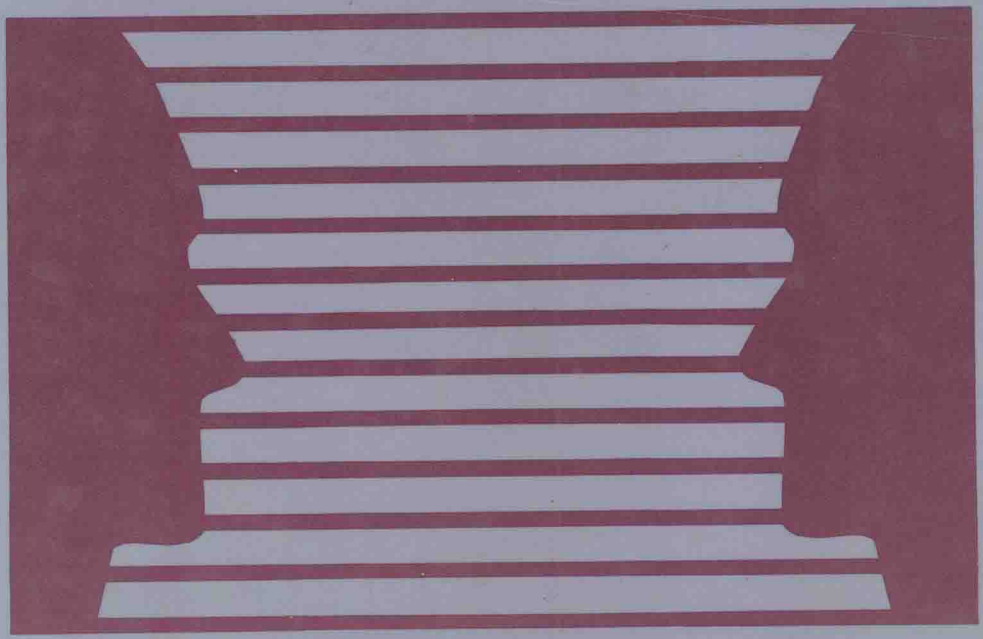
DEBATES IN MEDICINE



Gitnick
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DEBATES IN MEDICINE

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Preface

The study of medicine evolved out of controversy. It should not surprise us, then, to find that scientific literature is based on a history of controversy, nor that controversy remains such a fundamental part of this discipline. Regardless of our area of clinical or laboratory study and regardless of whether we are discussing treatment, causation, or pathophysiology, there will be differences of opinion, conflicting data, and contradictory concepts. Through the thoughtful study of all sides of these controversial issues, the astute clinician or student can become exceptionally well versed in medicine.

This volume devotes a chapter to each of ten prominent controversies. The associate editors and I have chosen contributing authors who are experts in particular areas, and have instructed each to provide the very best case to be made for a given position. In some instances, as is sometimes the case with oral debates, authors have been asked to present a view that may be opposite to the one they espouse. However, in most cases, the positions presented herein are consistent with the views expressed by the authors in their previous publications and public statements.

At the end of each chapter, we provide editorial remarks in the way of a brief summary and an evaluation of the strengths and weaknesses of the arguments. Our comments should also be taken as opinion, which has been said to be composed of a minimum of fact combined with prejudice and imagination. Nevertheless, we have tried to tie together the differing opinions and guide the reader through our current state of ignorance.

I am indebted to the associate editors and contributing authors who diligently developed their arguments and who were exceptionally cooperative in efficiently and promptly sending their chapters to me.

I wish to thank the associate editors who worked closely with me in the development of this volume. They are H. Verdain Barnes, M.D., Thomas P. Duffy, M.D., and Nicholas Fortuin, M.D. I wish to thank Mrs. Susan Dashe, who coordinated the development of this volume, and Mr. James Shanahan of Year Book Medical Publishers, Inc.; his support was of great assistance. Most readers will find opinions in this volume with which they greatly disagree. It is our hope that this disagreement will stimulate thought and insight, that knowledge of all sides of the controversies will expand basic knowledge of the diseases discussed, and that the reader will not only learn from but will also enjoy this book.

Gary Gitnick, M.D.

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Coronary Bypass Surgery or Angioplasty Should Be Used for Patients With Stable Symptoms

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Affirmative

Karl E. Hammermeister, M.D.

The answer to this problem is clearly yes—in some patients. The problem has been to determine through valid studies which subgroups of patients will benefit through prolongation of life and/or improvement of symptoms and functional capacity. A second, related problem has been to develop and validate inexpensive, safe, noninvasive techniques to identify such patients. The solutions to both of these problems are only partially known. This essay will discuss the available information relevant to the first problem.

First, it might be well to define what is meant by stable symptoms. Some patients will be severely limited by ischemic myocardial symptoms and yet be in a stable phase of their disease. Because there is abundant evidence that revascularization either by angioplasty in selected patients or by coronary bypass graft surgery (CABG) can improve symptoms and increase exercise capacity, there is little controversy about what to do in such patients; a revascularization procedure should be recommended if the anatomy is suitable and the operative risk acceptable. The greatest difficulty lies with those patients whose ischemic myocardial symptoms are mild or even nonexistent. Proponents of an aggressive approach point to the relatively high incidence of stable, mild symptoms or no symptoms in patients experiencing sudden cardiac death.

There are three major reasons to recommend any therapy: (1) to improve symptoms, (2) to preserve health and functional capacity, and (3) to prolong life. The remainder of this essay will concentrate primarily on the third indication, as patients with mild or no symptoms are unlikely to experience improvement, and little is known about the second indication. Because there are few or no data on the effect of angioplasty on survival, the discussion will concentrate on the results of CABG.

Our modern understanding of coronary death being due to ischemia arose following the description by Herrick in 1912[1] of acute myocardial infarction as being the result of obstruction of the coronary artery and the observation by Wood and Wolferth in 1931[2] that angina pectoris is associated with electrocardiographic evidence of ischemia. Soon thereafter, the first surgical procedures to correct myocardial ischemia were attempted. Although procedures such as pericardial poudrage with talc to stimulate anastomoses between the pericardium and epicardium, wrapping the omentum around the heart to provide blood flow to the epicardial surface from the mesenteric vessels, and internal mammary artery ligation were reported to result in symptomatic relief in the majority of patients, there were few controlled studies. The exception to this statement is the internal mammary artery ligation, where two controlled, blinded studies using

sham operations showed the procedure to have no benefit.[3, 4] These are two of the few instances in which it has been possible to use blinding and sham procedures to control for the placebo effect of a surgical procedure, something none of the modern randomized trials of CABG have been able to do. These procedures, like the internal mammary artery implantation procedure (Vineberg procedure), were doomed to failure because the amount of increase (if any) in blood supply to the myocardium was small in relation to the need.

However, soon after the introduction of the saphenous vein aortocoronary bypass operation by Favalaro in 1967,[5] it was possible to demonstrate that the surgically created conduits could carry 50% or more of the myocardial blood supply. This, coupled with the fact that the operation could be performed at a low operative mortality, led to the widespread conviction in the early 1970s that this was a life-saving procedure. This conviction was reinforced by nonrandomized, observational studies showing that virtually all subgroups except those with single-vessel disease involving the right or circumflex coronary arteries had improved survival with surgical therapy as compared with medical therapy.[6] It was not widely recognized then that this and many other similar studies did not adequately take into account differences between medically and surgically treated patients.

Needless to say, there was much disappointment and controversy when the results of the first large randomized trial comparing survival of medical and surgical therapy in patients with stable angina, the VA Cooperative Study, showed improved survival only in the small subgroup with left main coronary artery stenosis.[7, 8]

This introduction has deliberately set the scene by picking studies showing extremes in their results: (1) the very early Cleveland Clinic study purporting improved survival in the majority of patients operated on, and (2) the first reports of the VA Cooperative Study showing survival benefit only in a minority of their patients. It is now widely recognized that selection bias (selecting better-risk patients for surgery) strongly influences the outcome of nonrandomized studies, particularly if little or no attempt has been made to adjust for baseline differences. However, it is not generally accepted that randomized trials may present too conservative a viewpoint, primarily because the patients selected are not representative of the general population of patients with coronary heart disease being considered for CABG. This latter theme will be developed in more detail after presentation of outcome data from the four large randomized trials comparing surgical vs. medical therapy for coronary artery disease (CAD); these randomized trial data will be supplemented with data from observational studies where adjustments for baseline differences have been made.

Stable Angina Pectoris

Left Main Coronary Artery Obstruction

The first large, randomized, controlled study testing the hypothesis that surgical relief of myocardial ischemia prolongs life was the VA Cooperative Study. The first report of outcome from this study was on the relatively small subgroup with left main coronary artery stenosis (diameter reduction $> 50\%$), showing dramatically improved survival in the surgically treated group.[7] All subsequent studies in which this issue was seriously addressed have confirmed the result of the VA Cooperative Study. It is now generally accepted that patients with significant left main coronary artery stenosis should have CABG, regardless of whether symptoms are present, providing that the patient's general medical condition allows the surgery to be accomplished at a reasonable operative risk.

Single-Vessel CAD

All of the randomized trials and most of the observational studies show no improvement in survival in patients with single-vessel disease, because survival of patients with single-vessel disease is not appreciably different from that of the general population of similar age. The controversy over the effect on survival is in the patients with two- and three-vessel disease. Even here there is abundant evidence that CABG relieves symptoms that cannot otherwise be controlled with medical therapy. Most will agree that limiting angina refractory to medical therapy in patients with graftable distal vessels and who are acceptable operative risks should be treated with CABG or percutaneous transluminal coronary angioplasty (PTCA) if appropriate.

Three-Vessel Coronary Artery Disease

At first glance the randomized trial data concerning patients with three-vessel disease may seem confusing and conflicting. The initial report of the VA Cooperative Study showed no survival benefit for operative therapy of three-vessel disease,[8] whereas a later report did[9]; the European Coronary Surgery Study (ECSS) showed a marked reduction in mortality in the patients with three-vessel disease who were bypassed,[10] but the Coronary Artery Surgery Study (CASS) conducted in the United States and Canada showed no overall difference in survival.[11] Even now the conflict in the results of the European and VA studies on the one hand and CASS on the other is not easily resolved. Let us consider some of the issues.

The initial report of the VA study in 1977 showing no difference in survival between medical and surgical therapy was labeled by its authors as preliminary[8] but was regarded by many at that time as the "final word."

In a subsequent analysis, the VA investigators eliminated the data for the three hospitals with an average 23% operative mortality (which contributed only 13% of the patients to the study) and found a statistically significant improvement in survival for surgically treated three-vessel disease for patients operated on at the ten remaining hospitals, with a 3.3% operative mortality.[9] This post hoc analysis of a subset of patients selected on the basis of outcome clearly violates an important study design principle. On the other hand, an operative mortality of 23% is extraordinarily high, even for that era, and suggests technical problems in the performance of the surgery. Thus, I maintain that there is some validity to this analysis.

Other subgroup analyses from the VA study have shown improved survival with operative therapy in an angiographic high-risk subgroup and the high-risk tercile defined by noninvasive criteria.[10] The angiographic high-risk patients had three-vessel disease and abnormal left ventricular function; this group is similar both in angiographic characteristics and treatment effect to the group with three-vessel disease and abnormal left ventricular function in CASS. The noninvasive risk terciles were defined by four noninvasive variables: history of hypertension, prior myocardial infarction, ST segment depression on the resting electrocardiogram, and New York Heart Association functional class. The patients in the high-risk tercile who had two or three of the strongest risk factors (ST segment depression, history of myocardial infarction, history of hypertension) had significantly better survival when treated surgically. Thus, although the preliminary report of the VA study showed no survival benefit, longer follow-up and subsequent analyses have been able to identify several subgroups where survival is improved by CABG. It is important to note that the survival differences in all subgroups where surgery initially provided better survival appear to be narrowing after 8 years of follow-up.[10] This reemphasizes the fact that this is a palliative operation; the basic pathologic process, obstructive atherosclerosis, continues to advance in the native coronary arteries and develops de novo in the vein grafts.

The ECSS is a randomized trial comparing medical with surgical therapy in 768 men under the age of 65 years with angina pectoris of 3 months' duration or longer.[11] Patients with severe angina not controllable medically, or left ventricular ejection fraction less than 0.50, or single-vessel CAD were excluded. An exact comparison of symptomatic status between patients in the European study and the VA study or CASS is not possible because of the way the data were recorded; nevertheless, it seems likely that the majority of patients in this study may have had mild angina because of the exclusion of those with medically uncontrollable angina. Thus, in this regard the ECSS patients appear to have been similar to the CASS patients. Yet the results of the two studies are markedly different. The European study has shown a 67% reduction in mortality at 5 years for the surgically treated patients with three-vessel disease (6%) compared with medically treated patients (18%). This marked difference remains at 8