RESULTS OF TEN YEARS AORTO-CORONARY BYPASS SURGERY AT THE THORAXCENTER, ROTTERDAM

Resultaten na tien jaar coronariachirurgie

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
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PROMOTOREN: Prof. dr. E. Bos
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The truth of these days
is not that which really is
but what every man
persuades another man to believe

Montaigne, Essays, 1580–88.

In memory
of my father and grandfather.

CONTENTS

CHAPTER 1

INTRODUCTION.

Aorto-coronary bypass operations as a treatment for patients with angina pectoris and obstructive coronary artery sclerosis, were first performed in 1967[1,2]. In the Netherlands the first reported procedure dates from 1969 [3], while at present more than 6000 Dutch patients are operated upon per year. From the start it was evident that the operation afforded symptomatic relief in a large number of patients. However it also became clear that between institutions variations existed in surgical technique, operative mortality and medical management after the operation [4-6]. The final result of this by now very popular procedure is therefore influenced by the specific cardio-surgical team which performs the operation. Ideally, if a patient is referred for surgery to a particular institute, it should therefore be known what the results are for that particular team. This study represents an attempt to document our own results.

The aim of this thesis is the description of the outcome of isolated aorto-coronary bypass operations, both regarding the short term effects i.e. the operative mortality as well as the long term results i.e. the general well-being and survival probability of the patients over the years. The main indication for this type of surgery is and always has been, persisting angina pectoris despite extensive pharmacological therapy. The outcome of surgery therefore, should be judged, among other things, by the presence and severity of this syndrome in the post-operative period. To place these data in perspective, a review of the literature on surgical therapy of angina is provided in chapter 2. As discussed in chapter 3, it has become apparent over the years that the perception of the severity of angina pectoris is changeable and very difficult to quantify. Still an attempt has been made, to analyse the data on this complaint, although it is realised that it is fraught with errors as simplifications are required when large numbers are to be judged.

Improved survival has by now become an important issue to justify bypass surgery. A multivariate analysis of the factors which influence survival is

provided in chapter 4. For comparison, the survival probability of the general population in the Netherlands, matched for age and sex, has been related to the data of the patients under study. In chapter 5 the evolution in post-operative chest pain is documented, while the results of re-operations of patients who underwent their primary operation at the Thoraxcenter, are discussed in chapter 6. In chapter 7 a correlation is sought between the presence of pain in the chest and the extent of vascular involvement in the pre- and post-operative angiograms. Patency of the grafts and progression of disease in relation to post-operative pain is discussed as well in these chapters. Chapter 8 contains a general but critical discussion of bypass surgery in an attempt to view, from all angles, the relative merits and disadvantages of this currently so popular procedure.

This study would not have been possible without the generous help of our patients. First by their part in the design of the questionnaire and later by their responding to it in such large numbers. To emphasize that this material ultimately relates to the specific problem of the individual patient, the histories of 4 patients are represented in a detailed but compressed form. Their stories reflect, better perhaps than statistics, what it means to have a "BYPASS OPERATION".

Patient 1: Mr. P., 17-11-1930.

Mr. P., a sales representative at a beer brewery, had been healthy until 1971, when he experienced a heavy pain in the left arm while going from a warm environment into the cold. This happened for the first time on a December evening, while going outside after dinner. It repeated itself later but the pain always subsided in a few minutes. In 1972 he woke up several times at night, with this same pain, radiating to his chest, lasting 5-6 minutes. Nitroglycerin did not influence the pain duration or pain intensity. On examination in 1972 he was 10 kg overweight and had slight hypertension. The electrocardiogram showed a possible old inferior wall infarction. An exercise tolerance test was terminated because of anginal pain at 50% of the expected work load. Treatment was started with beta blocking agents, however, the complaints persisted. A cardiac catheterization was performed in October 1972. Narrowing of 2 coronary vessels was found with depressed left ventricular function. Nearly a year later, after he lost 8 kg of his overweight, an aorto coronary bypass operation was performed and 3 grafts were inserted. In the post-operative period he suffered multiple pulmonary emboli, but he recovered

well and could be discharged on the 12th post-operative day. Since then, he has had no anginal pain, the exercise tolerance as subjectively experienced, improved and as objectively measured was near normal in May 1974. Although the electrocardiogram did show ischemic changes at maximal exercise, he did not have precordial pain. He was able to resume his work at the brewery, he gained his lost weight back and he is able to play a game of tennis once a week. He does not feel limited in physical activities and considers himself cured.

Patient 2: Mrs. W-D., 21-10-1929.

Mrs. W. was sent to the out-patient clinic in 1972 by her family physician, because of pain in the chest. It was experienced at rest, radiated to the left shoulder and neck, and lasted 15-45 minutes. She was told to take bedrest during the last 3 weeks before the consultation. Still, pain attacks occurred nearly daily without any reaction to nitroglycerin. On physical examination no abnormalities were found. The electrocardiogram was consistent with a subendocardial infarction, age unspecified. Mobilisation was advised. Subsequently pain developed with slight exertion, and during periods of emotional stress but not at rest. Treatment with a beta blocking agent was started. She continued to feel badly: tired, with pain in the chest, sometimes lasting the entire day, sometimes a few hours. Her validity was estimated at class III of the New York Heart Association Classification.

In 1975, after many hesitations on her side, a cardiac catheterization was performed. Two vessel coronary artery disease was found, with a left dominant system, a totally occluded right coronary artery and a 90% narrowed left anterior descending branch. Half a year later a vein graft was placed between this artery and the aorta. She recovered without complications and was discharged 12 days after the operation. However, at home her old complaint of tiredness returned, while pain in the chest was experienced as well. The pain did have a relation to exertion and lasted sometimes a few minutes, but sometimes hours. Her validity was judged to be class II, her exercise tolerance was 78% of what could be expected. Her mood seemed depressed. In 1979 the complaints led to a re-catheterization, showing normal left ventricular function and an open bypass graft, while the recipient artery was totally occluded proximal to the anastomosis. There were otherwise no signs of progression of disease in the native coronary tree. Since then she continues to have pain complaints and she feels limited in her activities. Treatment

with beta blocking drugs was re-instituted in 1981 with slight improvement. The operation is technically a success but subjectively, this success is only partial. Her complaints are now ±60% of what they used to be pre-operatively, she has less pain, but she remains just as tired.

Patient 3: Mr. H., 05-02-1925.

Mr. H., came to the out-patient clinic for the first time in March 1975 because of an oppressive feeling in the chest, experienced with slight exertion since 2 weeks. In 1969 he suffered a myocardial infarction with an uneventful recovery. He had been able to resume his work as a filing clerk in subsequent years. At the first consultation hypertension was found. Treatment was instituted with nitroglycerin p.r.n. and a beta blocking agent 4 times a day. Symptoms decreased although angina pectoris could be elicited with heavy exercise. He was able to resume normal activities. During that period a healthy son was born and he was enjoying his domestic life.

Four months later, in August 1975, he presented himself for admission because of pain attacks lengthening in duration, with a slow reaction to nitroglycerin. They had occurred at rest during the previous night. A diagnosis of impending infarction was made and treatment started with the intra-aortic balloonpump. At cardiac catheterization, a left main stem narrowing of 75% and normal left ventricular function was found. Two days after admission he received 2 bypass grafts. Recovery was good and he was discharged in 2 weeks. However at home he again experienced pain at slight exertion. A re-catheterization showed one nearly closed graft and one severely narrowed graft. Re-operation was performed in October 1975. After that, he started to feel better and was able to join a cardiac rehabilitation program. He resumed his work for 5 hours a day. Except for anti-hypertensive treatment he did not need any specific medication until 1978 when angina pectoris re-occurred. This time it was mild in character and treatment was restarted with beta blocking agents. He was able to continue working half time. An exercise test showed decreased exercise tolerance at 70% of normal, the limitation being general tiredness and not pain in the chest. In 1980 he was admitted to the coronary care unit for observation of upper abdominal pain. No cardiac ischemia could be documented. He continues to come to the out-patient clinic once every few months. When questioned as to how he feels now, he reported that he felt improved as compared to before the first operation. He is happy to have been operated on but still has anginal attacks at ± 20% of what he had pre-operatively. He is

satisfied with his condition now, and does not want an extensive re-evaluation.

Patient 4: Mr. H., 20-02-1932.

Mr. H., a foreman in an ironscrap-yard started to experience an oppressive pain substernally in 1969 at age 37. Originally it occurred only with heavy physical work, later while walking outside at the yard directing others. The pain lasted 4-5 minutes and always subsided at rest. In 1974 an exercise test showed an exercise capacity of 60% of normal, the limitation being pain in the chest. The ECG showed ischemic repolarisation changes while he had pain but was normal at rest.

Treatment was started in 1974 with nitroglycerin, long-acting nitrates and beta blocking agents. He refused cardiac catheterization because he felt better with treatment (exercise tolerance increased to 80% of the norm). Also his wife did not want him to and he was afraid of the procedure. In his family, his father had died at 46 years of age of a myocardial infarction and his 3 uncles all had had infarctions and/or periods with angina pectoris. He was able to continue to work and in 1976 his condition improved to the extent that he rarely needed nitroglycerin, while that had been necessary 5-6 times a day before.

In 1978, during the winter time, the pain attacks increased in frequency (8-10 per day) and the pain lasted longer. Still he experienced it only at exercise and never at rest. The immediate reason for returning to the hospital was a severe pain attack while he was emptying the flooded cellar of his riverside home. A lot of fear had been caused by this experience as he had been unable to leave the cold, wet, darkness of the cellar for quite a while. The subsequently measured exercise tolerance was however the same as in 1976; he reached 80% of the norm, but the pain started at a lower level. A coronary angiogram was proposed and accepted after a long talk with the couple. At cardiac catheterization in December 1978, he was found to have a normal left ventricular function and a significant stenosis in two of the 3 major coronary vessels. Three months later 3 bypass grafts were inserted. Post-operatively he had transient rhythm disturbances but otherwise no problems. One month after the operation he was readmitted because of substernal pain at rest which did not subside with nitroglycerin, lasted 20 minutes and was more severe than he had ever had before. No myocardial necrosis had occurred according to the emzyme tests, and a Thallium scintigram was normal. Treatment was reinstituted

with beta blocking agents, later a calcium blocking agent was added. He was able to participate in a cardiac rehabilitation program but he felt unable to resume his work. In December 1979, 9 months after the operation, the medication could be decreased but he felt depressed, slept badly, lost all initiative and hardly left his house. He required psychiatric help. Any pain in the chest, be it traumatic or in the scar threw him into a mental panic. Yet he did not experience the same angina pectoris as he did before the operation. His exercise tolerance was excellent. Now, in 1983, he is feeling well physically, but he has lost his job and he feels incapable of being regularly employed. He remains anxious and seems to have changed in the last years from a capable, levelheaded man into a very insecure, hesitant person. Objectively, the operation has been a success but has it subjectively?

Each of these 4 patients had different complaints, each coped with them in their own way, yet all were severely restricted in their activities by angina pectoris before the operation. The recovery from surgery in the post-operative period was initially without problems but in the long run 3 patients developed recurrence of complaints, while 2 had severe mental problems. As can be seen by the varied responses of just these 4 patients, which are already hard to quantify, it is clear that each of the 1041 patients in this study had their own individual reaction pattern. In an effort to put it all into numbers, so that a quantitative analysis would be possible, generalisations were necessary. It is simply impossible to represent for all 1041 individuals the different shades of gray in which they might paint their condition. As long as it is realised that this study is about human beings, all willingly participating, those simplifications have to be accepted. In the next chapters the analysis is therefore performed on the condensed, impersonal, data.

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CHAPTER 2.

REVIEW OF THE LITERATURE ON SURGICAL THERAPY OF ANGINA PECTORIS.

The description of angina pectoris dates from 1768 by William Heberden in a lecture before the Royal College of Physicians. It was published in 1772 under the title: "Some account of a disorder of the breast". This description contains all aspects of the disease as we know it today[1]: The oppressive feeling in the breast causing anxiety, the relation to exercise, meals, the male sex and older age. It is all there, yet it was probably a rather rare disease, mainly found in the more prosperous individuals. That changed in the 1920's when the current epidemic of coronary heart disease began. Angina pectoris lost its predilection for the more prosperous people and started to involve younger and younger men from the entire population. Paul Dudley White, in an article on the historical background of angina pectoris [2] comments on this change, which must have happened early in his career.

The relationship between the complaint angina pectoris and diseased coronary arteries has been known for a long time as well. Caleb Hillier Parry extended the pathologic observations of Jenner in 1785 to a patho-physiologic concept in 1799 [3]. He postulated: "a quantity of blood may circulate through the arteries, sufficient to nourish the heart as appears, in some instances, there may probably be less than what is requisite for prompt and vigorous action. Hence ... when an unusual exertion is required its powers may fail under the new and extra ordinary demand". Those concepts, formulated at the end of the 18th century, form the basis of our traditional understanding of effort related chest pain in obstructive coronary artery disease. They form the basis as well for present day surgical intervention. However, the earliest attempts at surgical therapy in angina pectoris were not directed at the blood supply to the heart but at the pain perception by cutting the nerves transmitting the pain stimuli from the heart to the brain. This type of operation was first performed by Jonnesco in Bucharest in 1916[4]. He extirpated the cervical sympathetic chain bilaterally and removed the first dorsal ganglia. This approach was followed by many others. Preston estimates that 1000-3000 patients under-

went this type of procedure over a time span of 50 years[5]. Operative mortality was on average 10%, while 70 to 85% of the patients were improved after the operation. However it was noticed that late mortality in these patients was high, 50% in 2,5 years having been reported[6]. The procedure faded away, not because it was ineffective, but by lack of enthusiasm. Attention was drawn away by the idea that the approach should be more physiologic. If pain occurs because of lack of oxygen due to a decrease in blood supply, then the blood supply should be increased.

The greatest proponent of increasing the blood supply to the heart was Claude Beck, a surgeon from Cleveland, Ohio [7]. His work was based on many animal experiments in which he created artificial pericarditis resulting in inflammation tissue with ingrowth of blood vessels. Next he implanted muscle grafts from the pectoralis major, the muscle acting as a supplier of blood to the inflamed pericardium. In 1935 he performed the first operation in man and many have followed since then [8-9]. Modifications were used in the manner in which the pericarditis was started: mechanic abrasion, talcum powder, bone dust, magnesium silicate, asbestos etc. and in the type of graft used: omentum, lung, skin etc. But the basic idea remained the same: to increase coronary circulation by producing inflammation. Feil, the cardiologist working with Beck, reported on 37 patients[9], and was the first to find objective means in describing the post-operative condition. He used the Master two-step exercise test and compared the number of trips possible before and after operation. Improved were 83% of the 23 survivors. Operative mortality was 38% in this first series, this fell later, with increased experience, to less than 10%. Feil was also the first to compare survival of the operated patients with the average duration of life in sufferers of angina pectoris as reported in the literature. This example was quickly followed by others and thus started the practice of measuring survival of operated patients against "known" survival of those with "similar" disease as it is still done today, a comparison which remains difficult at best.

At the same time that Beck performed his epicardial irritant operations, others directed their attention to the coronary sinus. It was reasoned, that ligation of the coronary sinus would hasten the development of the coronary anastomotic system,thus increasing myocardial blood supply. This type of operation was first performed by Fauteux[10] in Boston who combined it with pericoronary neurectomy. Later, Beck added the venous ligation to his pericardial abrasion. The next step was to arterialise the coronary sinus, performed by Roberts [11] in 1943 and again by Beck in 1948 [12]. They postulated, that

blood with an arterial pressure would expand flow in the coronary sinus and thereby increase retrograde flow to the myocardium. To produce this, a vein graft was needed, connecting the aorta with the heart. The basis of modern day coronary surgery was introduced with that concept.

The arterialisation of the coronary sinus in itself never gained much popularity because two operations were necessary: one to ligate the coronary sinus and one to place the graft. This carried a high mortality with it. Moreover, the evaluation of the operative results remained a problem. As Harken said in 1958:"whenever an operation is advanced for the treatment of angina, one must start out with the assumption that the patients are relieved if the authors say so"[13]. He said this in connection with ligation of the internal mammary artery to increase blood supply to the heart and relieve pain. That operation had been proposed by Fieschi in Italy in 1939 because of the ease of performing it under local anesthesia. In fact it was employed by many over a short time. Among others, Battezzati et al[14] reported on 304 patients with 91% symptomatic improvement at 1 month after the operation and actually 64% showed objective improvement by electrocardiographic criteria.

Many investigators were not convinced by the physiologic basis of this operation, which led to two independent double blind trials: one by Cobb et al [15] and one by Dimond et al[16]. These two studies are among the few double blind trials involving surgical techniques. In Cobb's study[15], 17 patients were involved, 8 underwent ligation, 9 a sham operation. Follow-up time ranged from 3 to 15 months, 5 out of the 8 ligated patients and 5 out of the 9 non-ligated patients reported significant improvement. Striking improvement was seen in 2 patients, both non-ligated, with disappearance of the abnormalities on the electrocardiogram at exercise tests, which had been previously observed in the same patients. Dimond [16] reported on 18 patients, 13 ligated, 5 non-ligated. Improvement was reported by 10 of the ligated and 5 of the non-ligated patients. Here again, excercise tolerance increased and nitroglycerin consumption decreased in all 5 non-ligated patients. Follow-up lasted from 1 to 6 months. Both authors concluded that the improvement in pain could only be caused by the psychological effect of surgery.

The results of these studies are of great interest because they afford an opportunity to study the placebo effect of surgery on angina pectoris. The placebo effect is any treatment or aspect of treatment that does not have a specific action on the patient's symptoms or disease (definition from Shapiro[17]). It plays a role in any encounter of a patient with a medical person, be it a doctor, a nurse, or paramedical personnel. Assuming that in

the above cited double blind trials, the procedure was in itself not active - then 35 patients were involved of whom 25 (71%) showed improvement from an essentially useless therapy!

The next step in the efforts to increase blood supply to the myocardium was made by Vineberg, who proceeded in 1950 to implant a bleeding mammary artery into a 3 to 4 cm tunnel burrowed into the myocardium[18]. It was hoped that a collateral circulation would develop between the implanted artery and the coronary sinus. After it had been shown by coronary angiography that collaterals could indeed develop, this procedure became rather popular in the 1960's. Surgical mortality ranged from 3-10% with an overall subjective improvement of around 85%[19]. Several investigators however found that improvement did not correlate with patency of the implanted artery or formation of collateral circulation[19,20]. Clinically controlled trials were not performed.

In the mean time thoughts about the mechanisms causing angina pectoris developed further. In 1959 Levine postulated that a localised lesion was the essential part of the difficulty [21]: "if additional blood supply is brought in by any means, such as by the use of irritants .... or by new collaterals, anginal pain could be alleviated only if the ailing parts were improved". From that concept evolved the direct attack on the stenosed coronary artery. First via endarterectomy by Bailey et al in 1957[22] and later, after the technique of selective coronary angiography was developed by Sones, via patch grafts around the lesions [23]. Again an improvement in 65% of the patients was reported[22]. From the venous patch graft to the use of the reversed saphenous vein graft from aorta to coronary artery was a logical step. Both Favaloro and Johnson started with this operation in 1967, and reported on it in 1969[24,25].

In the Netherlands, surgery for angina pectoris started in 1965 in Nijmegen[26]. At first a modification of the Vineberg procedure was used. In 1969 a saphenous vein graft was inserted for the first time. At present ±6000 patients are operated on per year in this country, nearly all with vein graft implantations.

Thus, surgical treatment for angina pectoris has been going on for nearly 70 years. All procedures showed subjective improvement in 60-80% of the patients, although follow-up time was often short. Double blind evaluation was performed for just one procedure and showed that improvement might have been caused by placebo effect or the natural course of the disease. At present, it is not considered ethical to perform sham operations, but these results obtained in by-gone years with procedures now regarded as useless, should be kept in mind while evaluating present day operative procedures.

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CHAPTER 3.

THE RELIABILITY OF THE QUESTIONNAIRE AS EMPLOYED IN THIS STUDY FOR THE ASSESSMENT OF ANGINA PECTORIS.

He who fears he shall suffer
Already suffers what he fears
Montaigne, Essays 1580-88

3-1: INTRODUCTION

Coronary artery disease is not a static but a dynamic process with progression and regression of sclerotic lesions [1-2]. Angina pectoris (AP) as a complaint can appear, spontaneously disappear, remain stable or become more severe. A myocardial infarction can occur in a patient with hitherto stable angina pectoris, with, after recovery from the acute event, often a changed pattern of symptoms[3,4]. Thus, appraisal of symptomatic condition after coronary bypass surgery is only possible by studying large numbers of patients. In this study it was chosen to employ a questionnaire as a means to reach many in a standardised manner. Via the questionnaire we obtained information from 1041 patients who had had consecutive operations. This information concerned post-operative condition, subjective complaints such as pain in the chest and dyspnea, and a comparison of the post-operative condition with the condition of the patient before the operation. The data from the questionnaire were furthermore correlated with those obtained from personal interviews with a selection of the studied patients.

3-2: METHODS

The questionnaire contained 7 seperate questions directed at different aspects of possible complaints (for complete text, see appendix):

a. the occurrence of pain on the chest during the previous half year
b. the circumstances provoking pain
c. the frequency of pain complaints
d. the severity of anginal complaints in comparison to before the operation
e. a possible symptom free interval after the operation

f. the pain in scar tissue, either in the chest or the leg(s)
g. a limitation of activities by physical complaints.

Seventy-six patients were chosen at random to come to the hospital for a personal interview. Via the classical history-taking technique[5] it was decided if angina pectoris was present during the previous half year or not. These interviews were conducted by the same physician, in a standardised manner, without knowledge of the patient's answers to the questionnaire. The type of chest pain was classified according to the criteria employed in the Coronary Artery Surgery Study [6]. Typical angina was defined as substernal discomfort precipitated by effort or emotion, subsiding at rest or with nitrates within 10 minutes. For simplicity's sake atypical angina pectoris was classified as angina pectoris as well i.e. pain localised in the chest, but not necessarily substernal, nitroglycerin not always effective, pain duration 10-20 min. Chest pain was classified as probably not angina pectoris if it did not fit the above descriptions, in other words when the pain was unrelated to effort, was unrelieved by nitroglycerin, and/or lasted longer than 20 minutes.

3-3: RESULTS

Of the 977 surviving patients, 8 had moved away from the Netherlands. In total 969 forms were sent of which 920 (95%) were returned.

The first question, regarding pain on the chest experienced in the previous half year, was answered by all respondents: 434 (47%) still had pain, 486 (53%) not. The answers to the second half of the question on circumstances eliciting the complaint, are listed in table 3-1. Of the respondents reporting pain, 352 (81%) experienced this during emotional stress and 146 (34%) at rest. As pain can be provoked by different causes in the same individual, the total adds up to more than 100%. The severity of the post-operative pain was judged to be decreased after surgery by 332 individuals reporting pain, 36% of the total number of respondents. They and the pain free individuals (53%) together 89% can be regarded as improved.

Pain in the chest limiting physical activities was reported by 256 patients, 9 of which did not have the same angina pectoris as before the operation but did report pain in the chest scar. These last 9 patients could not be subdivided according to the circumstances, which precipitated the pain but the other 247 could, as shown in table 3-1. It is worth noting that the distribution over the various activities is very similar in the group with the limitation to that found in the entire group with pain.

As to frequency of pain attacks, in 85 (20%) patients it occurred daily

TABLE 3-1

CIRCUMSTANCES DURING WHICH PAIN ON THE CHEST WAS EXPERIENCED FOR THE TOTAL GROUP WITH ANGINA PECTORIS AND THE GROUP WITH LIMITING COMPLAINTS

	Pain present N=434	Pain limiting activities N=256
rest	146 (34%)	107 (42%)
light activities	91 (21%)	75 (29%)
medium activities	315 (73%)	205 (80%)
heavy work	318 (73%)	206 (80%)
emotions	352 (81%)	210 (82%)
unspecified	---	9 (4%)

TABLE 3-2

PAIN ON THE CHEST LIMITING PHYSICAL ACTIVITIES, IN RELATION TO THE FREQUENCY OF ATTACKS.

Frequency of pain attacks	Pain limiting activities N=256
daily	68 (27%)
several times a week	95 (37%)
several times a month	66 (26%)
seldom	24 (9%)
not analysed	3 (1%)
	256

and in 132 (30%) several times a week. Therefore,217 or 50% of the 434 individuals reporting pain attacks, experienced this less than weekly. Combining the subjective feeling of being limited in activities by pain, with the frequency at which pain is experienced gives the data listed in table 3-2. Apparently 90 individuals, 35% of those who feel themselves limited in physical activities, experience pain seldom or only a few times a month.

The answer to the question concerning the comparison between pain before the operation and pain at present, afforded an analysable result in 413 instances, that is 95% of those with pain. In 21 cases (5%) the answers were conflicting. These data were not analysed. In total, 332 individuals still had pain, but felt improved, or 77% of those with pain regarded it as less severe now, as compared to before the operation.

At the interviews of the 76 randomly selected patients, 41 were considered by the interviewer to have angina pectoris, while 44 reported pain in the questionnaire. In table 3-3 it can be seen that the interview agreed with the questionnaire in 65 instances (86%). In seven cases, the patient reported on the questionnaire to have the same pain in the chest as before the operation, while the interviewer classified this as pain, probably not angina pectoris, in 5 cases and twice as a mistake made in filling out the form. Four times, the patient reported no pain in the chest on the questionnaire while in 3 instances the history was that of (mild) angina pectoris, and once a mistake was made. In total, 3 questionnaires of these 76 interviewed patients were filled out erroneously (4%). Sensitivity of the questionnaire in relation to the interview was therefore 90% (37/41) and the specificity was 80% (28/35).

Improvement was found in 34 patients, 83% of those with AP. They judged their complaints to be in severity a mean of 34% (range 1 to 90%) of what they had experienced pre-operatively.

TABLE 3-3

ANGINA PECTORIS AS EVALUATED FROM THE QUESTIONNAIRE AND THE INTERVIEW IN 76 RANDOMLY SELECTED PATIENTS.

	Physician's interview		
Questionnaire	AP present	AP Absent	Total
Angina pectoris present	37	7	44
Angina pectoris absent	4	28	32
Total	41	35	76

3-4: DISCUSSION

Angina pectoris formed the primary indication for aorto-coronary bypass surgery. It follows therefore that the absence or presence of angina pectoris in the postoperative period should be the primary indicator for a succesful operation. However, the literature appraising the long-term results of surgery seldom addresses this topic. One generally finds discussions of operative mortality[7], long-term survival probability [8-10], patency of the grafts [11-12], excercise capacity[13-14], signs of myocardial ischemia on Thallium scintigraphy[15] etc. Reports on postoperative angina pectoris are rare [16-18]. This is probably because angina pectoris is hard to quantify because no standardised methods exist. Any study of the occurrence of AP is therefore open to criticism, whereas measurements of exercise tolerance or patency of grafts are obtained via well known and reasonably standardised techniques. In the few studies of post-operative AP, a different method was used each time. In one instance this was the information of a patient's physician[16], in another a a personal interview,[18] in the third, a standardised set of questions [17] was used. Not one of these studies contained more than 350 patients.

It was decided to use a questionnaire in our study because it provided a means of reaching a large number of patients. Moreover, all subjects were known to have coronary artery disease with complaints of angina pectoris in the past. This made a specially designed set of questions, using these past experiences preferable to employing, for instance, the Rose questionnaire, which was developed for screening chest pain in the normal population [19]. However it has to be realised that angina pectoris is a syndrome of complaints and not a patho-physiologic diagnosis. The perception by the subject of the signals arising in the chest is an important factor in defining the syndrome. This perception can vary from patient to patient[20] and within the patient as well [21]. Changes in weather, in emotional stress, in the amount of activity undertaken, in concomitant disease, might all vary the subjective symptoms of angina pectoris[21], not to speak of the generally recognised tendency of patients to please their physician and surgeon. The variation in complaints within a given patient and the difficulty in recognising, let alone quantifying angina pectoris make it difficult indeed to gather meaningfull data on pain.

Other investigators have made attempts at objectivity by performing exercise tests before and after surgery. Performance during an exercise test however is also influenced by subjective matters, both from the side of the patient and from the testing personnel[22]. This is, for instance,illustrated by

the improved excercise tolerance post-operatively in patients subjected to ligation of the mammary artery. In a well-documented study, 17 subjects with severe pre-operative AP underwent an operation which is now considered worthless and yet were able to exercise better afterwards [23]. The improvement was ascribed to higher expectations both from the patient and from the bystanders and possibly also to the natural course of the disease. But the fact remains that objective data are not available in the patients reported on in our study.

Furthermore the questions in our study were posed in such a format which made it possible to list only activities causing complaints and not those which could be performed without limitation. It is possible that the approach via the negative side gives an underestimation of what the individual can do in daily life.

Although the method of obtaining data via questionnaire does not necessarily lead to the same conclusion as a physician's interview, it did make it possible to study a large group of patients. The response to the questionnaire was good: 920 (95%) of the 969 patients who could be expected to answer, did so. Furthermore the answers to the several questions related to pain seemed consistent: when pain was reported to limit physical exercise, pain was also stated to be present in unrelated questions. A discrepancy existed only in 5% of the answers. Also, the agreement between the conclusions of the personal interview with the random sample of patients and the questionnaire answers of 86%, seems acceptable. Comparison of the answers obtained via both methods showed a sensitivity of 90% and a specificity of 80%. Differences were seen in both directions, i.e. pain was reported but not present according to the interview and pain was reported to be absent while it did occur. The personal interview did show up erroneous answers in 4% of the questionnaires. It seems to be unavoidable that some matters will not be properly understood if there is no chance for personal clarification. This last point is a definite disadvantage of questioning from a distance. Moreover, in retrospect it is in an omission that no data were gathered on the reproducibility in filling out the form.

Improvement in severity of angina pectoris after the operation was reported by the majority of the respondents: 89% of the total group. Of the 434 individuals with post-operative AP, improvement occurred in 332 or 77%. This compares well with the results of the interview, where 41 patients had AP and 34 (83%) felt improved. This improvement was considerable as evidenced by the

percentage of severity of current pain when compared to the pre-operative state: 34% on average with a range from 1 to 90%.

Unexpected in the pain history was, that many patients felt their pain complaints to be a limitation to physical activities although they did not experience pain frequently. As is illustrated in table 3-2, pain was experienced not more than several times a month by 90 individuals, 21% of the total group with angina pectoris, yet it was perceived as a limitation. Probably pain was avoided, thereby restricting the subject in activities. This also shows that a simple count of attacks to grade the severity of the angina pectoris does not afford a reliable result in judging the outcome of bypass surgery.

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APPENDIX IA.

QUESTIONNAIRE FOR OPERATED CARDIAC PATIENTS

Concerning pain in the chest

1- During the previous half year, have you regularly experienced pain in the chest, as you did before the operation? yes/no

If yes:(more than one time is possible)

- with light physical activities, like washing, dressing yes/no
- provoked by effort or emotion yes/no
- with moderate physical activities, like walking outside when it is cold yes/no
- with heavy physical activities, like cycling in cold weather, working in the garden, etc yes/no
- at rest, while sleeping in bed or sitting in a chair yes/no

2- Only if pain was experienced: How many times do you have pain in the chest? every day/ a few times a week/ a few times a month/ seldom/ never.

3- Only if pain was experienced after the operation.

The pain in the chest:

- disappeared at first, came back later, but less than before the operation.
- disappeared at first, came back later, the same as before the operation.
- disappeared at first, came back later, worse than before the operation.
- did not disappear, but it is less than before the operation.
- did not disappear, it is the same as before the operation.
- did not disappear, it is worse than before the operation.
- when the pain came back, was there a symptom free interval after the operation, if so, for how long? .....year

4- Have you taken any medication for pain in the chest in the last few months? yes/no

If yes:

- seldom (once a week or less)
- now and again (± once a day)
- regularly (more than once a day)

5- Were you admitted to a Coronary Care Unit after the operation? yes/no
If yes: how many times? ..... times

6- Did you have a second heart operation? yes/no
If yes: when? .....19..

7- Does the operation scar still bother you in the legs? yes/no
or in the chest? yes/no

8- Do you feel limited in your physical activities? yes/no
If yes: why?
pain in the chest/ dyspnea/ tiredness/ pain in legs/ something else.

Concerning work

10- were you employed during the last half year before the operation yes/no

11- Do you work now? yes/no
If yes: completely/ partial
If no: retired/ unfit to work (WAO,WW)

12- Smoking habits:
cigarettes/ cigar/ pipe.
Did you smoke in the year before the operation? yes/no
Do you smoke now? yes/no

13- Eating habits:
Were you on a diet for cardiac patients before the operation? yes/no
Are you now on a diet for cardiac patients? yes/no

14- Suppose you had to take the decision to be operated on again, presuming you were in the same condition, at the same age as then, would you let it be done? yes/no

15- Are you satisfied with the treatment at the Thoraxcenter after the operation? yes/no

16- Remarks.

APPENDIX 1B.

VRAGENLIJST VOOR AAN HET HART GEOPEREERDE PATIENTEN.

Betreffende pijn op de borst.

1- Heeft u het laatste half jaar nog regelmatig pijn gevoeld, zoals u die ook voor de operatie had? ja/nee

zo ja: (meerdere ja's zijn mogelijk!)

- bij lichte lichamelijke bezigheden, zoals wassen, aankleden ja/nee
- bij emoties of spannende momenten ja/nee
- bij matig zware arbeid zoals doorlopen buiten in de koude ja/nee
- bij zware arbeid zoals fietsen buiten in de koude, werken in de tuin, etc ja/nee
- in rust, zoals 's nachts in bed of zittend in een stoel ja/nee

2- Alleen bij pijn invullen: hoe vaak heeft u pijn op de borst?
iedere dag/ paar maal per week/ paar maal per maand/ zelden/ nooit.

3- Alleen bij pijn invullen: de pijn op de borst is na de operatie:

- eerst verdwenen, later terug, maar minder erg dan voor de operatie
- eerst verdwenen, later terug, even erg
- eerst verdwenen, later terug, maar erger
- niet verdwenen, maar minder erg
- niet verdwenen, even erg
- niet verdwenen, erger

- als de pijn terug is gekomen, hoe lang na de operatie? ...jaar

4- Neemt u de laatste maanden tabletten bij aanvallen van pijn op de borst? ja/nee

zo ja:

- zelden (1x per week of minder)
- zo nu en dan ± 1x per dag
- regelmatig, meerdere malen per dag

5- Bent u na de operatie nog op een hartbewakingsafdeling opgenomen geweest? ja/nee

zo ja: hoe vaak? .....keer

6- Heeft u na de eerste operatie nog een tweede operatie aan het hart ondergaan? ja/nee

zo ja: wanneer? 19....

7- Heeft u nog last van uw operatie littekens in de benen? ja/nee

in de borst? ja/nee

8- Voelt u zich beperkt in uw lichamelijke activiteiten? ja/nee

zo ja, waardoor?

pijn op de borst/ kortademigheid/ vermoeidheid/ pijn in de benen/iets anders.

9- Bent u na de operatie lichamelijk actiever dan ervoor? ja/nee

Wat werk betreft

10- Werkte u in het laatste half jaar voor de operatie? ja/nee

11- Werkt u nu? ja/nee

zo ja: volledig / gedeeltelijk

zo nee: gepensioneerd / afgekeurd (WAO, WW).

12- Rookgewoonten: sigaretten, sigaren, pijp

Heeft u in het jaar voor de operatie gerookt? ja/nee

Rookt u nu? ja/nee

13- Eetgewoonten

Volgde u voor de operatie een soort dieet voor hartpatienten? ja/nee

(vetarm, dieet margarine, etc)

Volgt u nu een dieet voor hartpatiente? ja/nee

14- Als u weer, zoals jaren geleden, voor de bslissing zou staan om zich te laten opereren, zou u het dan weer doen, aannemend dat u weer zo oud was als toen? ja/nee

15- Bent u tevreden over de opvang in het thoraxcentrum na de operatie. ja/nee

zo niet: dan graag toelichten onder 16.

16- Eigen opmerkingen, mag ook op een apart vel.

CHAPTER 4

SURVIVAL IN 1041 PATIENTS WITH CONSECUTIVE AORTO-CORONARY BYPASS OPERATIONS.

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4-1: ABSTRACT

To determine their prognosis, the first 1041 consecutive patients who underwent an isolated aorto-coronary bypass operation in the same institution since it opened in 1971, were followed for up to 10 years. The mean follow-up time was 3.5 years. The probability of survival at 5 years was 94 $\pm$ 2% (95% confidence limits). This was similar to the survival of the general Dutch population matched for age and sex.

Multivariate survival analysis with the proportional hazards model, did reveal a relation between the rate of death and sex and age at operation which was, however, not significant. There was a trend to a higher death rate with more vascular involvement (rate ratio of 3 vessel - versus 1 vessel disease of 1.9, N.S.) and a significant association with a low ejection fraction (EF) (rate ratio EF $\leq$ 0.30 versus EF $\geq$ 0.55 of 2.9, $p<0.05$).

Though surgery seems to eradicate the poor long-term outlook for patients with more serious vascular disease the adverse influence of decreased left ventricular function on survival is not changed.

Keywords: aorto-coronary bypass surgery, survival, coronary artery disease, left ventricular function.

4-2: INTRODUCTION

Aorto-coronary bypass surgery as a possible treatment of severe angina pectoris, has become an accepted concept[1-3]. Apart from symptomatic relief and improved cardiac function, a return to normal life expectancy after the operation was hoped for from the outset, but the latter was hard to prove. Studies of survival in patient groups randomized to either medical or surgical therapy, have shown that patients with stenosis of the main stem of the left coronary artery have a better life expectancy with bypass surgery[4,5]. The same is true for patients with three vessel disease[6,7] and possibly, for some subsets of patients with two vessel disease[8,9]. In the analysis of results it became clear as well, that operative mortality, skill of a particular surgical team and selection criteria into the study, were major determinants of outcome[10]. It is therefore of interest to study long-term results of aorto-coronary bypass surgery, not just in groups of selected patients, but also in consecutive series of patients from one department. This study describes the survival in such a series and attempts to elucidate which pre-operative characteristics might influence late survival.

4-3: METHODS

All 1041 consecutive patients who underwent a first aorto-coronary bypass operation between February 1971 and June 1980 provide the basis for this study. Pre-operatively, all had angina pectoris stable, or unstable, despite intensive pharmacological therapy. Excluded were those patients with additional surgical interventions such as valve replacement. Clinical characteristics of the series are presented in table 4-1.

At catheterization a vessel was considered diseased when a luminal diameter narrowing of 50% was seen in a major coronary artery in more than one projection. This resulted in a classification of 1, 2, 3 or Left Main coronary artery disease. Ejection fraction (EF) was calculated, where possible, with the area length method adjusted for single plane view [11,12]. Values of ≥ 0.55 were rated as normal (N), ≤ 0.30 as poor (P); and 0.31 - 0.55 as moderately impaired (M).

TABLE 4-1

CLINICAL PROFILE OF PATIENTS IN THIS STUDY.

Number of patients	1041	
males	915	88%
females	126	12%
Age males, mean	52.6	SD 7.7
Age females, mean	55.5	SD 8.2
Diseased 1 vessel	192	19%
2 vessels	320	31%
3 vessels	444	42%
Left main	85	8%
Ejection fraction ≥ 0.55	600	58%
0.31 - 0.55	248	24%
≤ 0.30	27	2%
unknown	166	16%

At operation the aim was to bypass all proximal lesions in the major coronary arteries, making the revascularisation as complete as possible. As the years went by, the surgical team became more experienced at this, as evidenced by the average number of implanted grafts per patient which rose from 1.33 in 1971, to 2.17 in 1975 and 3.04 in 1980.

Follow-up was via direct contact or, after a search in the civil registry, via a telephone conversation either with the patient or the general practitioner. At the reference date, August 1981, the follow-up was complete for vital status in 1035 (99.4 %) of the patients. For the six patients lost to follow-up, the last date of an out-patient clinic visit was taken as the last moment of being alive in the analysis. Length of follow-up ranged from 1-10 years, the average was 3.5 years. Mortality was subdivided into operative mortality when it occurred within 28 days of surgery and late mortality, when it occurred subsequently. The cause of death was determined via contact with the treating physician or autopsy report where available.

The survival data were analysed by the Kaplan Meier method of actuarial survival probability [13]. Since survival generally depends on more than one factor, multivariate survival analysis was performed. A stepwise non-linear algorithm of the Cox proportional hazards model was used to select variables that predicted survival[14].The following variables were considered: age at operation, sex, number of pre-operatively diseased vessels, pre-operative ejection fraction and number of grafts placed at operation.

4-4: RESULTS

A total of 64 (6.15%) patients died during follow-up. As presented in table 4-2, operative mortality (12 patients,1.2%) constituted one fifth of the total mortality. Operative mortality was slightly higher for women: 2.4% versus 1.0% for men. However this difference was not statistically significant.

Of the 52 late deaths, 39 (75%) were cardiac: 17 were caused by an acute myocardial infarction, 15 were sudden, 5 were due to congestive heart failure while 2 occurred during re-operation for recurrent angina pectoris. In only 13 instances (25%) was the late death non-cardiac: twice a suicide, 5 times carcinoma and 6 times from various other causes.

TABLE 4-2

MORTALITY AND CAUSES OF DEATH.

	total	%	women	%	men	%
number of patients	1041	100	126	100	915	100
operative mortality (28 days)	12	1.2	3	2.4	9	1.0
late mortality						
cardiac, sudden	15	1.4	2	1.6	13	1.4
cardiac, at re-operation	2	0.2	-		2	0.2
cardiac, infarction	17	1.6	4	3.2	13	1.4
cardiac, chronic failure	5	0.5	-		5	0.6
non-cardiac	13	1.3	1	0.8	12	1.3
total mortality, all causes	64	6.2	10	8.0	54	5.9

As appears from figure 4-1, the actuarial survival probability at 5 years was 94 ± 2% and at 8 years 90 ± 4%. Corresponding survival probability of the general population in the Netherlands, matched for age and sex, would have been 94,6% at 5 years and 90,0% at 8 years[15]. In figure 4-2 the influence of pre-operative vascular involvement on survival is shown. Patients with 1 vessel disease had a 5 year survival probability of 94 ± 4%, with 2 vessel disease of 96 ± 3%, with 3 vessel disease 92 ± 4% and with left main disease 88 ± 6%. At 8 years, this was respectively: 92.5 ± 6% , 93 ± 5%, 88 ± 7% and 77 ± 21%.

Pre-operative ejection fraction was clearly related to survival. As can be seen in figure 4-3, survival probability with a normal EF at 5 years was: 95 ± 2%. For those patients with a moderatly impaired EF it was: 92 ± 4% and with a poor EF: 83 ± 17%.

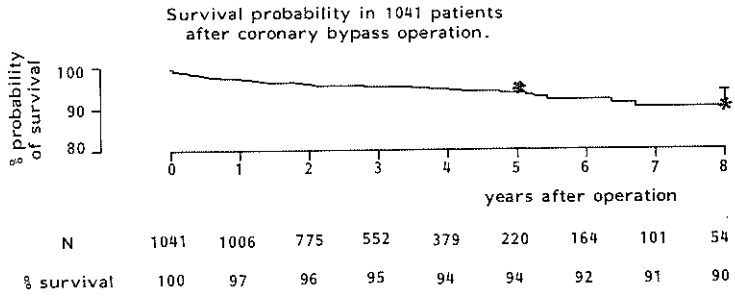

Figure 4-1.

Probability of survival in total patient group plotted against time after surgery: at 5 years 94%, at 8 years 90%. N denotes number of patients alive at the end of each year. The asteriks show the expected survival at 5 and 8 years of the general Dutch population matched for age and sex, at 5 years: 94.6% at 8 years 90.1%. The vertical bars represent 95% confidence limits.

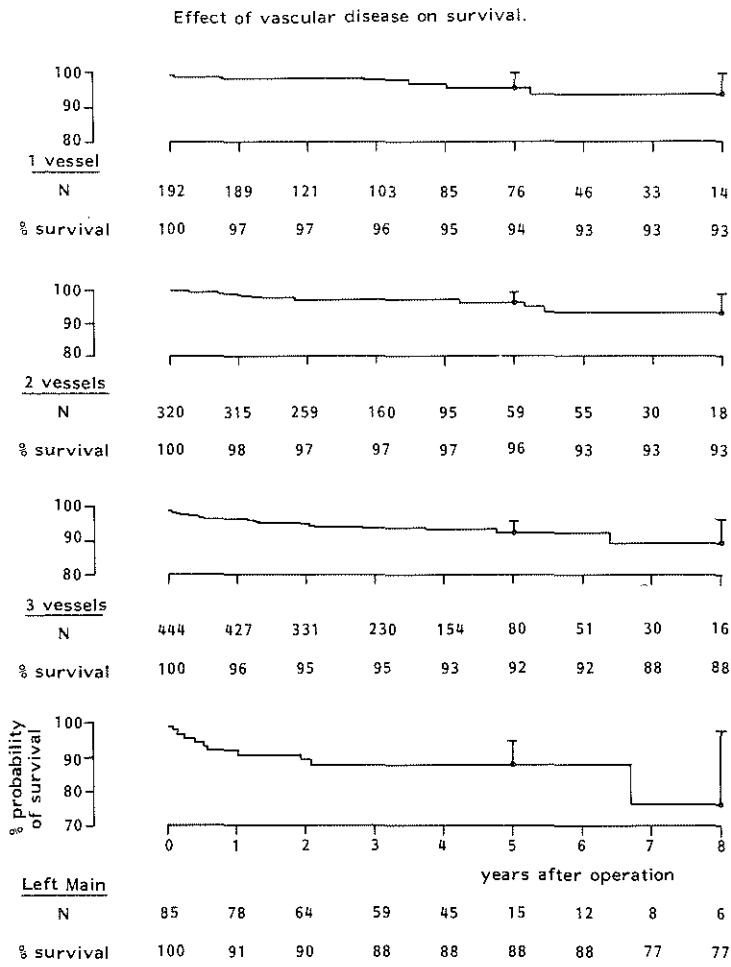

Figure 4-2.

Probability of survival for patients with 1, 2, 3, and left main vessel disease, plotted against time after surgery. N denotes number of patients in each group alive at the end of each year. The vertical bars represent 95% confidence limits.

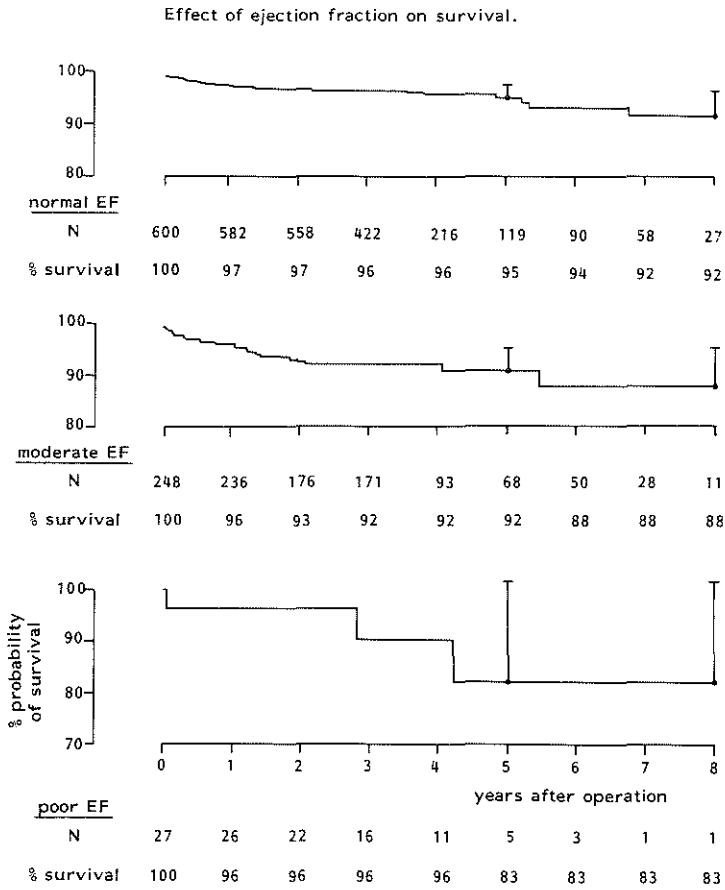

Figure 4-3.

Probability of survival for patients with normal, moderately impaired and poor ejection fraction, plotted against time after surgery. At 5 years this is respectively: 95%, 92% and 83%. The vertical bars represent 95% confidence limits.

Multivariate analysis was possible in 875 patients for whom all information was available. In this group 51 deaths (5.9%) occurred. Excluded from analysis were the patients with incomplete data: the 166 without a calculated EF. The number of deaths among these last patients was 13 (7.6%). The results of the analysis are expressed as rate ratios, i.e. the death rate (expressed as number of events per unit person-time of follow-up) in a particular category divided by the death rate in a reference category given that other characteristics entered in the survival model are equal. From the rate ratio point estimates presented in table 4-3 it can be seen that age and sex were important predictors of survival, although not statistically significant. Vascular involvement did show a trend of increased death rate the more extensive the disease proved to be, resulting in a rate ratio of 2.7 for left main stem disease compared to 1 vessel involvement. This difference was again, not significant.

Ejection fraction did have a statistically significant influence on survival probability ($p<0.05$), with a risk ratio of 2.9 in those patients with a poor EF. The number of grafts placed at surgery varied according to the number of vessels diseased. As can be seen in table 4-4, there is no difference in the number of grafts placed per disease group between those patients who survived and those who died. This overall impression of equality was supported by the multivariate analysis: the number of grafts per patient appeared not to be a relevant predictor of survival probability. A summary of post-operative results from other centers is shown in table 4-5 with the data from Rotterdam added as comparison.

4-5: DISCUSSION.

It is remarkable, how similar the survival of surgically treated patients in the various reported series appears to be [6,16,17], despite the differences which presumably exist in inclusion criteria and in population. In the centers reporting just surgical data, mostly of consecutive series of patients, the survival probability varied at 5 years from 97% to 87%. In these centers the operative mortality was low, recently being less than 2%, while it was 10% before 1970 [16,17]. Therefore the 1.2% reported in our series falls well within that range as does the late survival with 96% to 88% at 5 years.

Survival showed a slight downward trend, when the coronary artery disease was more severe, although this was not statistically significant. Extent of vascular involvement is a significant predictor of survival in medically

TABLE 4-3

RATE RATIO FROM COX'S REGRESSION ANALYSIS OF SURVIVAL (N = 875).

Variable	N	rate ratio*	P
age at operation:			
<50 yrs	321	1.0	
50 - 60 yrs	408	1.3	NS
>60 yrs	146	1.7	
sex: women	99	1.0	
men vs women	776	0.6	NS
vascular involvement:			
1 vessel	161	1.0	
2 vessels	267	1.2	
3 vessels	374	1.9	NS
left main	73	2.7	
Ejection Fraction:			
≥0.55	600	1.0	
0.31 - 0.55	248	1.7	<0.05
≤0.30	27	2.9	

ve = vessel. EF = ejection fraction

rate ratio = incidence of mortality in one group divided by the incidence in the group with which the comparison is made.

TABLE 4-4

NUMBER OF GRAFTS PLACED IN SURVIVORS AND NON-SURVIVORS.

Vascular disease	number of grafts/patient	
	survivors (n=977)	non-survivors (n=64)
1 vessel	1.4	1.4
2 vessels	2.1	2.3
3 vessels	3.0	3.4
LM	3.5	3.3

TABLE 4-5

FIVE YEAR SURVIVAL IN SEVERAL SURGICAL SERIES.

	nr. of patients	1 vessel	2 vessels	3 vessels	LM
Cleveland (Cosgrove) (16)	4391	97%	94%	91%	88%
Houston, St Lukes, Texas (6)	846	94%	94%	93%	-
Birmingham, Alabama (17)	1800	94%	88%	89%	87%
Rotterdam	1041	94%	96%	92%	88%

LM = Left Main disease.

treated patients[7,18,19]. Surgery therefore, seems to eradicate pre-operative vascular disease as a risk factor for decreased survival postoperatively. This has been found as well by Detre et al.[20] and Kirklin et al.[17] but not by Lawrie et al.[21]. In this last study, reporting on 10 year survival, the patients were operated on before 1974, when revascularisation was less complete than it is at present. This might be an explanation for the discrepancy in results of Detre and Kirklin.

Multivariate analysis of the usual risk factors in our patients showed no significant relation between survival and age at operation, sex, vascular involvement and number of grafts placed at operation. With the exception of age at operation these findings are in accordance with those reported in the literature[6,20,22]. Since so few older patients were included, it is possible that the influence of age could not be ascertained. Only 5 (0.5%) of the studied patients were above 70 years of age and 168 (16%) above 60 years. Furthermore it has to be realised that the multivariate analysis had a low statistical power due to the relatively low total mortality: 64 patients (6.2%) died out of the 1041 included in the study.

The finding that the number of grafts placed at surgery does not influence late survival is again evidence that the severity of pre-operative vascular involvement as a risk factor is changed by surgery, since the more vessels are involved, the more grafts will be placed.

Pre-operative ejection fraction, however, did influence late survival markedly. This has been observed by many others, both in straight surgical series[17, 21] and in the VA randomized study [20]. Burggraf [19] and Mock et al. [23] reported that in medically treated patients EF is the strongest predictor of survival, even stronger than the number of diseased vessels. It may be postulated, therefore, that when left ventricular function is compromised, extensive scarring in the ventricular wall will be present. This condition cannot be altered by increasing the bloodflow to the scar. Thus, the beneficial effect of the bypass is limited unlike that in ischemic myocardium, which is rendered less ischemic by flow through the bypass graft. Since, after surgery, left ventricular function is hardly changed, as described by Hugenholtz et al.[24] in a subset of these patients, a poor EF remains a risk factor even after bypass surgery, while the risk connected to the number of diseased vessels is changed by surgery.

The evaluation of results after aorto-coronary bypass surgery has evoked much discussion. Ideally, each large surgical center should have done a randomized

study. However, this was not possible because of public clamour for operations even before evaluation was completed. Lacking the data for evaluation from each institution, those data arising in randomised studies elsewhere, might be used. The ongoing studies are the Veterans Administration Cooperative Study (VA study) [4], the European Coronary Surgery Study Group (ECSSG)[7] and the National Heart, Lung and Blood Institute Coronary Artery Surgery Study (CASS)[25]. A problem with the analysis is the high operative mortality (5.8%) in the VA study, rendering the survival in surgically treated patients lower than is usual in other series and the restrictive inclusion criteria in the ECSSG. These criteria are stable angina, involvement of 2 or more coronary arteries and a normal EF. Thus the many patients with unstable complaints or a low EF who have a known lower survival probability [19,23] are excluded. Moreover, inclusion in a randomized study takes place at the moment of randomization while, in straight surgical series, it occurs upon entering the operating theatre, thus creating different starting points. In the case of CASS, so far only the data on 3 year survival of patients with left main coronary artery disease have been published, confirming increased survival after surgery[5]. In table 4-6 are listed the 5 year survival data from the VA study and the ECSSG. As can be seen, the survival is higher in the operated group than in the medically treated group for patients with 3 vessel- and left main stem-disease. Moreover, it is evident that the higher operative mortality in the VA hospitals has an adverse effect on the long-term results.

TABLE 4-6

FIVE YEAR SURVIVAL IN TWO RANDOMIZED STUDIES.

Treatment	nr.of patients	1 vessel	2 vessels	3 vessels	LM
VA-Cooperative (27)					
medical	354	88%	87%	76%	
surgical	332	93%	79%	82%	
European CSSG (28)					
medical	373		87%	81%	67%
surgical	395		91%	94%	89%

LM = Left Main disease.

Confounding the evaluation of survival after aorto-coronary bypass surgery is the changing mortality of coronary heart disease in the last 10 years. In the USA, mortality has decreased by 25%[29] and in the Netherlands probably by 15%[30], rendering comparison with historical series from the 1960's of limited value. Therefore, as a standard against which results can be measured, data from the contemporary general population matched for age and sex must be used, as Greene[31] and Kirklin[17] have done. In theirs, as well as in our study, 8 year survival of the total patient group was the same as that in the general population. However, this cannot be taken as direct evidence of the therapeutic efficacy of bypass surgery. Therefore, as in other straight surgical series, the data from our study do not prove that aorto-coronary bypass grafting improves life expectancy in individuals with angina pectoris due to coronary artery disease. It can be concluded however that life expectancy with surgery as performed in our institution is quite good and possibly better than without surgery in those patients who had a decreased life expectancy due to severe coronary artery disease i.e. triple vessel or left main stem involvement and who had severe angina pectoris originally. Symptomatic treatment of anginal complaints with aorto-coronary bypass surgery remains therefore a therapeutic option with acceptable risks, provided the operative mortality is low.

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CHAPTER 5

ANGINA PECTORIS, 1 TO 10 YEARS AFTER AORTO-CORONARY BYPASS SURGERY

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5-1: ABSTRACT.

The incidence of angina pectoris (AP) after bypass surgery was assessed in 1041 patients operated consecutively between 1971 and 1980. Of the 977 survivors, 920 (94%) participated in the study with a follow-up time varying from 1 to 10 years (mean 3.5 yrs). Post-operative angina pectoris was present at one year in 277 patients (30%), at 3 years in 46%, at 8 years in 50%. The pain limited usual physical activities in resp. 17.5%, 30% and 25%. None the less, 89% of the respondents felt improved by surgery. Factors without predictive value for late outcome were sex, number of pre-operative diseased vessels and pre-operative ejection fraction. A correlation was found between post-operative AP and younger age at surgery in the males only ($p<0.001$); between AP and patency rate of the bypass graft ($p<0.005$) and with the status of the coronary arterial tree at three years post-operatively ($p<0.001$) in both sexes. The percentage of patients with recurrent AP increased with time after surgery up to three years, but remained stable thereafter. In conclusion, post-operative AP seems initially related to decreased functioning of the bypass graft, later to progression of coronary sclerosis in the native circulation.

Keywords: coronary artery bypass surgery, angina pectoris, graft-patency, progression coronary sclerosis.

5-2: INTRODUCTION.

Aorto-coronary bypass surgery as treatment of angina pectoris was introduced in 1968[1,2]. Since then,it has become an accepted procedure particularly when pharmacological management has failed to relieve the symptoms. Today, large numbers of patients have been operated upon with more then 85% symptomatic improvement in the first year after surgery [3-5]. But, as more time elapsed after the operation, angina pectoris has recurred in an appreciable number of patients[6-10]. This study reports on the re-occurrence of chest pain during a post-operative follow-up, of up to 10 years in 920 patients out of 1041 patients consecutively operated at the Rotterdam University Hospital. Pre-operative characteristics determining late outcome were sought for. Moreover an analysis was made of specific causes, which might explain or predict the return of symptoms in the post-operative period.

5-3: Material and Methods.

Patient selection: All 1041 patients who underwent isolated aorto-coronary bypass surgery from the time of opening of our institution in February 1971 to May 1980 were included in the study. All patients were symptomatic before operation despite intensive pharmacological therapy. The anginal complaints could be either stable or unstable. Those patients undergoing left ventricular aneurysmectomy or valve repair in addition to the bypass operation, were excluded. At the reference time, May 1981, 64 (6.2%) of the patients had died. The 977 survivors were sent a questionnaire to ascertain their post-operative condition. Of these, 920 (94%) returned their forms. They comprise the study population (table 1). This group consisted of 109 women, aged 55.5 ± 8.2 years and 811 men aged 52.6 ± 7.7 years. All patients were operated by the same surgical team. Follow-up time varied from 1 to 10 years with a mean of 3.5 years.

TABLE 5-1

RESPONDENTS TO QUESTIONNAIRE CONSTITUTING THE STUDY POPULATION, SHOWN IN RELATION TO THE TOTAL NUMBER OF PATIENTS OPERATED CONSECUTIVELY FROM 1971 TO JUNE 1980.

	total	men	women
Alive	977	861	116
respondents	920 (94.2%)	811 (94.2%)	109 (94.0%)
Died	64	54	10
peri-operative	12 (1.2%)	9 (1.0%)	3 (2.4%)
late	52 (5.0%)	45 (4.9%)	7 (5.5%)
Total operated	1041	915	126

Respondents to questionnaire shown as percentage of those alive in May 1981.

Pre-operative catheterization: All patients underwent a pre-operative right and left-heart catheterization with selective coronary angiography. Coronary artery stenosis was judged to be present when a luminal narrowing was seen of 50% or more in the diameter of one of the major coronary arteries in more then one view. The main stem of the left coronary artery was graded separately from the anterior descending and circumflex branch of this artery.

Ejection fraction (EF) was calculated from the left ventricular angiogram in the right anterior oblique projection with the area length method adjusted for single plane views[11,12]. A normal (N) EF was considered present if it was $\geqslant 55\%$, a poor (P) EF if $\leqslant 30\%$ and a moderately decreased (M) EF when $> 30\%$ but $< 55\%$.

Post-operative catheterization: Recatheterization was performed at 1 and 3 years post-operative in 169 patients with near consecutive operations between 1976 and 1979. This recatheterization was carried out as part of an ongoing national study, irrespective of complaints[13]. The coronary angiograms were first analysed for patency of the aorto-coronary bypass. In addition the coronary score was calculated as described by Leaman et al in 1981[14], which was based on a scheme accepted the by American Heart Association[15]. This score takes into consideration the amount of luminal diameter narrowing both in the native coronary arteries and in the aorto-coronary bypass. Moreover it is weighted according to the expected flow to the left ventricle in each coronary vessel. The score thus represents the "resistance" to the expected blood flow to the myocardium. The place of anastomosis of the bypass on the coronary artery determines which segments of the coronary tree are reached with flow from the bypass as well as the segment which cannot be reached because of intervening stenoses, thus providing the opportunity to correct the score after bypass surgery. The coronary score varies between 0 in normals and 50 in severe three vessel disease.

Data storage and analysis: Data concerning pre-operative catheterization, number of grafts placed at operation, post-operative catheterization, when available and subjective data from the questionnaire were stored using MUMPS on a PDP-11 computer. The nature of this data handling system makes it possible to combine data originating in various sub-departments[16] of the cardiology and the thoracic surgery division. For each patient, 46 items were stored. Analysis was performed with sorting programs written in BASIC and executed on a

Hewlett Packard 85 micro-computer. Statistical testing was done with the Hewlett Packard statpack Chi-square contingency test [17], the Mantel-Haenszel test [18] the Friedman's two way analysis by rank[19] and the Wilcoxons rank sum test[19].

5-4: RESULTS.

At follow-up, angina pectoris (AP) was present in 434 (47%) individuals. Of the 109 women, 60 or 55% experienced AP and of the 811 men, 374 or 46%. The difference in the occurrence of post-operative angina pectoris between men and women, 46% versus 55%, was not statistically significant (X^2=3.07,p=0.079). The data for both sexes were therefore pooled for further analyses unless stated differently.

With regard to severity of the pain in the chest: of the 434 individuals with post-operative angina pectoris, 332 (or 36% of the total population) had less severe complaints after the operation than before. The complaints were reported to be "as bad or worse than before" by 81 patients. These 81, and the 21 patients, who provided unspecific replies constitute 11% of the total population. They were regarded as unimproved by surgery. On the other hand, we found that 486 patients were pain free, while 332 patients described their anginal complaints as less severe. Thus, 818 (89%) of the total group can be regarded as improved.

The various circumstances under which post-operative AP was experienced are listed in table 5-2. It is possible for an individual to have complaints provoked by more than one event, causing the absolute number of patients to be larger than the total who reported pain. The high fraction with pain provoked by emotion is noteworthy: 38% of the total and 81% of those with pain in the chest. Angina pectoris "never disappeared" after the operation in 111 of the 920 patients (12%), as shown in figure 5-1. This fraction was slightly higher in the early years of this study. In 24 (17%) of the 140 patients operated in the years 1971 through 1975, AP never disappeared, while of the 780 operated between 1976 and 1980 this was in 87 (11%) the case. The difference is significant (X^2 = 4.012, $p<0.05$).

TABLE 5-2

EVENT DURING WHICH ANGINA PECTORIS WAS EXPERIENCED
BY THE 434 PATIENTS REPORTING SYMPTOMS.

Event	no.of patients	% of respondents	% of group with AP
		n=920	n=434
At rest	148	16%	34%
Light physical work (dressing, bathing)	91	10%	21%
Medium physical work (walking outside,shopping)	315	34%	73%
Heavy physical work (bicycling, gardening)	318	35%	73%
Emotions	352	38%	81%

AP = angina pectoris.

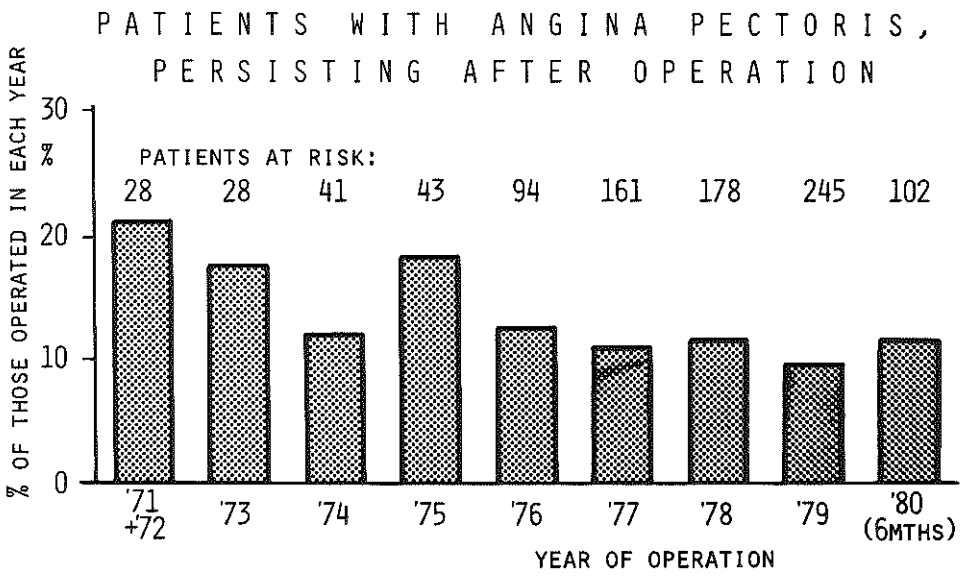

Figure 5-1.

Patients with post-operative angina pectoris, persisting after surgery, expressed as a percentage of those operated on in that year. In the 140 patients operated before 1976, pain persisted in 24 (17%), of the 780 patients operated thereafter this occurred 87 times (11%). The difference is significant at $p<0.05$.

The incidence of AP in the years following operation increased steadily from 16% at 3 months to 46% at three years. No further increase in the number of symptomatic patients in the population at risk is evident after three years (fig. 5-2). Not only the occurrence of AP showed a trend in time, the severity of complaints did so as well. Angina pectoris, sufficiently severe to limit physical exercise is shown as a percentage of the population at risk.

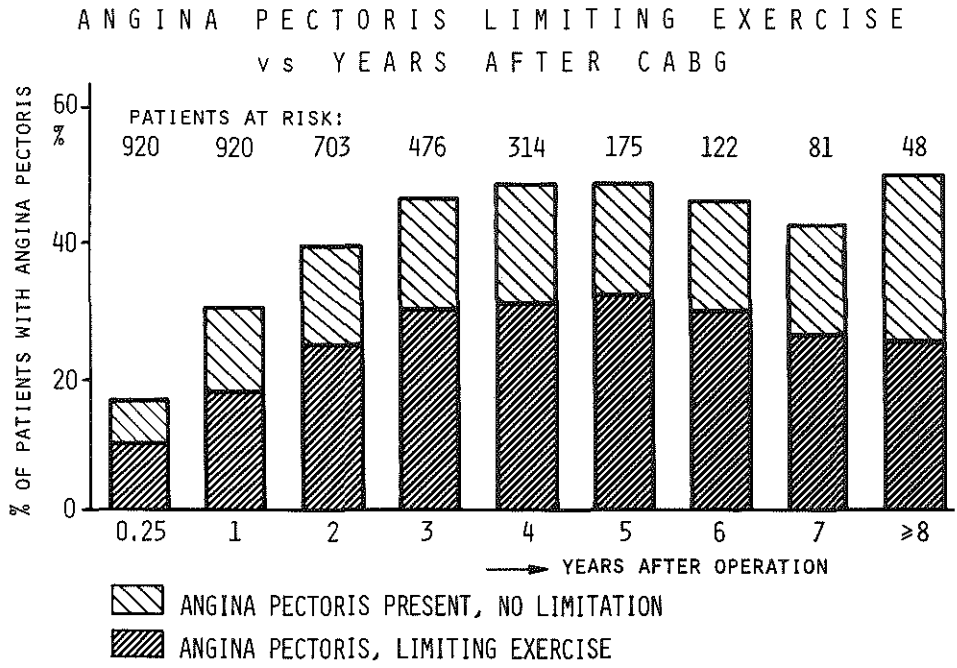

Figure 5-2.
Number of patients with angina pectoris at yearly intervals after aorto-coronary bypass surgery. The number of patients at risk indicates those followed up to the end of that year. Symptoms are subdivided into pain limiting physical activities and pain experienced but not limiting activities.

The number of the individuals experiencing pain, which did not influence their daily activities, was rather constant at 15%. The increase in the number of patients with pain in the first three post-operative years is seen in the group which feels it as limiting their activities. To study the influence of age at operation on the post-operative results, the total population was subdivided in 4 age groups: younger then 40 yrs., 40 - 49 yrs., 50 -59 yrs. and 60 yrs. and older. The incidence of AP in men was 58% for the youngest, 55% and 44% for the two middle groups, against 33% in the oldest. This age trend was highly significant ($p < 0.001$)[18]. No trend could be discerned in in the women (see fig.5-3).In those males who feel limited by pain, there is a trend with age as well: the younger the age at operation the higher the incidence of AP limiting physical activities ($p < 0.005$). This age trend is, again, not seen in women ($p = 0.84$).

Anatomical correlates:

Extent of pre-operative vascular lesion

Pre-operative vascular disease varied from involvement of 1 vessel in 171 (18%) of the patients, to 2 vessels in 291 (32%), 3 vessels in 386 (42%) and the left main stem in 72 (8%). In table 5-3 it can be seen that post-operative angina pectoris ranges from 48% in patients with 2 vessel disease to 42% in those with a lesion in the main stem of the left coronary artery. Analysed with the Chi-square contingency test, these observed differences could only be attributed to random variation ($p= 0.78$).

Pre-operative ejection fraction

In table 5-4, the occurrence of post-operative AP is demonstrated between groups with various ejection fractions. There appeared to be no statistically significant difference, even when the worst group, those with a poor EF, were tested versus the group with a normal EF ($p = 0.09$).

Number of grafts placed at operation

There is no significant difference in the number of grafts placed at surgery in those who later experienced angina pectoris compared to those who did not (table 5-5).

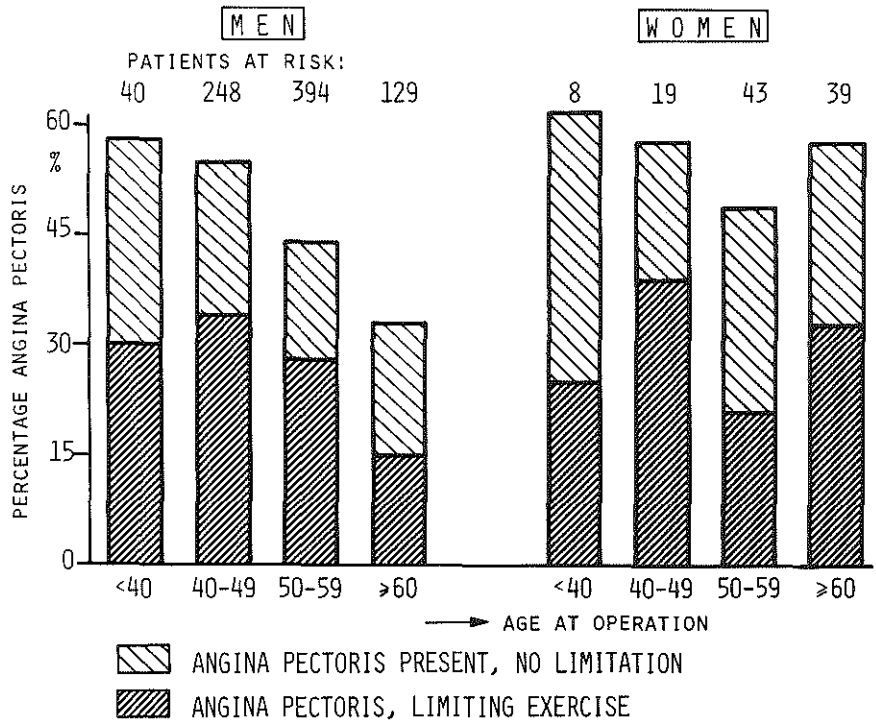

Figure 5-3.

Post-operative angina pectoris at mean follow-up of 3.5 years, occurring in men and women, with a subdivision according to age at operation. Angina pectoris present and angina pectoris limiting physical activities shows an age trend in men ($p<0.001$) but not in women.

TABLE 5-3

POST-OPERATIVE ANGINA PECTORIS (AP) IN RELATION TO PRE-OPERATIVE NUMBER OF STENOSED VESSELS, AS REPORTED BY 920 PATIENTS.

Stenosed Vessels	patients with AP		patients without AP	
1 vessel	81	(47%)	90	(53%)
2 vessels	141	(48%)	150	(52%)
3 vessels	182	(47%)	204	(53%)
LM	30	(42%)	42	(58%)
total	434	(47%)	486	(53%)

These differences are not statistically significant (X^2 1,07 p=0.78)
LM = Left Main coronary artery.

TABLE 5-4

POST-OPERATIVE ANGINA PECTORIS (AP) IN RELATION TO PRE-OPERATIVE EJECTION FRACTION.

Ejection Fraction	patients with AP		patients without AP	
Normal	256	(47%)	287	(53%)
Moderately impaired	92	(43%)	120	(56%)
Poor	15	(65%)	8	(35%)
Unknown	71	(50%)	71	(50%)
total	434	(47%)	486	(53%)

These differences are not statistically significant when tested for Normal versus Poor (p=0.09).

TABLE 5-5

POST-OPERATIVE ANGINA PECTORIS (AP) AND NUMBER OF GRAFTS PLACED AT OPERATION IN RELATION TO THE NUMBER OF STENOSED VESSELS PRE-OPERATIVELY.

Stenosed vessels	Number of grafts / Patient	
	patients with AP	patients without AP
1 vessel	1.44	1.27
2 vessels	2.32	2.10
3 vessels	3.36	3.52
LM	3.17	3.26

LM = Left Main coronary artery.

Patency of the grafts.

In table 5-6 it is shown that the patency rate in the 169 re-catheterized patients is 74% at one and 71% at three years for those with AP after the operation. This is significantly lower than the observed 85% respectively 83% in the patients who did not have pain ($p<0.005$). On the other hand, 17% of the grafts were closed three years after the operation in those patients who did not complain of angina pectoris. Patency rate, overall, was 79% at one year and 76% at 3 years after the operation. Patency rate did not differ significantly in relation to age: at 3 years it was 78% in those 40 yrs of age. 79% at 40 - 49 yrs, 76% at 50 - 59 yrs and 74% at 60 yrs and older.

TABLE 5-6

GRAFT PATENCY AT 1 AND 3 YEARS AFTER OPERATION, IN PATIENTS WITH AND WITHOUT ANGINA PECTORIS, IN A SUBSET OF 169 PATIENTS WITH 2 RECATHETERIZATIONS.

	nr. of grafts patent/nr. of grafts placed	
	Patients with AP (n=98)	AP absent (n=71)
1 year post-op.	189/225 74% *	155/182 85%
3 years post-op.	181/255 71% *	151/182 83%

Post-op. = post-operative

* significantly less often patent. 1 year $X^2 = 7.737$ $p = 0.005$

3 year $X^2 = 8.359$ $p < 0.005$

Coronary score

The mean pre-operative score in those later suffering AP was calculated to be 13.8,SD 8.0. In those without late AP a mean of 14.2, SD 7.0 was found. These differences were not significant. Surgery lowered the coronary score in both groups. At one and three years post-operatively the mean score in the AP group was 6.4, SD 4.0 and 9.3, SD 6.5 respectively. In the asymptomatic group, these values were 4.7, SD 4.0 and 4.8, SD 5.1, as illustrated in figure 5-4. With two way analysis of variance it could be concluded that surgery lowered

the coronary score significantly at one and three years post-operatively in both the symptomatic and asymptomatic group ($p<0.001$). At the first post-operative study the difference in coronary score between groups did not reach statistical significance ($p= 0.07$), however at the second post-operative study the coronary score in the group with AP was significantly higher than in the asymptomatic group ($p<0.001$, by Wilcoxon's rank sum test [19]).

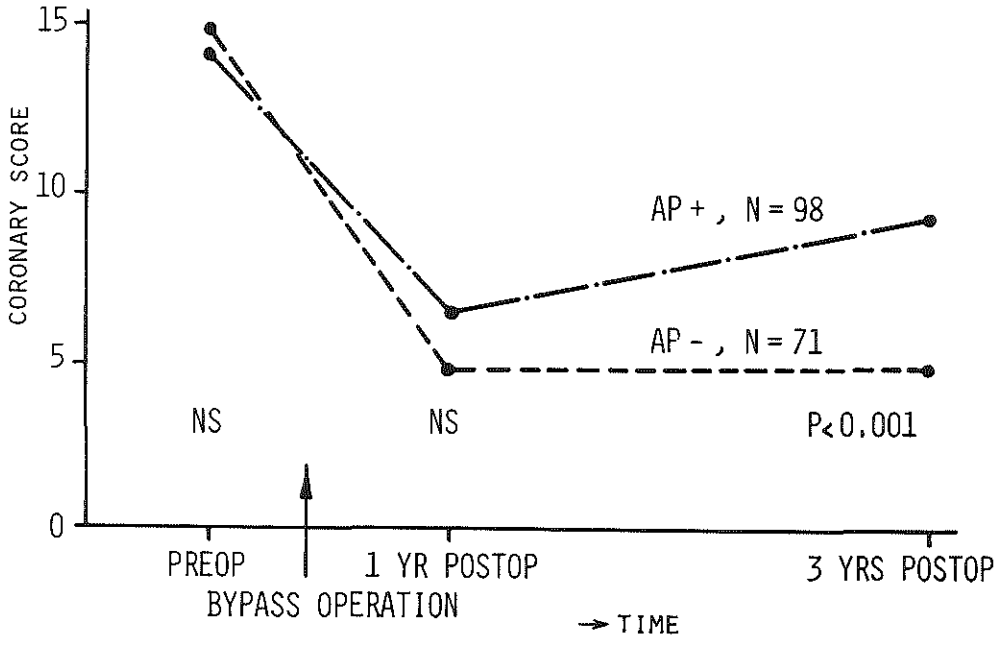

Figure 5-4.

Mean coronary score, determined pre-operatively and at 1 and 3 years post-operatively, in the group experiencing AP and the group without AP at the reference date. Number of patients indicates those catheterized 3 times, with follow up data on AP via questionnaire. The coronary score worsened significantly in AP group between 1 and 3 years postoperatively ($p<0.001$), which did not happen in the group without AP.

5-5: DISCUSSION.

Loss of improvement late after aorto-coronary bypass surgery was first commented on by McNeer in 1974[20]. He reported a drop in angina free patients from 62% at one year to 53% at 2 years post-operatively, as seen by yearly follow-up of 260 patients. Campeau et al[6] also found a deterioration of results. Their patients experienced angina at one year after operation in 38%, at 3 yearsin 45% and at 7 years in 63%. In a 7 year follow-up by Cameron et al [21] angina recurred at a linear annual rate from 21% at one year to 37% at 6 years with an increase to 50% at 7 years. The only large scale European study with follow-up data is that of the European Coronary Surgery Study Group[22] showing angina pectoris in the surgical group at one year in 42% and at 3 years in 51%. These results, seen in the first three post-operative years, are similar to ours and are, given the initally favorable results,in fact disappointing. However, we did not see a continuation of the increase in symptomatic patients beyond the third post-operative year.

One possible shortcoming in this study was the fact that a questionnaire was used to assess the postoperative state. As all patients suffered angina pectoris before the operation, it could be expected that after surgery these same patients would be able to recognise their old complaints. Therefore, if a patient reported symptoms similar to those prior to surgery, angina pectoris was assumed to be present. Nevertheless we realize that a questionnaire rather than an interview could be the cause of some misinterpretations.

A second shortcoming might be that this is not a longitudinal study of individual patients, but a sample of a large patient group at one moment. Thus it is possible that a patient at first experiences mild recurrence of angina, and only later severe symptoms. As a consequence, the symptoms are classed as severe and the mild period is missed. Similarly, the 53 patients who required re-operation, were categorised according to their condition after the second operation thus missing cross-over from severe symptoms to their present improved state. In this respect, the late mortality in our population is noteworthy as well. In total, 52 patients (5%) died during the follow-up period of a mean of 3.5 years, an average death rate of 1.4% per year. As it is not known if these patients had post-operative AP or not, they have been omitted from the analysis. Assuming that they did have AP, a bias has been introduced, albeit not a very large one, favoring the group without complaints.

A third criticism might be that the timing of the questionnaire led to separation in time between the answers to the questionnaire and the moment of re-catheterization. We elected to do this, because it made a comparison possible with patients who were not re-catheterized, as the history was obtained in the same manner in all 920 studied patients. The mean interval between the return of the questionnaire and the moment of the last re-catheterization was 7.7 months. As the number of patients reporting recurrence of symptoms in the third and fourth post-operative year was respectively 7 and 2% (fig.5-2), the error introduced by this time gap seemed acceptable. Neither of these three possible sources of errors can however, explain why the loss of improvement was limited only to the first three post-operative years.

The exact causes of angina pectoris after aorto-coronary bypass are still unclear. Several investigators have commented on early failure after surgery [8,9] and later loss of improvement after an apparently successful, initial operation[6,7,10]. The following five possibilities have been put forward: (1) poor functional state of the bloodvessels, (2) impaired ventricular function prior to surgery, (3) insufficient revascularization at surgery, (4) closure of the bypass graft or,(5) progression of coronary sclerosis in either the bypassed artery or the unbypassed arteries resulting in a loss of blood flow to the myocardium during the post-operative period. These possibilities will be discussed in relation to the findings of this study.

The first 3 factors could not be shown to influence late symptoms, since the difference in prevalence of post-operative AP did not reach statistical significance in respect to pre-operative number of stenosed vessels, pre-operative ejection fraction, or number of grafts placed at operation. However, the cardio-surgical team's amount of experience did seem to influence results as evidenced by the slightly higher percentage of patients in which the pain persisted after surgery in the years before 1976 compared to later. Thus, insufficient revascularization due to technique may bear a relation to post-operative angina pectoris.

Related to surgical technique is point 4, the closure of the bypass graft. As Bourassa et al[23] have shown, early closure, within one month of surgery, is clearly influenced by technical factors and due to thrombosis in the graft. It commonly occurs in 12-15% of the grafts. Late closure, from 1 to 12 months post-operatively, is caused by fibrous intimal proliferation which is seen in 5-15% of all grafts. Closure after 1 year is rare. An attrition rate of 1-2% per year has been reported. It is often seen as a progression of a formerly localised stenosis or, rarely, as a new athero-sclerotic lesion[23,24].

In our patients, no data are available on the patency immediately after the operation. At one year, overall patency rate in the recatheterized subset of patients was 79%, 74% in those with AP and 85% in those without, thus showing a correlation between closed bypass grafts and angina pectoris. This fact is in accordance with findings for instance in the Veterans Administration Cooperative Study[25]. Between 1 and 3 years after the operation 2-3% of the bypass grafts closed in our patients, very similar to the reported attrition rate elsewhere[23,24]. But the percentage of patients with angina increased from 30% at one year to 46% at 3 years, which clearly cannot be explained by a loss in patency of the grafts.

In terms of the assessment of progression of coronary artery sclerosis, the coronary score was chosen to express the potential extent of reduction of flow to the myocardium. The higher the score, the higher the degree of stenosis in the more proximal arteries. As reported before[14], the level of the score did not correlate directly with the severity of angina pectoris but the score could be used to evaluate the effect of surgery by comparing the pre- and post-operative figures in the same patient, while it also indicated progression or regression of coronary sclerosis in the vessels not touched by the surgeon. In our study, the coronary score was lowered markedly by surgery,both at 1 year and at 3 years after surgery, suggesting that surgery indeed improved blood flow to the myocardium and that this result was maintained in the course of three years. In those patients with post-operative AP, the score increased significantly between the two post-operative studies, while this did not happen in those without AP. The change in score at that time cannot be explained by the attrition rate of the bypass: 3%, respectively 2% of the grafts closed in the two intervening years in the group with and without AP. Thus, only progression of atherosclerosis in the native coronary vessels can explain the increased score. This leads to the conclusion that late post-operative AP is related to the progression of coronary artery sclerosis.

The influence of age at the time of operation on post-operative angina pectoris, has not been commented on by others. In this study, younger men fared worse regarding post-operative angina pectoris than older men. It has been shown by Kramer et al[26] that coronary sclerosis progresses faster in men below the age of 50 years than in older individuals. This could be the reason why post-operative angina pectoris was more often seen in the younger age groups, although it has to be realised that the complaint angina pectoris was an entirely subjective one. No objective data on exercise tolerance are available in these patients. It is not unreasonable to presume that older individu-

als undertake less physical activity and therefore experience less AP. Why this age-trend did not occur in women is unclear.

Progression of coronary sclerosis not only shows a relation to age, but to elapsed time as well. Both Kramer et al[26] and Bruschke et al[27] showed this in a study of unoperated patients, while in postoperative patients it has been demonstrated by Campeau et al[6]. In this last study there was a clear correlation between progression of sclerotic disease and post-operative angina pectoris. These findings make it all the more remarkable that we did not find an increase in the incidence of angina pectoris beyond the third post-operative year (fig. 5-2). One would have expected that, with more time elapsed after surgery, new stenoses would be formed with more angina pectoris as a result.

In conclusion, aorto-coronary bypass surgery remains a significant addition to the management of patients with severe angina pectoris, even with present day pharmacological therapy. Improvement after surgery is common, but angina pectoris at late follow-up occurred in nearly half of the patients, especially in younger men. When angina pectoris persists after surgery, incomplete revascularization is usually the reason. On the other hand, deterioration after the first post-operative year is mainly caused by progression of coronary sclerosis.

These findings should give cause to rethink the present day tendency to operate on young(er) patients, often with minimal symptoms, to "prevent" future complaints. As long as progression of coronary sclerosis cannot be arrested, "preventive" surgery would seem to be unwarranted.

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CHAPTER 6

RE-OPERATION AFTER AORTO CORONARY BYPASS PROCEDURE: RESULTS IN 53 PATIENTS BELONGING TO A GROUP OF 1041 WITH CONSECUTIVE FIRST OPERATIONS.

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6-1: SUMMARY.

Of 1041 patients with consecutive aorto-coronary bypass operations, 53 (5.2%) underwent a re-operation during a mean follow-up time of 3.5 years. Operative mortality of first operations was 1.2%, of re-operations 3.8% (NS). The anatomical reason for re-operation was failure of the bypass graft in 41 (77%) patients, in 18 accompanied by progression of disease. Progression only was seen in 7 (13%). When symptoms occurred within 6 months after the first operation, failure of the bypass graft(s) was nearly always found, in 32 out of 36 instances this was the case. Progression in non-bypassed arteries was seen only when symptoms occurred later.

Late results regarding angina pectoris were less favorable in the re-operated group: 31/48 (65%) of the twice operated and 406/877 (46%) of the once operated patients still had anginal complaints at late follow-up (p 0.02). However, the same fraction in both groups was improved by surgery 88% versus 89%.

6-2: INTRODUCTION.

Aorto-coronary bypass surgery has become an established form of treatment in angina pectoris (AP). Although the majority of patients feel improved after surgery, severe symptoms persist or re-occur in approximately 10% of the subjects[1-3]. As time increases after the operation it may be expected that, due to progression of disease, the number of symptomatic patients will grow [4,5]. Re-operations in still symptomatic patients have been performed as early as 1971[6]. It has been established that such a procedure is possible with an acceptable mortality[6-8], however, results at follow-up vary[9-11]. The aim of this study is to describe late results after re-operation while searching for common findings why patients require this procedure. Thus, a comparison is made of pre-operative vascular lesions, extent of revascularization at the initial surgery and symptomatic state at follow-up in re-operated patients and in patients who had had one operation only, with all patients originating from the same consecutive series of aorto-coronary bypass procedures carried out at one institution over a 10 year period. Furthermore, in the re-operated patients a relationship was sought between the onset of recurrence of angina pectoris after the first operation and the presumed anatomic cause of failure of this procedure.

6-3: MATERIAL AND METHODS.

Patient selection.

Consecutive patients undergoing single aorto-coronary bypass surgery at our institution between 1971 and June 1980 constituted the study population. Indication for surgery was angina pectoris (AP) despite intensive medical therapy. In 53 of the 1041 patients, symptoms necessitated a re-operation before the end of 1981 at a mean interval of 24 months after the initial operation. Re-operation was generally performed by the same surgical team, except in 3 cases where it was executed at another institution. The data of these 3 cases are included in this study.

Coronary angiograms.

Selective coronary angiography was performed in all patients before operation. A vessel was considered diseased when a luminal narrowing of 50% or more was seen in one of the major coronary branches or in the main stem of the left coronary artery. At recatheterization, before the second operation, the bypass graft was injected selectively when possible. If the bypass was not opacified and if it was found to be not functioning at surgery, it was considered closed. The bypass graft was considered to be failing when it was closed completely or when severely narrowed with a 95% or more diameter narrowing. A bypass was considered functioning when it could be opacified and did not show a narrowing of 95%.

Progression of disease.

In the native coronary arteries progression of disease had occurred, when at the second catheterization a major coronary artery showed an increase in luminal narrowing: a previously normal or 50% narrowed lumen showing a more than 50% lesion or a 50% lesion becoming a total or subtotal occlusion. Progression could be seen in either bypassed or non-bypassed arteries.

Regression of disease.

Regression had occurred if at the second catheterization a totally occluded artery or a major artery with a 50% luminal narrowing showed a 50% lesion.

Insufficient revascularization.

Insufficient revascularization at the primary operation was considered to have taken place when a severely narrowed major vessel could not be bypassed at the

primary surgery, when the bypass was anastomosed between two severely narrowed spots or when just one graft was anastomosed to one minor branch of a diseased major coronary artery.

Technical aspects at surgery.

At surgery the aim was to bypass all severely narrowed areas in the major coronary arteries. As experience increased, more distal anastomoses were placed at surgery. In 1971 a mean of 1.33 anastomoses per patient were accomplished, but in 1976 2.50 and in 1980 3.04. The saphenous vein was preferably used to form either a single graft or a jump graft with multiple peripheral anastomoses. During surgery, just after the patient was taken from the heart-lung machine, the flow in the functioning aorto-coronary vein graft was measured with an electromagnetic flow probe. At re-operation a failing bypass was either replaced or, in the case of a local narrowing, reconstructed. If a new lesion in a major coronary artery had formed, a new graft was implanted.

Follow-up.

All surviving patients were sent a questionnaire to ascertain the presence of AP or dyspnea limiting exertion. The questionnaires were sent out in May 1981 and received up to November 1981, thus giving a follow-up time of a minimum of 1 year and a maximum of 10 years (mean 3.5 years).

Reoperation procedures were included up to the end of 1981, giving a follow-up time after the second procedure of a minimum of 0.1, a maximum of 8.5 and a mean of 2.4 years. Follow-up data on symptoms were complete for the re-operated group; for those who had had just one operation 94.4% of 929 survivors responded. Vital statistics were complete in 99.4% of the patients.

Data storage and analysis.

Data were stored in MUMPS on a PDP-11 computer. Sorting and analysis was performed on a Hewlett-Packard 85 micro-computer. For statistical analysis the Hewlett-Packard statistical package was used (Student's t test and X^2 contingency test).

6-4: RESULTS.

The group of 1041 patients with consecutive first operations consisted of 126 women (12%) and 915 men (88%). Of the 53 patients who had had a re-operation, 4 were female (8%) and 49 male (92%). The mean age at first operation was

slightly lower than in the later re-operated group: 49.7, SD 6.7 yrs versus 52.6, 7.7 yrs in the group operated once, a significant difference ($p<0.001$). There were 12 deaths within 28 days of surgery (1.2%) and 2 at re-operation (3.8%, see table 1). This difference is not significant. There were 47 late deaths or 4.5% of those who had undergone one procedure and 3 deaths or 5.7% in those who had had two, again not significantly different. Re-operations were undertaken infrequently in the early years of aorto-coronary bypass surgery. At our institution the first re-operation was performed in 1973. In table 2 the gradually increasing number of re-operations is shown, from one in 1973 to 15 in 1980. At the end of 1981 this resulted in a total of 53 (5.1%) of the cumulative number of first operations performed before June 1980. Moreover it is evident, that the fraction of patients needing a second operation has decreased over the years: 7.1% of the patients operated before 1977 to 6.4% in 1977 and 1.8% of the patients operated on in 1980.

TABLE 6-1

DEATHS IN THE TOTAL PATIENT POPULATION, SUBDIVIDED INTO PATIENTS WHO HAVE UNDERGONE ONE AND TWO AORTO-CORONARY BYPASS OPERATIONS AT A MAXIMUM OF 10 YRS AND A MINIMUM OF 1.0 YRS FOLLOW-UP.

	number of patients		number of deaths
	initial operation	reoperation	
At first operation	1041		
operative mortality			12 (1.2%)
late mortality			47 (4.5%)
Undergone second operation		53	
operative mortality			2 (3.8%)
late mortality			3 (5.7%)
Died in total			64 (6.2%)
Survivors			
Two operations		48 (100%)	
follow-up data		48 (100%)	
One operation	929 (100%)		
follow-up data	877 (94%)		

TABLE 6-2

NUMBER OF AORTO-CORONARY BYPASS OPERATIONS AND RE-OPERATIONS PERFORMED OVER THE YEARS.

Year	First operation	Re-operations			
	nr. of patients	nr. of patients	% of cumulative first operation	per year of first operation	
1971	6	-	0	2	
1972	27	-	0	3	
1973	34	1	1.5%	4	
1974	46	2	2.7%	3	(7.1%)
1975	54	4	4.2%	3	
1976	114	0	2.5%	5	
1977	172	5	2.6%	11	(6.4%)
1978	204	8	3.0%	11	(5.4%)
1979	271	14	3.7%	9	(3.3%)
1980 5 months	113	15	4.7%	2	(1.8%)
1981	-	4	5.1%		
total	1041	53	5.1%	53	

TABLE 6-3

PRE-OPERATIVE NUMBER OF DISEASED VESSELS AND NUMBER OF GRAFTS PLACED PER PATIENT AT THE INITIAL OPERATION, FOR THE GROUP OF PATIENTS HAVING HAD ONE AND HAVING HAD TWO OPERATIONS.

Vessels diseased before first operation	one operation only		two operations	
	number of patients	grafts per patient	number of patients	graft per patient
1 vessel	179 (18%)	1.4	13 (25%)	1.2
2 vessels	306 (31%)	2.3	14 (26%)	2.4
3 vessels	423 (43%)	3.4	21 (40%)	3.5
LM	80 (8%)	3.3	5 (9%)	2.2
total	988		53	

LM = left main stem disease.

Data at the first operation and at follow-up.

The extent of atherosclerotic disease pre-operatively and the number of grafts placed at the initial operation were compared in those operated on again and with those operated twice. As can be seen in table 6-3, three vessel and left main stem disease is about equally prevalent in both groups. The number of grafts placed per patient is the same as well, except for those with left main stem disease, whereas the number in the re-operated group is slightly lower: 2.2 versus 3.3 grafts per patient. However, this difference is statistically not significant.

Angina pectoris was still experienced by 31 (65%) of the 48 surviving re-operated patients, while AP was reported by 406 (46%)of the 877 patients with asingle operation. Thus the patients operated on twice fared significantly worse regarding occurrence of post-operative AP ($p<0.02$). As can be seen in figure 6-1 dyspnea or AP limited physical activities in 35 (73%) of the re-operated patients and in 583 (66%) of the other group. This, however, was not a significant difference. Subjective overall improvement after surgery was not different in either group: 88% versus 89%.

The cause of recurrence of symptoms in the re-operated group, i.e. failing bypass graft or progression of disease influenced late results slightly. Those with (a) failing bypass graft(s) fared worse in the long run than those whose symptoms could only be attributed to progression of the atherosclerotic process. In the last category, 4 out of 6 patients (66%) became pain free while this was only 12 out of 38 (32%) when there was failure of the grafts (table 6-4).

Data on the re-operated group.

The indication for re-operation was, in all instances, angina pectoris as severe or more severe in comparison with symptoms before the first operation. The moment of appearance of angina pectoris in the post-operative period varied from immediately after the operation to 83 months. Of the 53 patients having had a second operation, 9 or 17% never lost their complaints and by 3 months 53% suffered angina pectoris. At 12 months this fraction had risen to 75%. Thus most re-operated patients had symptoms in the first year after the initial surgery. In figure 6-2 the cumulative percentage of patients with post-operative AP is shown versus time elapsed since the original operation. As can be seen, the increase is small but gradual from 36 months onwards.

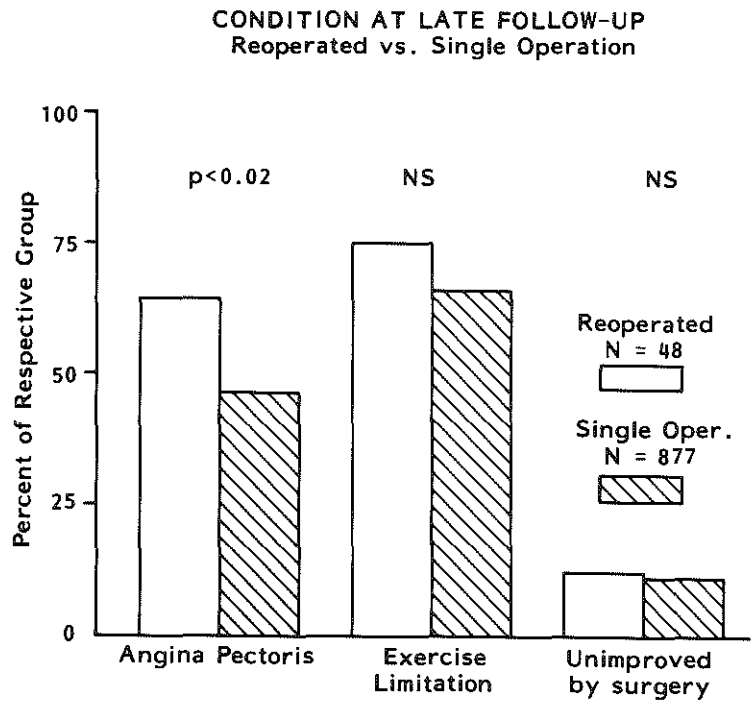

Figure 6-1.

Condition at late follow-up. Re-operated patients experienced AP more often: 65% versus 46% in those operated once ($p < 0.02$). Limitation of activities by physical complaints occurred in 73% versus 66% (NS) and an unimproved condition compared to before any surgery occurred in respectively 12% and 11% of the patients (NS). Follow-up time averaged 3.5 years after the initial surgery.

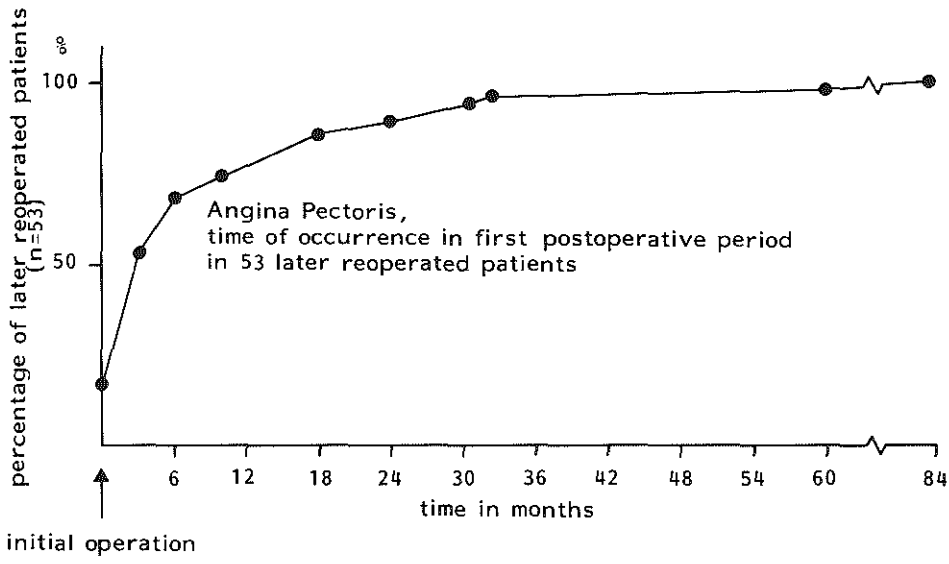

Figure 6-2.

Patients with post-operative AP, shown as cumulative percentage of all re-operated patients versus time elapsed since the first aorto-coronary bypass operation.

At the time of recatheterization, (a mean of 20 months after the primary operation), 77 of the 130 inserted bypass grafts were closed, a patency rate of 59%. In addition to the 77 closed grafts, 6 had a luminal narrowing of 95%. Thus 83 (64%) of the grafts were failing, while 47 (36%) could be considered to function normally.

In table 6-4 it is shown that, of the 23 patients with pure bypass graft failure, 20 had symptoms within half a year of surgery. The other frequently seen problem in patients with early symptoms was the combination of a new lesion the bypassed artery and a failing graft. Thus, out of the 53 patients 36 had symptoms within 6 months of whom 20 had pure graft failure, and 11 graft failure with progression in the bypassed artery, together 86% of the patients with early symptoms. Progression of lesions in non-bypassed arteries was only seen if symptoms had started later than 6 months post-operatively, except once when a combination with a failing graft was found. An exception to the 6 month cut off point of symptoms were: a) 3 patients with pure graft failure and symptoms at respectively 7,7 and 11 months and b) pure technical failure of the initial operation causing persistence of symptoms after surgery in 4 patients. This occurred twice because of inability to find a to be bypassed artery, and twice the distal anastomosis was made in between two severely narrowed areas. Regression of disease was not seen.

Flow in the graft.

At the first operation flow was measured in 127 of the 130 inserted grafts. The mean flow in the 46 later functioning grafts was 56.4, SD 39 ^{ml}/min, and in the 81 later non-functioning grafts 42.3, SD 20 ^{ml}/min. According to the Student's t test, the flow was significantly higher in the later functioning grafts ($p < 0.001$).

Re-operation.

The 53 patients had their re-operation at a mean of 24.4 months after the first procedure, with a minimum of 1 and a maximum of 91 months. In total 83 grafts had been found to be failing at recatheterisation. At the second operation 73 new grafts were inserted and 11 times a reconstruction of a severely narrowed area was performed. In 2 instances a stenotic aortic valve was replaced by a valve prostesis. In all patients but one, some improvement of vascularization was realised at surgery. The one exception received a valve prosthesis.

TABLE 6-4

FINDINGS AT RECATHETERIZATION RELATED TO TIME OF (RE)OCCURRENCE OF ANGINA PECTORIS AFTER THE FIRST BYPASS OPERATION AND INCIDENCE OF SYMPTOMS AT FOLLOW-UP AT A MEAN OF 3.5 YEARS POST-OPERATIVELY.

Primary finding at recatheterization	appearance symptoms first post operative period in months					total nr. of pats.	nr. of survivors	AP at follow-up (% of survivors)
	3	3-6	6-12	12-24	24			
failing graft(s)	16	4	3	-	-	23	21	14 (67%)
failing graft(s), progression bypassed artery	7	4	-	-	-	11	10	6 (60%)
					2	2		
failing graft(s), progression non-bypassed artery	1	-	1	3	-	5	7	6 (86%)
graft(s) open, progression bypassed artery	-	-	1	-	-	1		
					1	1	6	2 (33%)
graft(s) open, progression non-bypassed artery	-	-	-	2	3	5		
technical	4	-	-	-	1	5	4	3 (74%)
total						53	48	31 (65%)

6-5: DISCUSSION.

After the initial reports on late results of coronary bypass surgery with disappearance of angina pectoris in the large majority of patients, it was soon noticed that a small number of patients did not benefit. Mc Neer[12] reported an increase in patients experiencing AP from 38% at one year to 47% at 2 years after the operation. Campeau[13], in a 7 year, span saw an increase from 21% to 50%. In both series 10-15% of the patients were unimproved by surgery.

In the 1041 patients with consecutive operations at our institution, 47% of the survivors experienced angina pectoris at a mean follow-up time of 3.5 years, and 11% of these patients felt unimproved by surgery. Out of this pool of 150 patients 53 were re-operated. Selection criteria for re-operation were severe, often unstable, angina pectoris as well as the desire of the patient to be re-operated and technical feasibility. The re-operated group was slightly younger than the total patient population but did not otherwise differ in pre-operative number of stenosed vessels or the number of grafts placed at surgery. This is at variance with the experience of Barboriak et al[14] who noted inadequate initial revascularization reflected by a lower average number of bypass grafts in patients later undergoing a re-operation. His study is the only one on consecutively operated patients, he found the younger age in the re-operated group as well.

Reason for failure of primary operation.

In our patients, failure in the function of the bypass graft(s) was the most frequently found problem at recatheterization. Of the 53 patients, 41 (77%) patients had failing grafts. Of the 130 grafts placed at the initial surgery only 47 (36%) were functioning. This is much lower than the average patency rate at our institution of 79% at one year and 76% at 3 years post-operatively [15]. This low patency rate could be caused by unfavorable anatomy in the distal coronary vascular bed. Such a hypothesis is supported by the fact that at operation the flow was significantly lower in the later failing grafts, 42 ml/min versus 56 ml/min in the later functioning grafts. However a clear cut off point cannot be given, due to overlap in values.

Progression of disease in the native vessels was rather rare in this group: 7 (13%) patients had such progression as their primary problem. It is possible however that this was caused by selection, as patients with extensive new changes in distal coronary arteries were not primarily selected for a reoperation. Moreover, it is possible that the follow-up time of a mean of 3.5 years after the initial operation was not sufficiently long to see progression

of disease. Loop et al [8] reported for instance, that AP recurred a mean of 3.1 years after surgery if progression was the reason for failure of the primary operation.

The fact that 4 (7.5%) of our 53 patients had a purely technical reason for inadequate primary surgery is regrettable, but in view of the complexity of the surgery involved, probably unavoidable. Data are scarce in the literature but Stiles et al[16] reported inadequate first operations in 13 (26%) out of 50 re-operations and Kobayashi[7] mentions previously un-bypassed lesions in 14 (29%) of 48 reoperated patients. Is is clear however that experience of the surgical team influences the number of re-operations, as evidenced by the decrease over the years, from 7.1% to 1.8% in our series. Time of onset of angina pectoris after the initial operation appeared to be an indication of the cause of problems. If angina pectoris occurred in the first 6 post-operative months either a malfunction of the bypass graft, with or without an occlusion in the bypassed coronary artery, or a technical failure of the primary operation, was found to be the cause. When the symptoms recurred after 6 months post-operatively, than progression of atherosclerotic disease in the native coronary circulation was the reason. This is in accordance with the findings of Culliford et al [17] who reported an even shorter interval (2 months) in which the patients with failed bypass grafts became symptomatic.

Operative mortality at re-operation of 3.8% compared to 1.2% for first operations seems acceptable. Figures in the literature vary between 10% reported by Johnson et al in 1972[6] and 3.7% reported by Irarrazaval etal in 1977[10], both for re-operations. Late mortality of 5.7% in 3.5 years in the re-operated group falls within that quoted in the literature as well[6,7,16]. Late outcome in respect to anginal complaints is disappointing. Only 17 (35%) of the 48 surviving patients were free of chest pain and only 12 (25%) were completely asymptomatic after 2 coronary bypass operations. Of those who were operated once, the results were significantly better: 54% were free of pain and 34% asymptomatic.

The low percentage of patients completely relieved of symptoms in the re-operated group, has also been found by others. Kobayashi et al[7] reported 38% of their 79 patients to be angina free at 12-70 months, Allen et al [18] 31% of 71 patients at a mean of 26 months and Norwood[11] 30% of 26 patients at 6-48 months. In contrast with these results, Loop et al reported that 60% of

500 re-operated patients were angina free at an average of 40 months after operation. As these series of re-operated patients were not part of a consecutive series of first operations, no comparison could be made.

In conclusion, re-operations after aorto-coronary bypass surgery are sometimes necessary because of failure of improvement after the initial procedure. Technically, the operation is feasible with a low mortality rate and few late deaths at follow-up. The cause is most often a failure of the bypass graft(s) especially when the patient becomes symptomatic within 6 months of surgery. Although improvement in symptoms of angina pectoris occurs in the majority of such patients, only one quarter of the patients become entirely symptom free. As the number of initial aorto-coronary bypass operations is expected to increase in the coming years, it is important to realise this when advising a symptomatic, but operated, patient on the course to follow.

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CHAPTER 7

Br Heart J 1983; 50: 42–47

Long term follow-up after coronary artery bypass graft surgery

Progression and regression of disease in native coronary circulation and bypass grafts

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SUMMARY Angiographically demonstrable changes in bypass status and their relation to the disease in the native coronary circulation were studied in 221 patients one year and three years after coronary artery bypass graft surgery. The extent of coronary artery disease was scored according to the recommendations of the American Heart Association and quantified following the method of Leaman. Patency in 570 grafts at one year was 79·6% and at three years 76·5%. The majority of grafts (83·5%) showed no change from one year to three years, 11·4% showed progression in disease, and 5·1% showed regression. The majority of grafts which occlude do so in the first year after surgery. After the first year, the graft attrition rate is 1·6% of grafts per year.

The coronary score (0, no disease; >30, serious three vessel disease) before surgery was 14·2±1·92 (mean ±95% confidence) and dropped to 5·3±0·76 at one year when corrected for patent grafts. The coronary score remains greater than zero because of early graft closure and/or untreated lesions. By three years the corrected coronary score increased to 7·2±1·06 primarily because of progression of disease in the native coronary circulation. Two subgroups, formed on the basis of angina pectoris at three years, showed that progression of disease in the native circulation was identical, but that return of angina was highly correlated with whether or not this disease occurred in segments perfused by patent grafts.

Those factors known to be risk factors for coronary artery disease do not appear to have a bearing on progression or regression of disease in the graft, nor does the extent of coronary artery disease at the time of surgery correlate with eventual graft patency.

There remains relatively little information on the progression and regression of disease in bypass grafts in the long term after coronary artery bypass graft surgery. This work was undertaken to document angiographically demonstrable changes in bypass status, the relation to the disease in the native coronary arteries, and the clinical factors possibly affected by this process.

This study was made possible by the existence of a large data bank designed for the three year follow-up of patients after bypass grafting.[1] The pertinent aspects of this data bank are that it specifies recatheterisation at one year and three years after bypass surgery with complete scoring of the coronary angiogram and bypass graft status. A complete physical examination and history are also obtained at these points. The development in this laboratory of a coronary scoring system to quantify the extent of coronary artery disease and its changes over the follow-up period has been previously reported.[2] This method is also applied here in this study.

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Methods

The selection criteria for this study was the availability in Rotterdam of selective graft and coronary angiograms at one year and three years after coronary artery bypass graft surgery. All patients were also evaluated before surgery. In total 221 patients met

these criteria. All were adults, mean age 52 years, and 96% were men. On the basis of clinically available information on medical treatment and functional class, these patients did not differ from those refusing recatheterisation but seen in the out-patient clinic as part of the routine follow-up after coronary artery bypass grafting.

The purpose of the coronary score, developed by Leaman *et al.*,[2] was to quantify the severity of underlying coronary artery disease before surgery, and the effectively untreated disease remaining after coronary artery bypass grafting. The different coronary vessels carry different volumes of blood to the left ventricle, and the coronary score was derived to take this into account.

The left coronary artery carries approximately five times the amount of flow to the left ventricle compared with the right coronary artery.[3-5] It has also been shown that in the usual right dominant coronary system, the flow in the left coronary artery is 66% into the left anterior descending and 33% into the circumflex coronary artery.[3] Thus, the left anterior descending carries approximately three and a half times and the circumflex one and a half times as much blood as the right coronary artery. This then was the basis for assigning different weighting values to the different coronary arteries. The coronary arteries were subdivided into segments according to the scheme devised by the American Heart Association.[6] The right coronary artery does not supply blood to the left ventricle until the posterior descending branch is given off, so only the segment with the most severe disease was analysed. The left anterior descending and circumflex coronary arteries, however, were further subdivided and weighting factors were assigned to each segment (Fig.1). As shown in the figure, different weighting factors were assigned in the event of left dominance.

The degree of stenosis was also considered in deriving the coronary score. If the vessel was totally occluded, the coronary artery segment value was multiplied by 5·0. If there was a 90 to 99% occlusion (luminal diameter narrowing), it was multiplied by 3·0. For a 50 to 90% obstruction, it was multiplied by 1·0. The segmental scores were then added to derive the total coronary score. A score of zero would indicate no obstructive coronary artery disease, and the higher the score, the greater the obstruction. The role of coronary collaterals has been previously studied and found not to effect the outcome of surgery.[7]

In deriving the postoperative coronary score, a vessel segment was considered normal if it was supplied by a patent aortocoronary bypass graft that was free of occlusive disease. If the aortocoronary bypass graft was occluded, the score was derived from the degree of disease in the native coronary system; that is, the score was derived as if no graft had been placed. Hypertension was defined as a diastolic arterial pressure in excess of 95 mm Hg.

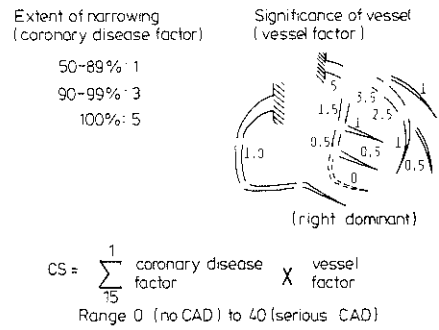

Fig. 1 *The coronary score was formulated to give a single number representing the severity of coronary artery disease as it affects perfusion to the left ventricle (Leaman et al.*[2]) See text for *detailed description. A value of zero represents no coronary artery disease, while 40 would represent very serious three vessel disease.*

Statistical analysis included the Student's paired t test, χ^2, or analysis of variance where appropriate. The lower limit for significance was taken as $p=0{\cdot}05$, two sided distribution. Unless otherwise stated, data are presented as the mean ± the 95% confidence interval of the mean.

Results

There were 221 patients who met the inclusion criteria of angiography performed at one year and three years after surgery according to the study procedure.

The ejection fraction before operation was 0·60±0·12 (mean ±SD), at 1 year it was 0·60±0·13, and at 3 years it was 0·59±0·12. There was thus no clinically important change in global left ventricular function for the group as a whole.

The coronary score (native and corrected for grafting) is summarised in Table 1, and for the sake of clarity illustrated in Fig. 2. At operation the mean coronary score for the entire series was 14·2±1·02 (mean ±95% confidence interval for the mean). One year after operation the corrected coronary score fell to 5·3±0·76. This is not zero because some grafts have already occluded, and not all disease could be effectively bypassed.

From one year to three years there was some progression on average in the corrected coronary score (from 5·3 to 7·1). During this period the uncorrected

Table 1 *Coronary score before surgery and one and three years after surgery in all 221 patients, group 1 (126 patients, no evidence of angina pectoris at three years), and group 2 (95 patients, angina pectoris present at three years)*

	Mean	*95% confidence*	*p<*
Preop, native coronary score, all patients	14·2	1·02	—
Preop, native coronary score group 1	14·3	1·39	—
Preop, native coronary score group 2	14·1	1·69	† NS
One year, native coronary score, all patients	18·1	1·12	* 0·00001
,, year, native coronary score group 1	18·8	1·52	—
,, year, native coronary score group 2	17·3	1·65	† NS
,, year, corrected coronary score, all patients	5·3	0·76	* 0·00001
,, year, corrected coronary score group 1	4·1	0·89	—
,, year, corrected coronary score group 2	6·6	1·25	† 0·001
Three years, native coronary score, all patients	20·7	1·29	* 0·00001
,, years, native coronary score group 1	20·8	1·69	—
,, years, native coronary score group 2	20·5	1·98	† NS
,, years, corrected coronary score, all patients	7·2	1·06	* 0·00001
,, years, corrected coronary score group 1	5·2	1·14	—
,, years, corrected coronary score group 2	9·4	1·75	† 0·00005

Native coronary score is shown as well as that corrected for patent grafts. Data presented as the mean ± 95% confidence interval. Abbreviations: *comparison of difference with respect to preop coronary scores (Student's paired t test); †statistically significant difference between groups 1 and 2 (Student's unpaired t test); NS no significant difference

coronary score in the native circulation increased from 18·1 to 20·7 (16% increase).

The graft status is summarised in Table 2. There were 570 grafts scored, giving a revascularisation rate of 2·6 grafts per patient. The patency rate at one year was 79·6% and at three years 76·5%. That is, 3·1% more grafts occluded during the two year interval between follow-ups, giving a graft loss rate of 1·6% of grafts per year after the first year. During the follow-up period the majority of grafts (83·5%) showed no change within the scoring limits used in this study, but 11·4% of grafts were coded as progressing in severity of stenosis by one or more classes while 5·1% were classed as regressing by one or more classes. As the corrected coronary score was computed based on patency vs occlusion of the graft (see methods) the progression in the corrected coronary score is the result primarily of progression of disease in the native coronary circulation.

The relation between recurrence of angina pectoris and progression of disease was also studied. At three years after operation 43% of patients reported they experienced some angina, though usually of less severity (ease of provocation and frequency of attacks) than previously.

Two groups were formed on the basis of angina pectoris at three years (group 1: no evidence of angina pectoris, and group 2: presence of angina pectoris at three years), and the coronary score was compared for all follow-ups (Table 1).

The preoperative coronary scores for groups 1 and 2 were, respectively, 14·3±1·39 (mean ±95% confidence interval) and 14·1±1·57 (no significant difference). That is, there were no differences in

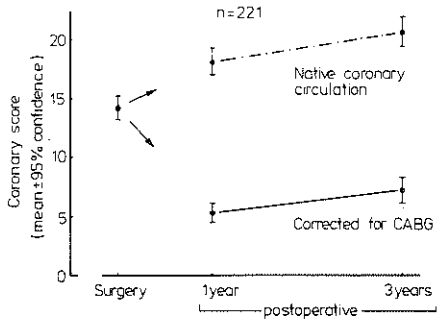

Fig. 2 *The coronary score in the native circulation and corrected for bypass grafting before surgery, and one and three years afterwards. Vertical bars represent the mean ± 95% confidence limits for the mean in 221 patients.*

Table 2 *Summary of graft status at one year and three years after surgery*

1 year \ 3 year follow-up	Normal	50%	50–90%	91–99%	100%
Normal	309	31	5	1	10
50%	15	34	6	1	4
51–90%	3	8	19	1	2
91–99%	0	1	1	1	4
100%	0	0	1	0	114

Total number of grafts: 570
progression 65 11·4%
stability 476 83·5%
regression 29 5·1%

Five classes of occlusion are shown: 100% occlusion, 91 to 99% occlusion, 50 to 90% occlusion, less that 50% obstruction, and normal graft. Entries on the diagonal represent stability in graft status from one year to three years. Entries above the diagonal represent progression of disease, while entries below the diagonal represent regression.

Table 3 *Summary of risk factors, associated with coronary artery disease, but studied in relation to progression, stability, or regression of disease in graft (n = 570 grafts, see Table 2) from one year to three years; analysis of variance of χ^2 contingency table used for statistical analysis*

	Progression	*Stable*	*Regression*	*p*
Cholesterol (mmol/l) (mean ± SD)	(7·88 ± 2·01) n = 52	(7·60 ± 2·03) n = 353	(8·42 ± 2·0) n = 23	NS
Smoking (yes or no)	y = 30 n = 35	y = 206 n = 270	y = 12 n = 17	NS
Use of anticoagulants (yes or no)	y = 29 n = 36	y = 193 n = 279	y = 17 n = 12	NS
Hypertension (yes or no)	y = 22 n = 43	y = 154 n = 322	y = 12 n = 17	NS
Preop coronary score (mean ± SD)	14·5 ± 8·0	16·1 ± 7·8	12·0 ± 7·7	NS

coronary score between the two groups at the outset. At one year the uncorrected (native) coronary score was 18·8±1·52 and 17·3±1·65 (no significant difference), while the corrected score was 4·1±0·89 and 6·6±1·25 ($p < 0·001$). At three years, this trend is even more apparent; the uncorrected coronary score was 20·8±1·69 and 20·5±1·98 (no significant difference), while the corrected coronary score was 5·2±1·14 and 9·4±1·75 ($p < 0·00005$). Thus, in those patients reporting angina pectoris at three years, the coronary score (corrected for patent grafts) shows a clear trend towards preoperative values while those patients without angina pectoris showed minimal progression in the corrected coronary score. This occurred in spite of the fact that the coronary score for the native circulation (uncorrected) was virtually identical in the two groups. It appears that progression of disease in the coronary arteries is present to a similar extent in both groups, but group 1 (without angina pectoris) had this disease more effectively bypassed than group 2 patients.

The relation between risk factors for coronary artery disease and graft status from one year to three years after surgery is summarised in Table 3. The first entry gives the mean and standard deviation of cholesterol for the three classes of bypass grafts: those where there was progression of disease, stability, and regression of disease. Results for smoking, use of anticoagulants, presence of hypertension, and preoperative coronary score are also summarised in Table 3. There were no significant correlations found for any of these risk factors.

Discusssion

There are a number of limitations to this study which should be pointed out at the outset. The analysis obviously excludes those patients who died within three years of operation and this could bias any conclusions based on the surviving patients. To place this factor in perspective, the mortality for uncomplicated bypass grafting over the period of this study was 2·1% in the first year and an additional 1·9% from one year to three years. Therefore, this source of bias is not large, but would tend in any event towards one being overly optimistic concerning progression of disease. Secondly, in deriving the corrected score after bypass surgery the grafts were characterised as either patent or occluded. As shown in Table 2, this is an oversimplification necessitated by the fact that there is no accurate way of determining whether the combined disease in a patent graft and coronary artery is effectively limiting blood supply except in the extreme when the graft is occluded.

The magnitude of this problem can be estimated from Table 2. At one year 79·6% of grafts were classed as "patent"; this includes 7% of the total which had disease in the grafts scored between 51 and 99%. At three years, 6% of grafts were so scored in spite of more grafts becoming occluded. Thus, while this system of classifying grafts as either patent or occluded is an oversimplification, it would not appear to bias the study as far as progression of disease is concerned.

It could be argued that progression/regression of disease is sufficiently gradual that only small changes are likely to occur between the one and three year follow-up studies and that the American Heart Association recommendations for scoring coronary angiograms (five disease classes, 15 segments)[6] may not be sufficient. There is a limit, related to the inter- and intra-observer variability, to which small changes can be reliably scored. Reports of observer variability provide some guidelines,[8–10] but the analysis has not been taken to its logical conclusion, that is development of an optimal scoring system commensurate with the "signal to noise ratio" of the diagnostic technique and experienced observer.

The above cited reports all employ a coronary map of about the same number of segments as we used, but most use only two or three classes of disease compared with our five. For example, Sanmarco *et al.*[8] report a 95% consistency in an expert panel when scoring the presence or absence of a significant lesion (> 70% area

stenosis or > 50% diameter stenosis). Only two classes clearly provide a very limited resolution for studies of progression of disease, but could still be useful. Whether two or five classes are used, it is essential to keep these criteria in mind when evaluating changes in disease status.

Bourassa *et al.*[11] have reported that there is an accelerated progression of disease in proximal segments of grafted coronary arteries occurring primarily in the first year, but then remaining relatively stable afterwards. Natural progression of disease in non-grafted arteries continues over the long term though possibly in bouts.[12] The progression in the corrected coronary score from one to three years therefore primarily reflects the development of disease in non-grafted segments, and to a lesser extent the consequences of graft occlusion. Nevertheless, between one and three years, we do find some progression of disease in segments either directly or indirectly bypassed. Providing that the graft remains open, this progression is not associated with the return of angina pectoris in contrast to the situation where progression of disease occurs in arteries not bypassed.

The data summarised in Fig. 2 lead to several speculations. For example, if the dashed line connecting the one year and three year native coronary score is extrapolated to the time of operation, it projects a coronary score 2·6 units above that obtained at the time. This may be ascribed to damage to the coronary arteries as a result of the operation itself or indirectly by the establishment of new perfusion pathways. It is also apparent that the line connecting the corrected coronary score could be extended into the future where it would eventually intersect the level of the coronary score before surgery. While little confidence can be attached to such a long term extrapolation, this point can be calculated to be about 10 years after operation. This estimate is probably too pessimistic as the majority of disease progression is known to occur early in the follow-up.

It was found that a minority of grafts (5·1%) show some regression in disease. In view of the above mentioned observer variability in scoring angiograms, it can be debated whether this figure represents true regression as opposed to observer variability. Studies conducted in our laboratory suggest that an observer variability of 5% is not unreasonable, and that the entire series showing regression could be ascribed to observer variability. Therefore, all these angiograms were reviewed at least twice, and in our opinion these results do reflect actual regression of disease. Bruschke *et al.*[13] have also reported regression of disease in 4·7% of patients not operated upon.

No significant correlations were found between the conventional risk factors and progression of disease in the grafts (Table 3). This also appears to be the case for progression of disease in coronary arteries.[12–15] Allard *et al.*,[16] however, have reported that hypertriglyceridaemia, a factor which we did not examine, is associated with a higher risk of graft occlusion. It is particularly interesting to note that the preoperative coronary score had no bearing on disease in the bypass graft. This most clearly indicates the decoupling of conventional risk factors in coronary artery disease with later development of disease in the graft. On reflection, this approach to the problem is an oversimplification. These risk factors for a patient are equally present for all the patient's grafts, yet it is a common observation that only one graft will show progression of disease while the others are stable or vice versa. The data presented in Table 3 therefore only confirm that the conventional wisdom of risk factors in coronary artery disease does not apply to the graft itself. Other factors, including intimal hyperplasia which is not well understood, are playing a more decisive role.

Several conclusions are apparent. The majority of bypass grafts which occlude do so in the first year after bypass grafting. Afterwards, there is a much slower graft attrition rate, but one which if continued at a steady rate would result in half of all grafts becoming occluded in 15 years. A far more significant factor appears to be the progression of disease in the native circulation, part of which is bypassed and part of which is not. In the latter case, there is a clear connection between the return of angina pectoris at three years and progression of coronary artery disease. Between one year and three years after coronary artery bypass surgery we find that most grafts are stable, there is progression of disease in 11%, and regression in 5%. Regression of disease in the graft is infrequent, but can occasionally be shown. Those factors known to be risk factors for coronary artery disease do not appear to have a bearing on progression or regression of disease in the graft.

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CHAPTER 8

GENERAL DISCUSSION

8-1: INTRODUCTION.

Coronary artery bypass surgery has been available in our institution for the past 13 years and has become an important addition to the management of patients with angina pectoris. However there are a number of aspects of this form of treatment which require further analysis beyond that provided in the Journal articles which constitute the main body of this thesis. This chapter is intended to, at least in part, redress this shortcoming. Among the aspects which will be considered are the pitfalls of a retrospective study, the evolving treatment goals of therapy and the relationship between costs and results. Furthermore, recommendations are made for further evaluation studies. Finally, the implications of the results of this study for the physician faced with the individual patient are discussed.

8-2: THE PITFALLS OF A RETROSPECTIVE STUDY.

This thesis is quite literally an afterthought and bears therefore the disadvantages of retrospective analysis. A prospective randomized study was, in fact, proposed in 1971, however this was not approved nor supported by the government agencies. Instead a multicenter trial of the Inter University Cardiological Institute, the Netherlands Coronary Study (NCS), was started in 1976. Its primary aim was to document the influence of coronary artery surgery on left ventricular function, which required the use of invasive procedures in the post-operative period. Because not all patients consented to have follow-up studies, the patients admitted to the NCS were fewer in number than those operated upon in the collaborating institutions. Although Rotterdam participated actively in the NCS, from 1976 to 1979, only 423 patients could be recruited into the study while 761 were operated upon in that period. Therefore we were forced to use retrospectively collected data in the analysis of the results of consecutively operated patients. It is common to question the value

of retrospective studies, especially if they concern data collected over a large number of years. One has to take further into account that the patient population has changed over the years, that both pharmacological and surgical management have evolved and that to the primary treatment goal, relief of angina, expectations of increased survival and improvement of cardiac function after surgery have been added. Moreover the patient's perception of his or her complaints has been influenced by the passage of time and by the increased awareness of the surgical results that could be expected. These factors will undoubtedly influence the long-term assessment of aorto-coronary bypass surgery. Although changes are inevitable with any new procedure over a time span of 10 years, awareness of their influence is important for the correct interpretation of the data.

8-2-1: The changing patient population.

The introduction of coronary artery surgery, in the Thoraxcenter in 1971, meant that we were confronted with a backlog of patients for whom pharmacological treatment had not been effective in the past years. Today, the waiting list has been greatly reduced although is still in existence. One can only hope that a rate determined by the "natural incidence" of symptomatic coronary artery disease will soon be reached as it would represent a "true" population.

Due to the shorter waiting time today, the patients are offered surgery much earlier in the course of their disease than was the case 12 years ago. It is conceivable also that patients with stable complaints have a different "natural" course of the disease than those who have sudden severe symptoms requiring an immediate operation. At present, many more patients belong to this last group, while in 1971 most had stable complaints for many years, waiting for cardiac surgery to be introduced. To extrapolate from these results to those to be expected in the future is therefore not necessarily permissible.

8-2-2: The changing pharmacological management of angina pectoris.

Many articles which assess coronary artery bypass surgery define the indication for surgery as: "angina pectoris, not responding to intensive medical treatment". In 1971 this meant that, when nitroglycerin and propanolol did not relieve symptoms, angina pectoris was judged to be incapacitating. Ten years later, the same indication implies that the daily use of both short and

long acting nitroglycerin preparations, a choice out of the wide variety of beta-adrenergic blocking agents currently available and the recently introduced calcium channel blockers all be ineffective. All of these drugs, often in combination, have shown considerable therapeutic efficacy. Therefore, although the term incapacitating complaints resistent to drug therapy, is used in the entire period, this does not necessarily mean that the same type of disease is present in these patients as the symptoms are being treated more vigorously in later years before it is decided to advise surgical therapy.

8-2-3: The evolution of surgical technique.

Over the last decade, more and more bypass grafts have been placed in each patient in an attempt to achieve more complete revascularization. This is also evident in our series, as in 1971 only 1.33 grafts per patient were implanted, while by 1980 this had risen to 3.04 grafts per patient. Sequential grafting was introduced in 1976, which made it possible to increase the number of distal anastomoses without lengthening of the time on pulmonary bypass or the aortic cross clamping time. A similar trend has been noted by Kirklin [1] and Loop[2]. Furthermore, the increased awareness of the surgeon to myocardial injury during surgery led to the introduction of "cardiac preservation" techniques such as hypothermia, shorter cross clamping time and cardioplegic perfusion solutions. Cardioplegic solutions are not routinely used at our institution, but the other factors have changed the surgical technique. This makes a comparison of results obtained over a decade, problematic, as others have also pointed out [3].

8-2-4: Evolving goals of therapy.

The primary goal of coronary artery bypass surgery was and remains the relief of angina pectoris. Since the first description of angina pectoris by Heberden to this day, clinicians still debate the correct interpretation of the patient's complaints. Many attempts[4-6] have been made to objectively quantify the severity of restriction in the patient's daily life. However, it must be conceded that these attempts at classification are limited in their ability to serve as a measure of the effectiveness of any particular regimen of therapy.

Quite understandably, the search for an answer to the question "does coronary bypass surgery really help?" has turned to more objective measures of the cardiac status of the patient. Almost any parameter which can be measured, has

been included in such studies, ranging from the obvious one of enhanced survival, to various measures of left ventricular function, excercise tolerance, myocardial perfusion studies with Thallium-201 uptake and many others.

This search for assessment via objective criteria carries with it the danger that the original objective, the subjective alleviation of pain, is lost in the abundance of data. Also an improvement in a seemingly objective parameter may be confused with effective therapy. For example, as discussed in chapter 2, an operation now regarded as ineffective such as mammary artery ligation, was also followed by an improved exercise tolerance in 85% of the patients studied[7]. This operation even "resulted" in disappearance of ischemic changes in the resting electrocardiogram in some, and was therefore considered quite effective.

Notwithstanding the difficulties in the assessment of angina pectoris, we feel that the primary goal of the therapy deserves more attention than it is currently given. To our knowledge, there are but four other published studies [8-11] which try to assess the long term follow-up of incidence and severity of angina pectoris in the post-operative period. These studies each employ a different method to evaluate the severity of the complaint. This was in one instance via data forms sent to each patient's physician [8], once it was via personal interview or a patient's questionnaire [9], once it was obtained via yearly determination of the New York Heart Association Functional Classification by the same 2 observers [10] and once via a standardised set of questions introduced half way in a prospective study[11]. None of these studies contained more than 350 patients. As our population was so much larger it was decided not to use personal interviews but a questionnaire sent directly to the patient to obtain a truly subjective evaluation of the post-operative condition. Although the methods differ greatly in these various studies, it is remarkable that the outcome i.e. the frequency of angina pectoris observed in the post-operative period is very similar. As discussed in chapter 5, at 3-5 years post-operatively, 40-50% of the patients still experience angina pectoris whatever the method of data collection.

8-2-5: Pain and the passage of time.

Given the scarcity of information on the long term efficacy of coronary artery bypass surgery, an examination of our own results seemed to be in order. Yet in 1971, an accepted standardised measure of the severity of anginal complaints did not exist. It became, therefore, obligatory to either exclude the

early years of coronary bypass surgery in our institution or to accept the imperfections of the patient's own perception of recollected pain. We chose the latter, since the inclusion of all 1041 patients operated on successively, seemed to have sufficient, if not the most, virtues.

It has also been recognised that the results presented in this study may well have been confounded by both the placebo effect of the treatment and by pain amnesia. The inability to recollect the severity of pain is well documented in other areas, such as child birth, but has not been studied in angina pectoris specifically.

In our study, anginal complaints were present three years after surgery in 47% of the patients. Yet nearly 90% of the total group of patients felt "improved".Since nearly all of the patients had pain complaints prior to surgery, we may conclude that 53% lost their anginal pain, while of the total group 36% still have pain and describe it as less severe, only 11% feel their complaints to be unchanged or worse.

There are several possible explanations for the decrease in perceived severity of pain. It could be caused by the specific effects of surgery such as reduced ischemia or restored perfusion, the non-specific effects of surgery i.e. interruption of nerves, infarction of areas previously ischemic and causing pain, the "placebo effect" accompanying any surgery or imperfect recollection of the exact degree of pain prior to the operation by the patient. Evidence for a specific effect of surgery in reducing the presumed cause of the pain (ischemia) is extensively discussed in chapter 5 of this thesis. The potential role of the placebo effect is considered in chapter 2. Given the current state of knowledge, it is impossible to assess either the impact of non-specific surgical effects or pain amnesia, while myocardial injury during surgery has not been adequately measured.

As a consequence, I am forced to conclude that I do not know how one should attempt to take all these factors into account, when interpreting the results of coronary artery surgery. At the very minimum, cautious interpretation of our results is required and one may only hope that such confounding factors will receive more attention in future, prospective, studies.

8-3: THE ACHIEVEMENT OF TREATMENT GOALS.

The primary treatment goal was,and still remains the relief of angina pectoris. The results obtained in the Thoraxcenter have been presented in chapter 5 and it seems appropriate to briefly consider how our results compare with

those obtained elsewhere in the world.

The extent to which secondary goals have been reached also provides information on the therapeutic standards which have been achieved at the Thoraxcenter. Therefore, we will briefly consider both the probability of survival following coronary artery bypass surgery and the effect of surgery on objective measures of left ventricular function.

8-3-1: The relief of angina pectoris.

It is disappointing that nearly half of the patients still suffer from anginal complaints three years after their bypass operation. However, both the North American[10,12] and the European[13] results would appear to be no better. For example, the widely cited study of Campeau et al [10] shows an occurrence of angina pectoris at one year in 38% of the patients, rising to 45% at three years and to 63% at seven years after the operation. Cameron[9] found a linearly increasing fraction with angina ranging from 37% at one year to 50% at seven years. The European Coronary Surgery Group study has published results for the first three postoperative years[13]. At one year, 42% of the patients had anginal complaints and by three years this figure had risen to 51%. Broadly speaking, our own results are in agreement with these studies (see chapter 5), although we found after 3 years no evidence for the continued increase in incidence of angina such as was reported in the North American studies. It is not possible to distinguish between differences in study design and a true difference in recurrence rate of angina as the cause of these contrasting observations.

The necessity for re-operation provides another measure of the efficacy of the procedure, since the recurrence of severe symptoms is the indication for additional surgery. Comparison with the results reported by other institutions is confounded by differing policies and preferences, as discussed in chapter 6. The percentage of patients in our study in whom re-operation was carried out is 5% at a mean follow-up time of 4.8 years. In the literature a range of 3% to 9% has been reported[14-17]. Re-operations are feasible with low operative mortality rate, 3.8% in our study. The cause of complaints is most often failure of the bypass graft(s), especially if symptoms occur within 6 months of the initial operation. Progression of disease in the native circulation was seen if symptoms recurred much later. All in all we conclude that our results compare favourably with the international experience regarding re-operations for angina pectoris.

8-3-2: The increased probability of survival.

This study was not designed to specifically assess the effect of coronary artery bypass surgery on longevity. This would have required a concurrent group of matched patients treated by pharmacological means only.

Several aspects of the results of surgery can, however, be compared with results in the literature. Let us consider in turn, peri-operative mortality and long-term survival for both the entire patient population and selected high-risk subsets.

Mortality within 28 days of the operation wa s 1.2%, a result which compares well with that reported by other groups. As discussed in chapter 4, operative mortality has decreased in recent years from 10% before 1970 to less than 2% now. Therefore the 1,2% of our series falls well within that range.

An estimated survival probability of 90% at 8 years after surgery for the entire patient population as found in this study, is the same as one would have expected for an age and sex matched sample of the general Dutch population. This result is consistent with that reported by both Greene[18] and Kirklin[1]. In other series,the five-year survival probability has been reported to vary between 87% and 97%. We found a survival probability at 5 years of 94% $\pm$ 2% (95% confidence limits).

It has been reported [19,20] that the prospects for patients with impaired left ventricular function are less good. Neither we, nor others [17,20] have have been able to demonstrate that bypass surgery provides an improved probability of survival in this subgroup. Indeed, survival probability at 5 years for patients with a moderately impaired ejection fraction (EF) was 92%, for those with a poor EF 83%, while it was 95% when a normal EF was found pre-operatively.

Others have shown [1,21] that patients with left main disease or three vessel disease form a high risk sub-set. The survival probability of this high risk group was however not significantly different from that of the entire patient population. This shows that the higher risk connected to extensive vascular involvement is ameliorated by bypass surgery. Since more than half of our patients fell into this high-risk subset we regard this as a gratifying result.

8-3-3: The improved left ventricular function.

Left ventricular function is generally not changed by coronary artery bypass surgery. This is found when post-operative values are compared with the

patient's own pre-operative value or when compared with those of pharmacologically treated patients in prospective randomized studies [22]. In the individual patients there are different reactions to surgery: left ventricular function remains unchanged in the majority, but it improves in some and deteriorates in others. In all patients it is depressed in the immediate postoperative period. It has been shown by Serruys et al [23] from our laboratory that recovery of postoperative function occurs with time and is completed in three to six months after the operation. At one year following operation they found cardiac function to have returned to pre-operative values, sometimes modified by an intervening myocardial infarction or by the relief of ischemia at rest.

It seems important to recognise pre-operatively those patients who are likely to sustain a peri-operative myocardial infarction as well as those in whom an improvement in cardiac funtion is likely to occur. Meester et al [24] in an analysis of patients operated on in three Dutch centers, have shown that an increased wall mass index before surgery is associated with an increased likelihood of peri-operative myocardial infarction of 11% vs. 5% in the patients with normal wall mass. The identification of those patients whose myocardial function is likely to benefit from coronary artery bypass surgery remains an important challenge.

8-4: THE RELATIONSHIP BETWEEN COSTS AND RESULTS.

It is important to recognise from the outset, that no systematic study of the "cost-benefit" ratio for coronary artery bypass surgery in the Dutch setting has been done. Since hundreds of millions of guilders per year are devoted to these operations, the matter seems worthy of more attention than it has received to date. An in-depth analysis is beyond the scope of this study but neither can it be ignored completely.

Let us consider the costs, both material and non-material. The direct financial costs are those of the operation itself, with associated pre- and postoperative tests as well as the time investment (including the recovery period) of the patient. It is difficult to assign a number to this, but it is clear that the total costs are substantial indeed. Internationally these costs are estimated at U.S.$ 12.000 to 15.000 per procedure including recovery period. The non-material costs are nearly impossible to quantify, but include fear, anguish and pain, along with the disruption of the normal life pattern.

The benefits of surgical treatment of angina pectoris consist of increased

longevity for those patients with main stem or three vessel disease together with an improvement in quality of life, at least as measured by a reduction in the incidence of pain. Some published studies[25,26] have noted an increased employment rate as one of the beneficial effects of the procedure, however, this is not borne out by our findings. We found [27] that of the 558 men, aged 55 or younger at operation, 230 (41%) worked in the last half year before the operation. At a mean follow-up of 3.5 years, 41% was employed. Overall there was therefore no increase in employment rate in this group of patients. This negative result is not unique to the Netherlands and has also been reported in other North American studies [28,29].

A decrease in "late cardiac events", such as episodes of unstable angina pectoris and myocardial infarction, is a potential benefit of coronary artery bypass surgery. Data from the Seattle Heart Watch[30] show that in 6 years a 26% reduction in hospitalisation in the surgical group was achieved when compared with the medical therapy group. Collins et al [31] compared the expense of revascularization surgery with the cost of continued medical management in a consecutive group of 102 patients, taking the costs made in the 2 years before surgery as basis. In the 2 years after surgery fewer hospitalisations were necessary, which meant that the average amount of money spent on surgery would be amortized in 4 years. Kloster [32] found in his prospective study with randomization between medical and surgical management, no difference in the rate of infarction, but did find a decrease in the number of hospital admissions for unstable angina in the surgical group. Although extrapolation of these results to our patient population is difficult, a potential benefit seems plausible.

Clearly, the weighing up of the costs and the benefits of the procedure is a complex matter. In the United States, two studies have been published, one concentrating on the financial costs of treatment (Oberman et al,[33]), while the other also takes into account the "improved quality of life" (Weinstein and Stason,[34]). Oberman et al [33] showed that the costs in the year of catheterization were less for those receiving pharmacological treatment when compared with those who also had an operation in the same year. Beyond the first year no difference in medical care costs was found between the two groups, hence the initial cost difference between therapies persisted. This is in contrast with Collins'[31] conclusion which might be caused by a difference in method: the former group used a data bank of patients undergoing surgical and pharmacological therapy while in Collins' case the same patient was observed in the course of the disease. Weinstein and Stason [34]

concluded that there is a net gain from surgical treatment of symptomatic patients "per quality adjusted year of life". In the analysis of Weinstein this net benefit extended even to those with single vessel disease.

Complex analyses such as those of Weinstein remain controversial and are at the very least, culture dependent. There exists therefore a real need for a systematic cost-benefit assessment of coronary artery bypass surgery in the Netherlands.

8-5: THE PHYSICIAN AND THE INDIVIDUAL PATIENT.

What should we advise the individual patient with stable angina pectoris, today? An unequivocal recommendation cannot be extracted from the available information, including this study. What follows is my personal judgement, which represents a synthesis of the published experience of others, this study, and my own experience, which largely reflects that of my collegues with whom I work.

Medical treatment with nitrates, beta-adrenergic blocking agents and/or calcium channel blockers should be given initially to all patients with stable complaints i.e. the patient with complaints predictably induced by exercise and/or emotions and who experiences prompt relief at rest or with nitroglycerin. Fixed atherosclerotic lesions are generally found in this condition. When the complaints remain a serious impediment for a near-normal life style or if the treatment is not well tolerated, cardiac catheterization with coronary angiography should be performed. When three vessel disease or left main stem stenosis is found, and surgery is technically feasible, an operation should be advised. When one- or two-vessel disease is found the decision depends on the perceived severity of the symptoms despite optimal pharmacological management. If surgery is indicated and the lesion lends itself to this procedure percutaneous transluminal angioplasty should be performed by preference. With the techniques developed in the last 2-3 years this procedure is now feasible in 20% of the patients[35, 36].

If the angina pectoris is unstable i.e. symptoms occur at rest, are not promptly relieved by nitroglycerin or pain attacks occur with increasing frequency and severity, clinical observation and aggressive medical management are indicated[37]. If the situation remains unstable, which is fortunately rare, prompt coronary angiography and surgery is indicated, even if only one vessel is involved. When the situation becomes more favourable and mobilisation is tolerated, evaluation on an elective basis can be performed. Often

these patients revert to a stable phase of their disorder.

Finally, in each individual patient, it is most important that the patient comes to grips with the constraints which the disease will place on his or her life style. Both patient and physician must recognise that what is intolerable to one person may be quite acceptable to another. Ideally the judgement should be left to the patient, however the attitude of the physician to surgery, the opinion of relatives and experiences of others known to the patient, prove to be important influences as well.

Even though there is as yet no accepted "cost-benefit" analysis every individual patient is forced to do his or hers, and should herein be wisely guided by a cardiologist experienced in these matters.

8-6: RECOMMENDATIONS FOR EVALUATION STUDIES.

From the preceding considerations it can be concluded that future evaluation of the results of aorto-coronary bypass surgery would be greatly facilitated by:

a) The classification of the complaints of the patient in a standardised manner both before and after surgery.
b) A statement on the treatment goal in each individual patient before surgery.
c) The choice of post-operative measurements, which should be the result of a well thought out follow-up program and not be decided upon by ad hoc decisions.
d) An analysis in the Netherlands, via the currently available health care assessment techniques, of the results of aorto-coronary bypass procedures.

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CHAPTER 9

SAMENVATTING

Het doel van deze studie is een beschrijving te geven van de resultaten van aorto-coronaire bypass chirurgie bereikt in ëën Nederlands instituut. Hiermee kan duidelijkheid ontstaan over de doelmatigheid van de procedure en kunnen de verwachtingen van patient en verwijzende arts beter op de realiteit worden afgestemd. Bovendien schept het de gelegenheid om de uitkomst van de operatie te vergelijken met de resultaten bereikt in instituten elders in de wereld.

Van alle 1041 patienten die in de periode 1971 t.m. mei 1980 coronair chirurgie ondergingen, worden de resultaten van operatie besproken. De duur van de vervolg periode bedraagt maximaal 10, minimaal 1, gemiddeld 3,5 jaar. De indikatie voor de chirurgische ingreep was altijd angina pectoris, niet voldoende verlicht door middel van uitgebreide medicamenteuze therapie.

Hoewel de aorto coronaire bypass operatie, zoals die nu wordt uitgevoerd, pas voor het eerst werd toegepast in 1967, werd al in 1916 met chirurgische therapie voor angina pectoris begonnen. Zoals in hoodstuk 2 beschreven, evolueerde die aanpak via een aanvankelijke pijn bestrijding door doorsnijding van zenuwbanen, naar een diffuse vergroting van de bloed toevoer in het myocard door het veroorzaken van ontstekingsweefsel rondom het hart. Later poogde men extra arterieel bloed te brengen in specifieke delen van het weefsel, dat verondersteld werd ischemisch te zijn door vernauwingen in het toevoerende bloedvat o.a. door implantatie van de arteria mammaria in het myocard. De resultaten van deze vroege chirurgie laten een verbetering zien in klachten bij 60 tot 80% van de geopereerden onafhankelijk van de gebruikte operatie procedure. Dit brengt nog eens onder de aandacht hoe moeilijk het is om een operatie resultaat te beoordelen, zeker wanneer dit de behandeling betreft van een pijnklacht als angina pectoris.

In hoofdstuk 3 wordt de questionnaire waarmee de gegevens over de algemene toestand post-operatief werden verzameld, beschreven en de reaktie erop geanalyseerd. Benadrukt wordt hier dat, hoewel er geen objektieve gegevens voorhan-

den zijn over de mate waarin angina pectoris nog aanwezig is bij de respondenten, wēl eensluidend werd geantwoord op de diverse vragen die betrekking hadden op pijn op de borst. Er was bovendien een overeenstemming in de antwoorden bij de 76 patienten die persoonlijk werden ondervraagd van 86% met hun reakties via de vragenlijst. Deze 76 patienten werden willekeurig gekozen uit de totale groep van 920 respondenten. Het subjektieve gevoel van verbeterd te zijn na de operatie gevonden by 89% van degenen die de questionnaire beantwoordden, wordt bovendien gesteund door de uitkomst van het gesprek. Gezien het feit dat 95% van de 969 nog in leven zijnde patienten antwoordden, is aangenomen dat de data van de questionnaire representatief geacht kunnen worden.

De overlevingskans van deze 1041 patienten, wordt besproken in hoodstuk 4. De sterfte binnen 28 dagen na operatie bedroeg 12 (1,2%). De kumulatieve overlevingskans 5 jaar na operatie werd berekend op 94 $\pm$ 2% en 8 jaar na operatie 90 $\pm$ 4% (95% betrouwbaarheidsgrenzen). Voor de algemene Nederlandse bevolking met dezelfde leeftijdsopbouw en geslachtsverdeling, zou dit respectievelijk 94,6% en 90,1% zijn. Multivariaat analyse toonde verder dat er geen relatie was tussen sterftekans en sexse of leeftijd bij operatie. Er was een niet signifikante hogere sterftekans bij uitgebreidere afwijkingen aan de coronair arterien en een duidelijk signifikant samengaan van hogere sterftekans met verminderde linker ventrikelfunktie. Er werd derhalve gekonkludeerd dat bypass chirurgie de risikofaktor inherent aan de uitgebreidheid van het coronairlijden mitigeert, maar dat dit niet het geval is wanneer er van verminderde linker ventrikelfunktie sprake is.

Zoals besproken in hoofdstuk 5 is het op zich teleurstellend dat 47% van de 920 respondenten regelmatig angina pectoris als klacht ervoeren tijdens het vervolg onderzoek. Pijn op de borst kwam ēēn jaar na operatie bij 277 patienten voor (30%). Na 3 jaar was dat 46% en na 8 jaar 50%. Daarna nam de fraktie met pijn niet verder toe. Toch voelt 89% van de respondenten zich verbeterd ten op zichte van voor de operatie. Er wordt ook een correlatie gevonden tussen het opnieuw optreden van angina pectoris en jongere leeftijd ten tijde van de operatie maar dit geldt alleen voor mannen. Bij 169 patienten van de 920 die de questionnaire beantwoordden werden ook hartkatheterisaties verricht in de postoperatieve periode. In deze groep wordt een correlatie gevonden tussen angina pectoris en de doorgankelijkheid van de vaatent alsmede de aanwezigheid van progressie van afwijkingen in de coronair arterien. Dit onderzoek toont eveneens aan dat post-operatieve angina pectoris vroeg na de operatie gerelateerd is aan een verminderde doorgankelijkheid van de vaatent, terwijl dit later gerelateerd is aan progressie van de coronair sclerose in de eigen vaten.

In hoofdstuk 6 blijkt dat 53 patienten (5,2%) een heroperatie ondergingen gedurende de onderzochte vervolg periode. De operatiesterfte bij deze herhaalde procedure was niet signifikant hoger dan voor de eerste operatie: 3,8% ten opzichte van 1,2%. Het blijkt dat wanneer symptomen van angina pectoris optreden binnen 6 maanden na de eerste operatie, de oorzaak bijna altijd ligt in een falen van de bypass graft(s). Treedt angina pectoris later na de eerste operatie op dan wordt bijna altijd progressie in het eigen vaatstelsel gevonden.

Tenslotte worden in hoodstuk 7 de gegevens besproken bij 221 patienten, verkregen bij twee herkatheterisaties respectievelijk ëën en 3 jaar na de operatie. Tot deze 221 patienten behoren de 169 besproken in hoodstuk 5 en diegenen die niet reageerden op de questionnaire of elders in Rotterdam werden geopereerd. De gevonden afwijkingen in de vaatenten en de eventuele progressie of regressie van coronair vaatvernauwingen in de eigen vaten, worden gecorreleerd met de bekende risikofaktoren. Het blijkt dat er geen relatie bestond tussen risikofaktoren en eventueel optredende vernauwingen in de vaatent.

In hoofdstuk 8 worden de beperkingen besproken van deze retrospektieve studie. Bovendien worden de uitkomsten van de studie getoetst aan het behandelingsdoel, namelijk de verlichting van de klacht angina pectoris en daarnaast mogelijk een toegenomen overlevingskans of verbetering van linker ventrikelfunktie. Tevens worden aanbevelingen gedaan om toekomstige evaluatie van aorto coronaire bypass chirurgie te vergemakkelijken. Bij het onderzoek is gebleken, dat hoewel vele nuttige gegevens bekend zijn geworden, er toch nog vele belangrijke vragen niet beantwoord kunnen worden. Wanneer wij in de toekomst de individuele patient met stabiele angina pectoris klachten willen kunnen begeleiden naar de best mogelijke therapie, dan is verder vergelijkend onderzoek geboden. Desalniettemin blijft bij de huidige inzichten de aorto-coronaire bypass operatie een belangrijke aanwinst voor de behandeling van de patient met invaliderende angina pectoris met name bij hen bij wie deze klacht niet verlicht wordt door optimale medicamenteuze therapie.

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CURRICULUM VITAE

De schrijfster van deze studie werd op 1 mei 1940 geboren te Overschie. In 1957 behaalde zij het diploma HBS-B aan de van 't Hoff Dalton HBS te Rotterdam. In 1963 werd het doctoraal examen in de geneeskunde afgelegd gevolgd door het arts-examen in april 1965, beide aan de Gemeente Universiteit van Amsterdam.

De twee volgende jaren werden in Amerika doorgebracht, eerst als intern in het Flower Hospital te Toledo, Ohio, daarna als resident in internal medicine in het Roosevelt Hospital te New York. De opleiding werd in Nederland voortgezet in het AZR-Dijkzigt van 1967 tot 1969 op de afdeling inwendige geneeskunde onder toezicht van Prof. Dr. J. Gerbrandy, daarna op de afdeling cardiologie onder leiding van Dr. J.B. Verhey en Prof. P.G. Hugenholtz. In 1972 volgde opname in het specialisten register. Vanaf 1972 werden diverse staffuncties bekleed in het Thoraxcentrum,de laatste jaren die van hoofd van de cardiologische polikliniek.