CORONARY ARTERY SURGERY 1975

MEDICAL GRAND ROUNDS

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CONTENTS

Since its inception eight years ago, coronary artery surgery has rapidly risen to its present position of one of the most common surgical procedures in the United States, yet well designed studies of the efficacy of the procedure are notoriously few. Physicians caring for patients with coronary artery disease consequently have to make decisions as to the propriety and timing of surgery based on the multitude of less well designed studies which are currently available. Since this data is rapidly growing and frequently is apparently conflicting, these therapeutic decisions are often frustrating. This report summarizes our current state of knowledge and attempts to delineate the factors responsible for conflict. In the first section, I will discuss the specific procedure. In the second section, I will discuss objective studies of its effect. Finally in the third section, I will discuss factors relevant to making a surgical decision.

OPERATIVE PROCEDURE

Aortocoronary bypass using the saphenous vein was first performed in 1967 (1,2)*, at approximately the same time that direct internal mammary-coronary artery anastomosis was first performed (4). Considerably more saphenous vein grafts are now used than internal mammary grafts with the internal mammary usually reserved for low flow situations where vein graft patency is felt to be threatened. When the internal mammary is used, it is generally in conjunction with saphenous vein grafts placed to other coronary arteries. The advantages of the internal mammary over the saphenous vein are its high patency rate and the likelihood that long-term prognosis is better with an arterial rather than venous conduit. Its disadvantages are its limited number, limited flow capacity, ability to reach only the anterior surface of the heart, and increased operating time.

Operative Mortality

Overall surgical mortality for coronary bypass now averages about 5%. As expected and as shown below, this mortality varies between institutions.

*The initiation of vein bypass surgery is generally attributed to the authors of these reports in Cleveland and Milwaukee. However, in 1973 a case report was published claiming the first vein bypass graft was performed in Houston in 1964 (3).

Surgical Mortality

Ref. #	1967	1968	1969	1970	1971	1972	1973	1974
1	-----12%-----							
5		----------3%----------			1.6%	1.2%		
6				----------11%----------				
7							-----0%------	
8				----------6%---------				
9			---------6.5%---------					
10		---------6.5%---------			4.5%			
11					------7%------		0.8%	
12		-----12%-----		6%	3%	2.5%	1.5%	
13				----------3.5%----------				
14						------6.6%----		
15				----------4.4%----------				
16					12%			
17				10%	7%	6%		
18					------5.5%-----			
19				----------5%----------				
20*				----------5%----------				
21*					------0.6%-----			
VA (22)						7%	6%	4%
N.O. (23)	- - - - - - - - - - - - - - - - - -					----------8.7%---------		

*Internal Mammary

In those institutions reporting their experience over a period of years, the mortality decreases with time. This drop in mortality probably reflects increased technical expertise, but more importantly, greater experience in patient selection. The last two mortality rates in the table are particularly interesting since they represent an unbiased report of a group of surgical units, one the entire Veterans Administration system and the other, all of the hospitals in New Orleans.

Risk Factors for Operative Mortality

Undoubtedly, the most important factor determining surgical risk is resting left ventricular function. Second in importance is the presence of left main coronary disease. Unstable angina, number of vessels diseased, previous propranolol therapy, age, diabetes all contribute much less to operative mortality or are insignificant.

Left ventricular function. The drastic effect of poor resting ventricular function on operative mortality is illustrated below (15,24-26).

Ejection Fraction %	Operative Mortality %
Seattle VA (15)	
< 33	33
> 33	3
Peter Bent Brigham (24)	
< 50	35
> 50	3
Penn State (25)	
12-30	25
31-40	12
41-50	4
> 50	4
Duke (26)	
< 25	55
> 25	4

The measurement of ventricular function in these studies is the ejection fraction, which is the ratio of stroke volume to end diastolic volume. The lower limit of normal for the ejection fraction is 50%. Caution should be used in reading other studies comparing ejection fraction to mortality because some authors have used variations in the conventional technique of calculating ejection fraction, which results in grossly different values for this measurement.

Left main coronary disease. Left main coronary disease is found in about 4% of patients with coronary disease (28-32,40), and when present contributes significantly to an increase in operative mortality. Early mortality figures were as high as 31% (26,30); but with improved surgical technology (33), this figure has decreased to about 10% (28,29,31,34-40).

Unstable angina. The first attempts to operate on patients with unstable angina resulted in a higher mortality than surgery for stable angina by the same surgical group (41,42). However since initiation of the practice of stabilizing patients medically prior to surgery, this mortality has dropped (41,43-45) so that it is now about the same or only slightly higher than that for stable angina (27,43-49).

Number of diseased vessels. The number of diseased coronary arteries or the number of grafts placed generally has little influence on mortality (6,8,11,12,15,22,23,26,55). There is a growing sentiment among surgeons, however, that more important than the number of diseased vessels or grafts placed is that the number of grafts equal the number of diseased arteries, i.e. "complete revascularization" (12,55,56). However, one of the earliest groups to call attention to the possible increased mortality of "incomplete revascularization" has recently reviewed their experience with a larger number of patients and now finds no significant difference between complete and incomplete revascularization (6,26).

Propranolol. Chronic propranolol therapy up to the time of surgery was once accused of increasing surgical mortality, leading to the suggestion that such therapy be discontinued at least 2 weeks prior to therapy (58). However, more recent and complete reports do not substantiate this (14,59,60); and in the light of the discovery of the propranolol withdrawal syndrome (61, 62), patients are now kept on propranolol up to the time of surgery.

Age and diabetes. Older patients, especially those over 70 years of age, have a higher surgical mortality (17,23,63,64); however in at least one study, this higher mortality was attributed to a much higher incidence of poor ventricular function in this older group (63). Diabetes does not appear to significantly contribute to surgical risk (65,66).

Post recent myocardial infarction. Usually performed in desperation for post-infarct complications, surgery in the immediate post myocardial infarction period carries a mortality of 20-100% (50-52). The beneficial effect on mortality of delaying surgery after infarction is shown below (57).

Days post infarct	Surgical mortality %
0-7	38
8-30	16
31-60	6
> 60	6
no infarct	4

It is pertinent that when surgery is performed routinely immediately upon diagnosis of an infarction, surgical mortality is reasonable, 6% and 10% in 2 studies (53,54). These studies are complicated by poor definition of infarction, however, since surgery was undertaken immediately when infarct was thought to be in progress, eliminating the conventional diagnostic criteria of characteristic EKG and enzyme changes.

Morbidity

Perioperative infarction. Myocardial infarction occurs in about 10% of coronary bypass operations with the range reported to be 4-21% (5,8,13 16,17,19,56,64,67-75). Despite the popular thought that infarction during surgery is more benign than the usual non-surgical infarct, the reported perioperative infarction mortality of 20-40% (8,9,55,64,73,74) suggests that it carries the same significance. Infarction is probably the cause of most immediate surgical deaths and is associated with almost all deaths in the 1-30 day postoperative period (16,68,76). Although infarction is definitely associated with a higher than usual incidence of graft occlusion, about as many patent grafts as occluded grafts are found to the infarcted area (19, 76), and about 25% of infarcts occur in areas supplied by ungrafted vessels (70,76). Graft occlusion does not necessarily cause infarction - in one study only 15% of graft occlusions resulted in infarction (77).

Acceleration of native disease. By 6 months to a year, bypass grafting causes an increase in the progression of proximal coronary artery obstruction in about 60% of cases (range 20-73%) compared to 15% (range 10-23%) in ungrafted arteries in the same patients, and leads to proximal occlusion in about 50% (range 20-63%) compared to 5% (range 2-8%) in ungrafted arteries (78-85). Although the rate of progression is slightly lower in arteries with non-patent grafts (79,80,82), the combination of proximal vessel and graft occlusion does cause a net decrease in perfusion to some segments after

surgery (82). When graft closure occurs in the immediate postoperative period, proximal artery occlusion is very common, occurring in 12/13 cases in one study (82). This combination of obstructed graft and proximal artery is frequent in early postoperative deaths (76). Grafting affects the atherosclerotic process little if at all in the artery distal to the anastomosis (78,81,82,84).

Graft patency. In general, 10% of vein grafts occlude within 2 weeks of surgery and an additional 10-20% occlude between 1 month and 1 year for a 1 year patency rate of 75% (range 60-86%) (5,12,17,55,64,74,75,77,86,87). After 1 year, occlusion is rare and when it does occur, can be predicted by severe stenosis at the 1 year catheterization study (86,89). Early occlusion is due to thrombosis (76) and late occlusion to intimal fibrosis (76,88,90-93). Atherosclerosis in the vein graft has been reported, but has not yet been shown to cause obstruction (76,90,93).

Early occlusion is strongly dependent on the size of the coronary artery distal to the obstruction and the amount of myocardium it perfuses (94,95). In one study, a distal coronary less than 1.5 mm in diameter resulted in an 80% early occlusion rate (94). Coronary artery diameter can be accurately assessed from coronary angiography, although this accuracy diminishes when the vessel is perfused by collateral (95). Graft flow measured at surgery is also a good indicator of early occlusion with 40 ml/min. commonly considered the separation value between a good and bad result (87). In one study, all flows less than 25 ml/min. were closed 2 weeks later while all flows over 45 ml/min. were open (96). The cause of occlusion between 1 month and 1 year, i.e. the cause of intimal fibrosis, is unknown. The occlusion rate of 10-20% seems related little if at all to the factors responsible for early occlusion (96). Neither early or late occlusion appears related to specific coronary artery grafted, diabetes, hypertension, or occlusion in another graft in the same patient (66,87). The patency of internal mammary-coronary artery anastomoses is about 97% (4,20,21). Angiography of the internal mammary artery at cardiac catheterization is advisable to assure a healthy native vessel (97).

IMPROVEMENT IN CARDIAC PATHOPHYSIOLOGY BY SURGERY

Cardiac physiology in the patient with coronary artery disease must be evaluated in light of the unique ability of the circulatory system to regulate its function over a wide range in response to the activity of the patient. Normally between rest and maximum exercise, systemic oxygen delivery increases about 15x, heart rate about 3x, and coronary blood flow 3-4x. With the onset of progressive heart disease, the first effect is to gradually diminish the maximum capacity of the heart without affecting its resting function. Then only after this exercise reserve is lost, is resting function diminished.

This of course, parallels the clinical course of most patients with progressive disease. In testing cardiac function, tests are done in both the resting and exercising (or exercise equivalent) states. At rest, specific aspects of coronary flow and ventricular function are easier to study and measurements are more precise, yet they are only abnormal if disease is severe enough to diminish resting function. Thus, surgery may greatly improve the exercise capacity of a patient while not affecting some measure of his resting function. On the other hand, studies during exercise evaluate maximum capacity and therefore are more sensitive to change. However, they are usually more indirect, and specific factors of ventricular function or coronary flow cannot be evaluated as precisely.

Myocardial Blood Flow

Normally, resting coronary flow to the left ventricle averages about 125 cc/min. Vein graft flow measured directly immediately after placement, averages about 65 cc/min. (range of averages 57-60 cc/min.) (20,65,96, 98-100), while internal mammary flow averages about 45 cc/min. (range of averages 23-68 cc/min.) (20,99,100). These values do not necessarily imply a proportional increase in the overall myocardial flow since the graft flow may compete with the native coronary flow, and the values may vary considerably from their true resting value depending on the degree of extended reactive hyperemia to surgery (102,103). However when overall resting flow to ischemic areas is compared pre and post graft, flow increases up to 100%, especially when the graft is placed to a totally occluded vessel (99,104,105). Furthermore, when the hyperemic potential of the coronary system is tested by exercise, vasodilators, or adrenergic agents, patent grafts have been shown to return this potential to normal (100,104-109). The hyperemic potential of the internal mammary graft is uncertain, with evidence that it has none (100) and evidence that it has the same as the vein graft (110). This difference is probably related to artery selection and possibly to presence or absence of spasm during measurement.

Resting Ventricular Function

Considerable controversy exists over whether bypass surgery improves resting ventricular function. To presume that it does implies that at the time of the relatively elective catheterization, ischemia has progressed to the point of inhibiting contractile function, yet not to the point of causing tissue death, a situation which then could be reversed by revascularization. Disagreement over the reversibility of function can be partly resolved by clarification of whether ventricular segment or overall function is being analyzed, conditions of postoperative study, and patient grouping. Approximately 50% of patients studied for angina have some ventricular dysfunction. Of the preoperatively dyskinetic segments, about 20% will improve their contraction postoperatively (75,81,111,112), although one group reports a much higher rate of improvement (113,114). Conversely, segment function deteriorates at rates ranging from 15-40%

(75,81,111). Improvement usually occurs before 2 weeks after surgery and remains at 1 year, while deterioration occurs both early and late generally paralleling the time of graft occlusion (111). Factors bearing on segment improvement or deterioration appear to be acuteness of preoperative ischemia, preoperative and perioperative infarction, graft patency, and severity of preoperative hypokinesis (75, 81,111,113-119). Overall ventricular function as studied by the ejection fraction (ratio of stroke volume to diastolic volume) is not consistently changed at 1 year (75,101,111,116,120-124). The ejection fraction usually does not change even in patients where segment function changes, apparently because of compensation by non-ischemic portions of the ventricle (111,116,123,125). Increases in the ejection fraction at 2 weeks post surgery have been reported (113,114,119), but the implication that ventricular function is improved has been criticized on the basis of evidence of a high degree of stress and consequent adrenergic stimulation at the time of study (125,126).

In an attempt to better predict which ventricular segments will improve after surgery, the segmental response on the ventriculogram has been studied after epinephrine (127), nitroglycerin (128,129) and premature ventricular contractions (117,118,130-132). Improvement after these interventions correlates well with improvement after surgery (129,131,132).

In summary, surgery causes both improvement and deterioration of segment function and does not consistently affect overall resting ventricular function.

Symptomatic Improvement

The most striking beneficial effect of coronary bypass surgery is improvement of angina. When patients interpret their own change in symptoms, improvement in angina is found in 85% (range 69-100%) and complete relief in 70% (range 50-100%) (6,16-18,26,52,55,63,67,101,112,133-144). This is considerably better than the average medical relief of 25% in the few controlled studies (140-142). Deterioration in symptoms between the first and second year averages 20% (range 15-40) of initially improved patients (6,141,145,147). The improvement rates for unstable angina (41-48,146,147) and left main disease (28,32,35,36,148) are the same as for stable angina. Failure to improve is associated with pre-existing poor left ventricular function (149,162) and graft occlusion (74,133,137,139,144) although a considerable number of patients with occluded grafts have shown improvement (135,136). This remarkable symptomatic improvement has also occurred with previous less physiologic procedures to revascularize the heart (151, 152), however, making more objective evaluation of this reported improvement necessary.

Objective Improvement During Exercise

To understand the effect of surgery on exercise capacity, it is necessary to first understand the pathophysiologic basis for angina. This basis is illustrated below.

Body Work = Body O_2 Demand

Body O_2 Demand > Body O_2 Supply = Fatigue or Dyspnea

Body O_2 Supply = A-$VO_2\Delta$ x Stroke Volume x Heart Rate

Heart Rate x Blood Pressure = Heart O_2 Demand

Heart O_2 Demand > Heart O_2 Supply = Angina

Body work (exercise) demands a proportional rate of oxygen delivery to the body. As long as this demand is met by the oxygen supply, exercise continues; but when the supply is less than the demand, fatigue or dyspnea occurs and the subject stops. Body oxygen supply is met by the product of arterio venous oxygen difference x stroke volume x heart rate (153,154). Normally the body oxygen supply can increase about 15x by an approximate 3.5x increase in $AVO_2\Delta$, 1.5x increase in stroke volume, and 3x increase in heart rate. This increased work by the heart to deliver the oxygen to the body in turn causes an increased oxygen demand by the heart which is proportional to the product of heart rate x blood pressure (155-159). If this heart oxygen demand exceeds the heart oxygen supply, which is limited by the diseased coronary arteries, ischemia occurs resulting in angina. This point at which angina occurs, as measured by the heart rate - blood pressure product is remarkably constant in any given patient (158). The ischemia may also cause acute ventricular dysfunction and a consequent decrease in stroke volume leading to a decrease in body oxygen supply (160).

These factors linking body work to angina can be measured and used to assess the performance of patients with angina and their response to an intervention. Of all the factors the most commonly used are the body workload itself and the heart rate or heart rate - blood pressure product. These factors are complimentary in understanding the pathophysiology involved. Workload itself reflects the heart oxygen supply as well as all of the factors linking workload to heart oxygen demand. Since the heart rate - blood pressure product is a rather specific index of heart oxygen demand, measurement of the change in both workload and heart rate - blood pressure product after an intervention allows separation of the effect of the intervention into a change in the heart oxygen supply or a change in the workload - heart oxygen demand relationship. The primary goal of surgery is to increase heart oxygen supply, but frequently the workload - heart oxygen demand relationship is also altered. As will be discussed later, change in the workload - heart oxygen demand relationship is the essence of medical therapy.

Rate of improvement. About 60% (range 50-84%) of patients are able to perform a significantly greater workload on the bicycle or treadmill after surgery (101,134,140,150,161,162) and about 30% are able to perform a normal workload (162). Likewise, 70% sustain a higher heart rate with atrial pacing after surgery (141).

This rate of improvement is less striking when compared to medical control groups in the few cases in which this was done. In one study of 20 surgical patients non-randomly matched to 20 medical patients, the number of surgically improved patients was initially significantly higher than the medical group, but by 2 years the 76% surgical improvement rate was not statistically different from the 50% medical improvement rate (140,150). In a non-randomized study of isolated left anterior descending disease, exercise test improvement was documented in 10/15 (67%) surgical patients and 7/14 (50%) medical patients (161). In a prospective randomized study of 20 surgical and 21 medical patients, atrial pacing at 1 year post surgery showed an improvement in 70% of surgical patients and 48% of medical patients, a statistically insignificant difference (141).

Amount of improvement. As a group, patients can perform about 40% (range 16-89%) more work after surgery (135,137,141,160-165) and sustain a 25% (range 5-53%) higher heart rate or heart rate - blood pressure product (106,132-137,160-163,165,166). In the prospective randomized study, work capacity increased 89% in the surgical patients and 42% in the medical patients, a significant difference (164).

Objective improvement in exercise capacity correlates with graft patency (106, 135, 137, 162, 165), good preoperative ventricular function (162), and severity of preoperative impairment (162). This last factor is probably self-evident but bears re-emphasis. Patients with the worst angina improve the most after surgery.

Mechanism of improvement. In many cases, surgery works as it should, increasing the heart oxygen supply and thereby increasing the patient's work capacity. However in certain instances, there is a discrepancy between the expected and observed results.

In some patients, there is inadequate revascularization but improvement in maximum workload. One mechanism commonly postulated for this is that angina was due to a small ischemic segment which then infarcted at surgery. Another interesting observation is that 45% of pain-free patients retain an exercise EKG indicative of ischemia (43,120,133), suggesting a disruption of the mechanism whereby ischemia is interpreted as pain thereby allowing the patient to exercise past the point of ischemia.

The converse also occurs in which revascularization appears to be adequate, but there is an inappropriate lack of improvement in exercise capacity. In one study, this was shown to be due to a decrease in stroke volume (160,163) resulting in a decrease in body oxygen supply. This diminished stroke volume may be due to a detrimental effect of surgery, but also is found in deconditioned persons (154), a situation which can be reversed by an exercise program (168,169). Continuation of propranolol therapy in adequately revascularized patients also decreases maximum work capacity since it diminishes stroke volume and maximal heart rate (156,167,170).

Probably the most apparent discrepancy in surgical results is the number of patients who report symptomatic improvement, but who show no objective improvement. Several factors account for this including placebo effect and a less vigorous post operative life style, but a very important factor is the change in limiting symptom from angina preoperatively in 65-90% of patients to fatigue or dyspnea postoperatively in all but about 20% who retain their angina (101,137,161,162). Fatigue or dyspnea is a more familiar and desirable limiting symptom to most patients and therefore gives them a sense of improvement even when exercise capacity does not improve. The reason for this change in symptomatology is apparently a decrease in body oxygen supply through a diminished stroke volume. This decrease in stroke volume may occur acutely secondary to ischemia (160, 163) which is not perceived as pain, as discussed earlier.

Effect On Survival

Undoubtedly, the most important unanswered question regarding coronary artery surgery is its effect on survival. No adequately designed study has yet shown a statistically significant advantage of surgery (except in the case of left main disease). However some studies, which while lacking adequate design features, have indicated a surgical advantage. Controversy now exists over whether surgery should be recommended to improve survival on the basis of this available data. This controversy was exemplified by recent reviews in the *ANNALS OF INTERNAL MEDICINE* and the *NEW ENGLAND JOURNAL OF MEDICINE* which came to opposite conclusions (171,172). Since these conclusions are both controversial and critical, the data on which they are based will be reviewed. In the table below, the most important studies addressing the question of surgical improvement in survival for stable angina are listed, along with the design of the study and its conclusions.

Hospital	No. of Surgical Pts.	Control Same Hosp.	Control Same Hosp. Same Time	Prospective Randomized	Surgical Improvement in Longevity
Oregon (12)	532				+
St. Lukes (173) Houston	1492				+
Methodist (55) Houston	480				+
Stanford (147)	350				+
Cleveland (5)	1000	+			+
Duke (142)	379	+	+		±
Long Beach VA (140,150)	20	+	+		
Houston VA (141)	35	+	+	+	

It is readily apparent that the least controlled studies show the most significant improvement. It is further apparent that the best designed studies have the fewest patients making it necessary to have a relatively large difference between surgical and control mortality to be statistically significant.

The results of the first 5 studies along with their "control" group are shown below.

Hospital	Surgical Annual Mortality	"Control" Group Annual Mortality % Reeves Summary (174)	Cleveland (176)
Oregon (12)	3		9
1 vessel	1	2	2
2 vessel	3	7	7
3 vessel	5	11	11
St. Lukes (173) Houston	5		9
Methodist (55) Houston	8		9
Stanford (147)	5		9
1 vessel	2	2	2
2-3 vessel	6	7 and 11	7 and 11
Cleveland (5)	5		9

The mean follow-up was 2 years except at Methodist where it was 1 year and Stanford where it was 2.5 years. Operative mortality, which is included in the annual mortality was 3% at Oregon and Cleveland, 7% at St. Lukes, and 5% at Stanford and Methodist. In this table and all subsequent tables, annual mortality assumes a linear relationship for each year and is based on the original cohort. These surgical results are most commonly compared to the natural history data reported in Reeves' Summary (174) and the Cleveland study (176). The data for these studies came chiefly from the time period before surgery. With the exception of the Cleveland data, the surgical and medical groups came from different hospitals and were categorized by different observers. In the Cleveland study the groups came from different time periods. For comparison, the Cleveland group placed equivalent numbers of patients in the surgical and medical groups according to number of diseased vessels. The Oregon and Stanford studies subdivided their patients for comparison. Although the St. Lukes and Methodist studies were not well categorized, most were multivessel disease. The above table shows an apparent favorable influence of surgery on survival and is the basis for most of the statements to this effect.

In addition to the inapparent factors of bias in non-randomized uncontrolled studies, there are several more apparent objections to this conclusion. The data contained in Reeves' Summary (174-181) basically is the natural survival prognosis of patients with coronary artery disease relative to the number of vessels diseased. In summary, this relationship is:

No. of Diseased Vessels	Annual Mortality %
1	2
2	7
3	11

This subdivision of expected mortality by number of diseased vessels has certainly contributed to the comparability of medical and surgical survivorship. However, to use it as the basis for a control group from another hospital assumes no variance between observers. Furthermore, the natural history of the medical control groups all came from an earlier time period when cineangiographic equipment had less resolution than in the later period when the surgical patients were angiogrammed. This difference in timing may put patients today in the multivessel group who would have been put in the single vessel group at the time the natural history studies were done. Finally, these studies do not evaluate distal vessel disease, a condition which classifies a patient as a poor surgical candidate.

Another problem with accepting the poorly controlled data on surgical survival is that ventricular function was not systematically evaluated. Ventricular function is at least as important as vessel disease in determining natural survival prognosis as shown below.

ANNUAL MORTALITY %

Hospital	Ventricular Function		Determination of VF
	Normal	Abnormal	
Kingston, Ontario (175)	2	8	Visual-Angio
Alabama (177)	2	13	Chest X-ray
Cleveland (178)	5	8	Visual-Angio

Although when subdivided both by diseased vessel number and ventricular function the number of patients are few, the available data does indicate a similar influence of ventricular function on annual mortality within each vessel disease group as shown below.

ANNUAL MORTALITY

Hospital	Ventricular Function			Determination of VF
	Normal	Moderately Abnormal	Very Abn.	
Duke (142)				Angio-$AVO_2\Delta$
1 vessel	2	0	14	
2 vessel	0	9	20	
3 vessel	5	12	20	
Alabama (177)				Chest X-ray
1 vessel	0	3		
2 vessel	3	21		
3 vessel	14	24		

Since poor ventricular function is well known to adversely affect operative mortality, it is probable that this bias was present during selection of candidates for surgery and possibly had a significant influence on the results.

In an effort to better compare non-randomized medical and surgical patients at Duke, risk factors were extensively compared and if unequal, statistically cancelled. As shown below both before and after this process, there was no significant difference in overall mortality.

Hospital	No. Surgical Patients	Annual Mortality % Surgical	Medical	Significance
Duke (142)	379	7.5	8.5	NS
Long Beach VA (140,150)	20	7.5	5	NS
Houston VA (141)	35	4	6	NS

The statistician for this study estimated that if the mortality rates shown were true, it would take approximately 100,000 patients to show significance.

At the Long Beach VA, 40 patients were non-randomly matched both as to number of diseased vessels and ventricular function, and followed for 2 years. There was no significant difference in mortality.

Finally, there is one prospectively randomized study (Houston VA). In this study, over half of the patients had 3 vessel disease. Mean follow-up time was 28 months. Surgical mortality was lower but the difference was insignificant.

Several subgroups deserve special attention.

Left main. Left main coronary disease is more lethal than other types of coronary disease. Annual mortality in unoperated patients is about 20% (31,35,37-40,182) although this decreases as time after discovery passes, so that by 5 years post catheterization overall annual mortality drops to 10% (37). Mortality with the catheterization procedure alone has been reported as high as 10 and 16% (32,36), but figures of 0-2% are more common (28,29,31,34,35,37-40). With an operative mortality of about 10%, surgical annual mortality is about 10% with 1-2 years follow-up (28-31,34-40,182). In the VA Cooperative Study (182), 105 patients with left main disease were prospectively randomized and followed for a mean of 22 months. Annual surgical mortality was 9% and medical was 21%, a difference significant at the .025 level. Similar results were found in two controlled but non-randomized studies (39,40). Hence at least in the first 2 years after discovery, surgery increases the chance of survival in left main coronary disease.

Duke group - 3 vessel disease, abnormal contraction, normal $AVO_2\Delta$. Surgery appears to increase survival in another subgroup of patients in the non-randomized but well controlled Duke study (142). This group consisted of 169 patients with 3 vessel disease, abnormal ventricular contraction pattern, and an arteriovenous oxygen difference under 5.5 (implying adequate overall ventricular function) who were followed for a mean of 1 year. The surgical annual mortality was 5% and medical 12% ($p < .03$). With longer follow-up, however, this difference is decreasing although it has not been retested for statistical significance (personal communication).

LAD disease. Although the effect of surgery on survival is controversial in 2 and 3 vessel disease, it appears illogical to expect to improve on the 2% natural annual mortality of 1 vessel disease. However if the 1 vessel disease group is further subdivided, the left anterior descending has the worst prognosis with an annual mortality of 3-4% (174,175,179) leading to speculation that surgery may improve this figure. Two studies bear on this and as shown below, the data is inconclusive.

SINGLE VESSEL LAD

Study	No. Surgical Patients	Annual Mortality % Surgery	Control	Control Group
Cleveland (5)	?	0	4	Same Hospital, Earlier Time Period
Alabama (161)	29	3	0	Same Hospital, Same Time Period

Unstable angina. In addition to coronary anatomy and ventricular function, the clinical presentation of unstable angina appears to be an important variable in predicting natural survival, especially in certain poor risk groups (27,183). Since operative mortality in this group is essentially the same or only slightly higher as in stable angina (27,41-49), especially after medical stabilization (41,43-45), and late surgical mortality is the same as stable angina (27,41,42,44-48,147); it appears that any difference in medical and surgical treatment depends chiefly on the medical mortality rate. This figure varies widely from that near stable angina up to 50% in one year (184). Two randomized studies have reported preliminary data, one showing a surgical advantage (27) and one showing no difference (49). The data showing a surgical advantage was due to a 35% medical mortality over 8 months in a high risk subgroup. For a more extensive review, Dr. Smitherman's Grand Rounds of June 26, 1975, should be consulted (184).

In summary, the effect of surgery on survival is shown below.

Group	Surgery Helps	Inadequate Data, Surgery Appears to Help	Possibly Help	Not Help
Left main	X			
Unstable angina high risk		X		
2 and 3 vessel disease			X	
Isolated LAD disease			X	
Isolated right and circ. disease				X
Poor ventricular function				X

Hopefully, the question of survival will be further clarified over the next several years as data from the VA Cooperative Study, a study of over 1000 prospectively randomized patients is reported.

SURGERY IN PERSPECTIVE: MANAGEMENT OF THE PATIENT WITH CORONARY ARTERY DISEASE

Evaluation

After the preliminary workup of the patient with suspected coronary artery disease, exercise testing is performed to both aid in the diagnosis by change in the ST segment and to establish the degree of limitation on work performance and the heart rate - blood pressure product. At this point, cardiac catheterization can be done; but the indications are relative rather than absolute. The advantages of catheterization are to establish: 1) the diagnosis, 2) natural prognosis both for survival and likelihood of long range improvement, 3) presence or absence of a left main lesion, and 4) surgical candidacy. The high death rate during coronary angiography several years ago (185) has now dropped considerably in most laboratories to an acceptable rate of approximately 0.1% or less, probably due to the routine use of heparin (186, 187).

The necessity of angiography to establish the diagnosis of coronary artery disease depends chiefly on the clinical presentation and need of definitive diagnosis. A classical presentation of angina means coronary artery disease in about 95% of patients while atypical angina drops the likelihood to about 50% (188). This diagnostic accuracy is increased by exercise testing (189). Necessity of definitive diagnosis is relative depending on the patient and the therapy felt necessary by the physician, but certainly the practice of changing a person's lifestyle drastically on scanty evidence for coronary disease is to be condemned. The prognosis can be predicted from the extent of coronary disease and ventricular function as reviewed earlier. This is usually most helpful when single vessel disease is found as it is in approximately one third of angina patients leading to valid patient encouragement (142,175,179). In addition to indicating a good survival prognosis, single vessel disease also increases the likelihood of natural long range symptomatic improvement (176,190). In one study of 469 patients, 50% of one vessel disease patients were improved 6 years later compared to 25% of two and three vessel disease patients (176).

Since surgery improves survival in left main coronary disease (39, 40,182), routine catheterization of all patients with suspected coronary artery disease is a valid consideration. The incidence of this lesion is about 4% in patients with coronary disease (29-32,40). Since patients with left main lesions frequently have deep ST depression during exercise testing, this can be used to preselect patients with an increased likelihood of the lesion. ST depression $\geq$ 2mm is commonly suggested as the dividing point. Although prospective data on the likelihood of this amount of depression predicting left main lesions is unavailable, it is known that ST depression $\geq$ 2mm is about 80% sensitive (30,35,40) and 85% specific (191-193). These figures combined with the 4% incidence yield a crude likelihood of left main disease being present when ST depression $\geq$ 2mm of 18% and the likelihood of it not being present when ST depression $<$ 2mm of 99% (194).

The last advantage of early catheterization is determination of surgical candidacy. This is usually of value even before medical treatment in planning the approach to the patient, such as giving added emphasis to the positive aspects of medical therapy in poor surgical candidates.

The timing of catheterization varies among cardiologists. Some feel that the above mentioned factors are sufficient to make early catheterization routine. Others feel it is only indicated in selected cases or as a pre-surgical measure. The determination of whether surgery improves survival in non-left main disease will be a large factor in the timing of catheterization in the future.

Treatment of Angina

The therapeutic modalities generally available to treat angina are nitroglycerin (or similar agents), propranolol, exercise programs, and surgery. For mild or infrequent angina, nitroglycerin alone is frequently adequate, both after the onset of pain and prophylactically for known pain producing activities.

For more severe angina, nitroglycerin is still helpful but additional therapy is usually necessary. The three available modalities and their mechanisms of action are listed below, along with the table previously shown linking body work to angina.

Therapy	Body Work	Body O_2	$AVO_2\Delta$	SV	HR	BP	Heart O_2 Supply
Propranolol	↑	↑	↑	−↓	↓	↓	—
Exercise	↑	↑	—	↑	↓	↓	—
Surgery	↑	↑	—	—	↑	—	↑

Body Work = Body O_2 Demand

Body O_2 Demand > Body O_2 Supply = Fatigue or Dyspnea

Body O_2 Supply = A-$VO_2\Delta$ x Stroke Volume x Heart Rate

Heart Rate x Blood Pressure = Heart O_2 Demand

Heart O_2 Demand > Heart O_2 Supply = Angina

It is apparent that while all agents increase the body oxygen supply, all have a different mechanism of action. Surgery increases the heart oxygen supply thereby allowing all factors to increase. Propranolol and exercise training do not affect heart oxygen supply, but exert their influence by altering the relationship between body work and heart oxygen demand, and more specifically, by altering the relationship between body oxygen supply and heart rate. Propranolol does this by retarding the natural increase in heart rate with exercise thereby causing an increase in the arterio venous oxygen difference (167) while exercise training does this by increasing stroke volume (154,168,169).

Unless the physician has a liason with an exercise program, however, the practical management of the patient with moderate to severe angina revolves around propranolol and surgery. The logical approach is to first try propranolol and if this fails to alleviate symptoms adequately, to consider surgery. To assure an adequate trial of propranolol, it is best to first have an exercise test for baseline. Propranolol is then begun at 80 mg/day and this dose is increased to 160 and 320 mg/day as necessary (170,195-197). Adequate propranolol effect is present if the heart rate is reduced 20-25% at the same level of exercise that was maximal on the baseline test (170). It is best to keep the dosage as low as possible while still retaining the desired exercise heart rate reduction since high propranolol doses decrease ventricular function (197), which may in turn have an adverse effect on exercise tolerance by decreasing stroke volume. With many patients, this is effective therapy. However if after demonstrating adequate propranolol effect, sufficient relief is not obtained, then surgery should be considered.

Summary of Treatment of Coronary Artery Disease

Single vessel disease with normal or mildly abnormal ventricular function (EF > 40%). These patients have a good prognosis both for survival and long range symptomatic improvement. Medical therapy is strongly emphasized. Only if symptoms persist after aggressive medical therapy is surgery considered. It is possible that single vessel left anterior descending disease is a special variant of this group, and surgery may increase survival. However, no adequately designed study has yet suggested this; and it is currently our policy at the VA not to operate on any patients with single vessel disease to improve survival.

Multivessel disease with normal or mildly abnormal ventricular function (EF > 40%). It is not clear whether surgery improves survival in this group of patients. Consequently, cardiologists are divided as to whether to advise surgery in these patients solely for this reason. It is currently our policy at the VA to operate on these patients only for improvement of symptoms after failure of medical therapy.

Left main coronary disease. Due to the strong evidence favoring improved survival after surgery, it is our policy and that of most cardiologists to recommend surgery on all technically feasible patients with left main disease.

Poor left ventricular function (EF < 30%). Fortunately, most patients with poor ventricular function secondary to coronary artery disease have CHF as their chief symptom and not angina (198). Surgery is not advisable for these patients because of the high operative mortality and lack of improvement in ventricular function. In those patients with poor ventricular function who do have angina, this angina is not usually significantly improved by surgery (149). It is our policy at the VA not to operate on

patients with poor ventricular function. In patients with moderately abnormal ventricular function (EF 30-40%), relief of angina is frequently obtained but with added risk of operative mortality. Recommendation for surgery is made only for severe angina after aggressive medical therapy.

Unstable angina. Patients with unstable angina develop pain in response to a rise in the heart rate - blood pressure product similar to patients with stable angina, only these rises are generally spontaneous and of lesser magnitude (199,200). Propranolol is initially used which usually promptly lowers the heart rate and blood pressure resulting in disappearance of pain (45). Since the anatomy (45,184,201), operative mortality (after medical therapy), and late results of surgery are similar to that found in stable angina; after these patients are stabilized, they are generally managed as in stable angina. Persistence of pain at rest in spite of adequate propranolol effect, however, is usually managed by early catheterization and surgery.

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