, leaving a residual stenosis of 80% in one site and 60% in the other site, but resulting in reperfusion of the already infarcted myocardium, turning the anemic myocardial infarct into a hemorrhagic infarct. Re-thrombosis of the proximal PTCA lesion of the right coronary artery later occurred, resulting in 100% stenosis. Histologic dating of the patient’s infarct indicates that irreversible myocardial damage had already occurred before starting therapy. Finally, rupture of the heart occurred in the area of the infarcted left ventricle, leading to hemopericardium and death from cardiac tamponade.

Dr. Casscells

Not much is known about infarct expansion or infarct healing. Histologic studies show that myocyte necrosis is accompanied by proteolytic degradation of the collagen. (Collagen, together with the myocyte motor endplates, gives the heart its tensile strength.) Transmural myocardial necrosis, inflammation and associated lysis of collagen; increased left ventricular afterload; and late reperfusion influence infarct expansion.

Obviously, there might be some benefit to inhibiting collagen degradation, although a study in the rat showed no benefit. Transforming growth factor-β (TGF-β) is reported to decrease experimental infarct size. TGF-β stimulates collagen synthesis. However, the early benefits in these models may be attributable to the antiinflammatory effect of TGF-β, which may reduce free radical injury. A remarkable reduction in infarct size has also been described from the infusion of basic fibroblast growth factor (FGF) after experimental coronary ligation. Basic FGF inhibits collagen synthesis but is a well known promoter of angiogenesis, a process that takes several days. The early benefits observed with basic FGF infusion, if confirmed, may instead relate to its recently reported vasodilator actions, mediated by endothelial synthesis of nitric oxide and by ATP-sensitive potassium channels. Heparin may also prove to enhance infarct angiogenesis and regrowth of the arterial endothelium but delay scar formation.

Did the angiogram miss severe left main disease? Not really. The patient had considerable atherosclerosis in the left coronary system, with compensatory enlargement of the whole vessel. This is typical of early or moderate atherosclerosis. The contrast between angiography and pathology is also a function of agonist- or fixative-induced constriction. Bypass and PTCA are appropriately performed for luminal stenosis. Unfortunately, hemodynamically noncritical plaques may rupture, especially if they are eccentric, inflamed, lipid rich, and covered by just a thin fibrous cap. Small plaques...
are common and so, on aggregate, account for more cases of coronary occlusion than do the occasional severe stenoses (see References 13 and 74). The latter have often stimulated collateral development, and thus are less dangerous. Identifying which plaques are likely to rupture is a difficult and important problem for future research.

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A 49-year-old woman with hypertension who deteriorates after acute myocardial infarction.
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