Family Practice Grand Rounds

Unstable Angina and the Intermediate Syndrome

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DR. WILLIAM NORCROSS *(Assistant Clinical Professor)*: Today's Grand Rounds will focus on the diagnosis and management of unstable angina. Dr. Holve will present the case. We are pleased to have Dr. Curtis from the Division of Cardiology as our discussant.

DR. RICHARD HOLVE *(Second-year family medicine resident)*: Mr. Y.B. was a 64-year-old Mexican-American man with a history of adult-onset diabetes mellitus, hypertension, osteoarthritis, peptic ulcer disease, multiple abdominal and spinal surgeries, and depression. Therapy at the Family Medical Center had primarily been directed toward improved diabetic control, management of joint pain, and psychosocial issues.

The patient was seen a month prior to his death. He had experienced left wrist pain for which he had taken up to 10 aspirin a day with resultant burning epigastric pain. He was told to discontinue the aspirin and was placed on a regular schedule of antacids. One month later he went to the emergency room of a local hospital again complaining of epigastric pain. He was treated with meperidine and promethazine, started on cimetidine, and told to see his regular physician in the near future. Three days later he gave a history of several episodes of epigastric pain with occasional radiation to his neck, not associated with nausea, vomiting, or shortness of breath, and not related to ingestion or activity. His physical examination was unremarkable, but an electrocardiogram done while he was having pain showed anterior T wave inversions that resolved after sublingual nitroglycerin. The patient was felt to have angina and probable gastritis or peptic ulcer disease. He was treated with sublingual nitroglycerin in an attempt to assess the true frequency of his angina and continued on cimetidine. He was instructed to phone the resident on call if he had an increase in symptoms.

Overnight Mr. Y.B. had two to three episodes of dull retrosternal pain occurring both with activity and at rest, lasting up to 30 minutes, and now associated with a choking sensation. He was seen in the Family Medical Center and then admitted to the coronary care unit with the diagnosis of unstable angina.

At the time of admission his temperature was 98.8°F, blood pressure 110/60 mmHg, pulse 80 beats/min and respirations 16/min. He appeared tired and anxious but was in no acute distress. Examination of his neck revealed a normal jugular venous pulse with dominant A waves. Carotid pulse contours were normal, and there were no bruits. His breathing was unlabored, and examination of his lungs was unremarkable except for fine rales heard at the left base. The point of maximal impulse of his heart was 1 cm lateral to the midclavicular line, and there were no lifts, heaves, or thrills. S_1 and S_2 were normal, with a loud S_4 heard at the apex and a very soft S_3. There were multiple well-healed scars over his abdomen. Bowel sounds were normal, there was no organomegaly, and there were no masses or areas of localized tenderness. His peripheral pulses were all 2 plus, and there was no edema. The results of his neurologic examination were within normal limits.

The hematocrit was 45 percent; white cell count was 7,100/mm^3 with a normal differential; and platelets were 231,000/mm^3. The prothrombin time and partial thromboplastin time were normal. The

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sodium level was 128 mEq/L; potassium, 3.7 mEq/L; chloride, 93 mEq/L; bicarbonate, 28 mEq/L; and glucose, 494 mg/100 mL. The urea nitrogen was 30 mg/100 mL, and creatinine was 1.6 mg/100 mL. Serum glutamic oxaloacetic transaminase (SGOT) was 16 IU, lactic dehydrogenase (LDH) was 114 units/mL, and creatine kinase (CK) was 63 IU/L. His urinalysis was remarkable for trace proteinuria, 4 plus reducing substances, and negative ketones. An arterial blood gas test on room air revealed a pH of 7.44, a PO_2 of 66 mmHg, and a PCO_2 of 44 mmHg. His chest x-ray films showed a normal cardiac silhouette with normal pulmonary vasculature and no evidence of an infiltrate. His electrocardiogram showed anterolateral ST-T wave changes that were suggestive of ischemia or subendocardial infarction.

Treatment was begun with nitrates and beta blockers. During the next 48 hours he had several episodes of chest pain while sitting and eating despite intensive medical therapy. Serial creatine kinase values were within normal limits. On the second day after admission he had another episode of chest pain associated with a choking sensation, which was only partially relieved with nitroglycerin. An electrocardiogram showed new ST depression in chest leads V_3 to V_5. After achieving pain relief and normalization of his electrocardiogram, an emergency cardiac catheterization was performed. It revealed normal intracardiac pressures, high-grade proximal occlusion of the left anterior descending artery with multiple distal irregularities, 90 percent occlusion of the middle third of the right coronary artery, and high-grade proximal lesions of the circumflex artery. In view of the extensive proximal (surgically approachable) disease and continued angina with maximum medical therapy, the decision was made to proceed immediately with bypass surgery.

At the time of anesthesia induction the patient developed ventricular fibrillation and an emergency cardiopulmonary bypass was performed. Bypasses of the left anterior descending, right coronary, and obtuse marginal arteries were done. With difficulty the patient was weaned off the pump to intra-aortic balloon counterpulsation and intravenous pressor agents including nitroprusside, epinephrine, and dopamine.

Postoperatively his electrocardiogram showed new evidence of anteroseptal infarction. Additionally, a severe coagulopathy developed with significant blood loss. He was explored twice to ensure hemostasis at graft sites. On the second postoperative day he developed progressive hypotension despite maximum mechanical and pharmacological support. He died 38 hours after surgery.

DR. GUY CURTIS *(Assistant Professor of Medicine)*: I think Mr. Y.B.'s case serves as a good springboard for a discussion of unstable angina. There are many points we can note that might help in managing a similar patient in the future.

Unstable angina is a term coined fairly recently. Commonly used alternatives in the past include preinfarction angina, impending myocardial infarction, crescendo angina, acute coronary insufficiency, and status angiosus. Many have objected to these terms because they predict an outcome (as in preinfarction angina) that is not at all certain in many cases.

Many different pain patterns fall within the definition of unstable angina: (1) angina at rest, (2) angina of recent onset—usually within the preceding month, and (3) exertional angina with a changing pattern, ie, increasing frequency or severity of pain, increased autonomic symptoms associated with pain such as diaphoresis or dyspnea, or greater difficulty in achieving pain relief with medications. Many of these features were demonstrated in Mr. Y.B.'s course. Although his initial pain was somewhat atypical in that it was epigastric rather than the classic substernal location, he soon developed a changing pain pattern, pain at rest, and finally pain refractory to medical therapy.

In clarifying a diagnosis of myocardial ischemia, certain physical signs and electrocardiographic changes may be helpful. Findings on the cardiac examination that may be discerned only in the presence of acute myocardial ischemia and absent when the patient is pain free include an atrial (S_4) or ventricular (S_3) gallop (secondary to decreased myocardial compliance), a mitral regurgitant murmur (usually due to papillary muscle dysfunction), and paradoxical (reverse) splitting of the second heart sound (ischemia-induced delay in ejection from the left ventricle and late closure of the aortic valve).

Early changes in Mr. Y.B.'s electrocardiogram (2-mm depression of the ST segments in the anterior chest leads) are characteristic of myocardial

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one of the cornerstones of therapy in unstable angina.[11] Mr. Y.B.'s dose of metoprolol (propranolol, of course, may also be used) was increased until he became mildly hypotensive. A heart rate of 50 to 60 beats/min is evidence of good blockade. Calcium channel blockers such as verapamil and nefedipine will be available soon.[12] They have been shown to reverse coronary artery spasm and to reduce oxygen consumption in ischemic myocardial segments, thought to be a significant component of the chest pain of many of these patients.[13] Antiarrhythmic therapy should be begun as needed. Antihypertensive treatment is important (sometimes even in normotensive patients) to reduce afterload and myocardial oxygen consumption.[14] Anticoagulant therapy with heparin has not been shown to be effective in limiting infarct size in most controlled studies, and few cardiologists feel that it has a role in the management of these patients.[15,16] In some institutions with a large volume of extremely sick patients, there are teams available to aggressively treat severe angina with intra-aortic balloon counterpulsation. This device reduces oxygen consumption and decreases the work of the heart by decreasing systolic workload while maintaining diastolic pressure and perfusion.[17] Intra-aortic balloon counterpulsation is often most useful in the interim before surgery.

It was clear at the time of admission that Mr. Y.B. had unstable angina. After observation in the coronary care unit, we felt he fit into a subcategory termed the "intermediate syndrome."[18] This classification refers to patients who have persistent chest pain and electrocardiographic changes but no enzymatic (creatine kinase, LDH, SGOT) evidence of myocardial necrosis. This patient's creatine kinase readings were all normal despite his pain and repeatedly abnormal electrocardiograms. Our impression was he had probably had a small infarct which caused a rise in creatine kinase that we missed or that was simply not large enough to be clinically detectable. We assumed he had a large area of myocardium at risk for ischemia, and we treated him as aggressively as possible. Generally, if control of chest pain is not achieved in 24 to 48 hours with the measures outlined above, we proceed to cardiac catheterization and angiogra-

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phy. If the coronary anatomy is suitable for bypass, we proceed with surgery. If pain control is achieved within 24 to 48 hours, the catheterization is performed electively within the next week. The decision of whether to go on to surgery is then made after considering the clinical course, coronary anatomy, and other factors.

Angiography demonstrated Mr. Y.B. to have severe proximal three-vessel disease. The widely agreed upon indications for bypass surgery include (1) left main coronary artery narrowing of 50 percent or greater, (2) severe proximal three-vessel disease, and (3) persistent chest pain or other signs of unremitting ischemia (electrocardiographic changes, refractory arrhythmia, or intractable heart failure secondary to an operable lesion).[19] Contraindications to surgery are (1) no significant coronary lesions on angiography (pain secondary to spasm), (2) left ventricular ejection fraction less than or equal to 30 percent or an end-diastolic volume greater than 125 cc/m² of body surface area, and (3) pain responsive to medical treatment in a patient with distal coronary lesions not amenable to surgical treatment.[19] Mr. Y.B. fell into the first group, and surgery was undertaken on that basis.

There are several reasons for the unsuccessful outcome in this case. The patient had severe coronary artery disease, and it is clear that mortality is higher in patients with symptoms that are refractory to medical therapy. The most significant factor in this patient's death was the episode of ventricular fibrillation that occurred during anesthesia induction. The surgeons rapidly connected him to the heart-lung bypass pump during cardiopulmonary resuscitation, but perfusion must have been inadequate for 7 to 8 minutes, with resultant myocardial and central nervous system damage. Additionally, lack of complete heparinization prior to heart-lung bypass probably caused some defibrination of his blood and contributed to his coagulopathy. Despite good grafts his chances of survival were slim, and at autopsy large infarcts were noted in the anterior, posterior, and lateral ventricular walls.

DR. ELIZABETH WISE *(Third-year family medicine resident)*: The angiographic description of extensive disease in all vessels makes me wonder whether technically successful surgery would have been able to alleviate his pain?

DR. CURTIS: The decision to operate must be made in consultation with a surgeon. We rely on his judgement and experience in evaluating whether an operation is technically feasible. The feeling in this case was that the patient's pain could be relieved with surgery. Although it was not expected to be an optimal result, we have had acceptable results in patients with similar lesions.

The National Heart, Lung, and Blood Institute's Cooperative Study Group[19] compared intensive medical therapy and urgent coronary bypass surgery in the acute management of patients with unstable angina. Two hundred eighty-eight patients at nine medical centers were randomized to medical or surgical treatment groups between 1972 and 1976. The groups were comparable with respect to clinical, electrocardiographic, angiographic, and left ventricular function characteristics. Those who were not surgical candidates or those in whom there was a clear indication for one type of treatment over another were excluded from the study. Patients similar to Mr. Y.B. who are refractory to medical therapy were not included in this study because surgical therapy is clearly indicated if anatomically possible.

Figure 1 from this study shows that overall (patients with one-, two-, and three-vessel disease), there was not a significant difference in in-hospital or late mortality between medical and surgical groups. Interestingly, in the last four years of the study, hospital mortality dropped significantly for both groups. Myocardial infarction was significantly higher in surgically treated patients during their hospital stay in the first two years of the study, but in the last three years this difference became nonsignificant. I believe these changes in the infarction rate over time reflect improvements in both medical and surgical treatment.

Figure 2 shows that during the two years after discharge from the hospital, angina was much more common in the medically treated group with one-, two-, or three-vessel disease. (Class III angina occurs with minimal exertion, class IV angina occurs at rest.)

About the same percentage of patients return to work from both medically and surgically treated groups, but the latter tend to do so more comfortably. There is little question that surgery is far more effective than medical treatment in relieving symptoms in this group of patients. One other factor to consider is that while long-term mortality

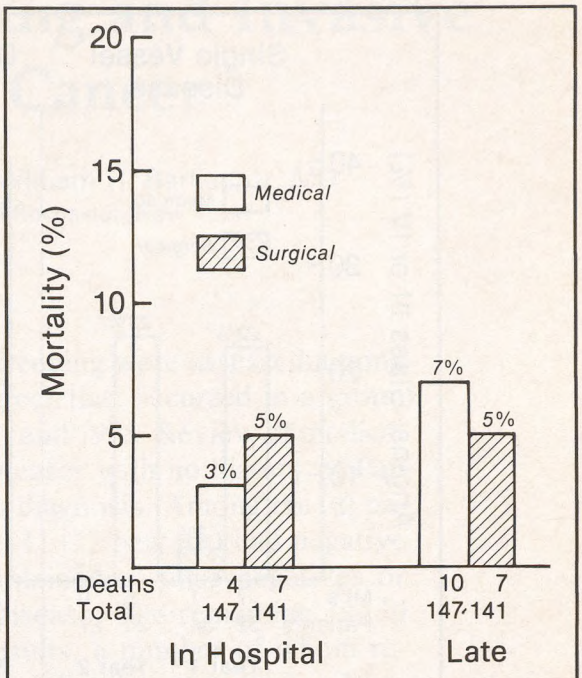

Figure 1. In-hospital and late mortality rates of medically and surgically treated patients From Unstable Angina Pectoris Group.[19] With permission from the American Journal of Cardiology

was comparable between the two groups, about 30 percent of patients "crossed over" after one to two years of medical therapy and underwent coronary artery bypass grafting.

In summary, the results of this study and our experience show that intensive medical therapy is indicated for patients with unstable angina and that there is a reasonably well-defined subgroup of patients who will benefit from early bypass surgery. It has been demonstrated that these people can be managed acutely with medical therapy. Medical therapy may be continued as long as it is effective in controlling symptoms. Elective surgery may be performed after chest pain is controlled, or postponed until angina recurs without increased long-term morbidity or mortality.

Finally, always remember that treatment must be selective with regard to the patient and his lifestyle. If the patient is a manual laborer who cannot support himself or his family at a sedentary job, you might be doing him a great disservice with medical therapy. Our recommendations about treatment carry a great deal of weight, but it is the

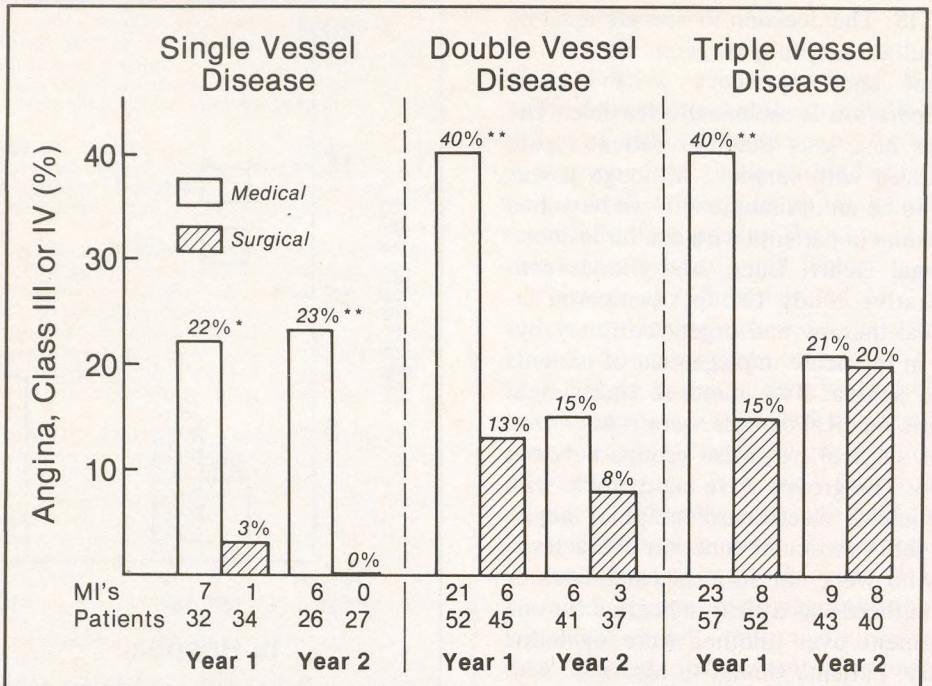

Figure 2. Worse degree of angina (Class III or IV) at any follow-up during the first and second years after randomization. MIs, myocardial infarctions; *$P < 0.05$; **$P < 0.01$
From Unstable Angina Pectoris Group.[19] With permission from the American Journal of Cardiology

patient who must make the final decision and live with that choice.

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