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# **NONINVASIVE EVALUATION OF THE EFFECTS OF CORONARY ARTERY BYPASS GRAFTING ON MYOCARDIAL FUNCTION**

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**”Varför ska man göra det lätt för sig, när det är så lätt att göra  
det svårt för sig”**

Ronny Eriksson (b. 1953-)

Stand-up comedian from Harads

To Petra, Anton and Fanny.

## ABSTRACT

Coronary bypass grafting (CABG) is an effective treatment of patients with coronary artery disease and leads to an improvement in both cardiac symptoms and long-term survival. The effects of CABG on global left ventricular systolic and diastolic function at rest and during stress, and the long-term effects on right ventricular function and their significance and relation to early graft occlusion and residual myocardial ischemia have however not been fully elucidated. It is known that early graft occlusion depends mainly on thrombotic mechanisms. Thrombosis and inflammation are closely related. However it remains unsettled if preoperative inflammatory activity predicts early graft occlusion and late cardiac events in patients subjected to CABG.

The present study comprises 99 patients accepted for CABG because of angina pectoris and significant coronary artery stenosis at angiography. Exclusion criteria were a history of recent myocardial infarction (4 weeks before preoperative angiography), atrial fibrillation, significant valvular heart disease or previous CABG. Eighty-five men and 14 women aged  $65 \pm 9$  years (range 40-82) were included. All patients underwent preoperative blood tests, exercise ECG testing, first pass radionuclide angiography (FPRNA), single photon emission computed tomography (SPECT), echocardiography and a dobutamine stress test before CABG. The same tests and a coronary angiography were repeated 3 months after CABG, and a third echocardiography was performed 12 months after CABG.

Of 286 operated grafts 32(11%) grafts were occluded and 31% of the patients had at least one occluded graft 3 months after CABG.

In patients with a moderately decreased left ventricular ejection fraction (LVEF) CABG improves LVEF under stress ( $P < 0.001$ ) but not at rest. Despite this lack of improvement in resting LVEF, CABG relieves angina, improves myocardial perfusion both at rest ( $P < 0.001$ ) and during stress ( $P < 0.001$ ), and augments the work capacity of the patients as evaluated by a symptom-limited exercise test ( $P < 0.001$ ).

CABG also improves the left ventricular diastolic function ( $P < 0.01$ ) as assessed by Doppler tissue imaging (DTI), but not by conventional Doppler echocardiography. The enhancement of diastolic DTI parameters was observed both at rest and during stress.

Right ventricular function evaluated by tricuspid annular motion was still decreased 1 year after CABG and septal motion remained paradoxical in the majority of patients, suggesting that these defects might be permanent. This finding was independent of the state of the right coronary artery as well as grafts to this artery. Despite the reduced tricuspid annular motion, exercise performance was improved 3 months after CABG ( $P < 0.01$ ).

Furthermore, we found that elevated preoperative IL-6 levels are predictors of both early graft occlusion ( $P < 0.01$ ) and late cardiovascular events ( $P < 0.01$ ) after CABG. Elevated preoperative CRP levels can predict early graft occlusion ( $P < 0.05$ ) after CABG.

In conclusion: CABG improves systolic left ventricular function predominantly at stress as well as the diastolic left ventricular function as measured by DTI. The decrease of right systolic ventricular function as evaluated by tricuspid annular motion after CABG was present also at the 1-year follow-up and may be permanent. Preoperative inflammatory parameters predict early graft occlusion and late cardiac events after CABG.

*Key words: Coronary artery bypass grafting, C-reactive protein, dobutamine stress test, Doppler tissue imaging, echocardiography, exercise test, interleukin-6, myocardial perfusion scintigraphy.*

## **ABBREVIATIONS**

CABG	coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CRP	C-reactive protein
DSE	dobutamine stress echocardiography
DTI	Doppler tissue imaging
ECG	electrocardiogram
EF	ejection fraction
ET	endothelin
FPRNA	first pass radionuclide angiography
IL	interleukin
LAD	left anterior descending artery
LIMA	left internal mammary artery
LV	left ventricle
PCI	percutaneous coronary intervention
RCA	right coronary artery
RV	right ventricle
SPECT	single-photon emission computed tomography
SR	sarcoplasmatic reticulum
TAM	tricuspid annular motion

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## LIST OF ORIGINAL PAPERS

This thesis is based on the following original papers, which will be referred to by their Roman numerals.

- I. Hedman A, Zuber E, Alam M, Samad BA. The Effect of Coronary Artery Bypass Grafting on Left Ventricular Function and Perfusion at Rest and During Stress. *Submitted for publication.*
- II. Hedman A, Samad BA, Larsson T, Zuber E, Nordlander R, Alam M. Improvement in diastolic left ventricular function after coronary artery bypass grafting as assessed by recordings of mitral annular velocity using Doppler tissue imaging. *Eur J Echocardiogr. 2005 Jun;6(3):202-9. Epub 2004 Dec 18.*
- III. Hedman A, Alam M, Zuber E, Nordlander R, Samad BA. Decreased right ventricular function after coronary artery bypass grafting and its relation to exercise capacity: a tricuspid annular motion-based study. *J Am Soc Echocardiogr. 2004 Feb;17(2):126-31.*
- IV. Hedman A, Larsson T, Alam M, , Zuber E, Wallén NH, Nordlander R, Samad BA. C-Reactive Protein, Endothelin-1, and IL-6 Levels in Patients Undergoing Coronary Artery Bypass Grafting. Do Preoperative Inflammatory Parameters Predict Early Graft Occlusion and Late Coronary Events? *In press: Int J of Cardiology.*

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# INTRODUCTION

## **Atherosclerosis and coronary heart disease**

Atherosclerosis commonly starts in the second and third decade of life in the western world. It begins with an intimal thickening of the vessel wall. This is followed by an intimal lipid accumulation which triggers an inflammatory response in the vessel wall with migration of leucocytes. The leucocytes begin to accumulate lipids and develop into foam cells. As the disease progresses the vessels initially undergo positive remodelling with the lipid plaque growing outwards and leaving the lumen of the vessel intact. This is followed by intraluminal narrowing leading to stenotic lesions and ischemic symptoms (1, 2). Stenoses represent the tip of the iceberg of atherosclerosis.

Symptoms of the disease usually do not develop until several decades later, characteristically later in women than in men. Known risk factors that accelerate the process include smoking, hypertension, diabetes mellitus and hyperlipidemia. The classical symptom of stable angina pectoris is central chest pain that occurs during exercise. The degree of angina is commonly classified by the Canadian Cardiovascular Society (CCS) grading scale of angina as follows:

### **CCS Classification**

Class 0: Asymptomatic

Class I: Angina with strenuous exercise

Class II: Angina with moderate exertion

Class III: Angina with mild exertion

Class IV: Angina at any level of physical exertion and at rest.

The feared complications of atherosclerosis such as unstable angina, myocardial infarction, cardiac death or stroke may occur suddenly after a silent period (3).

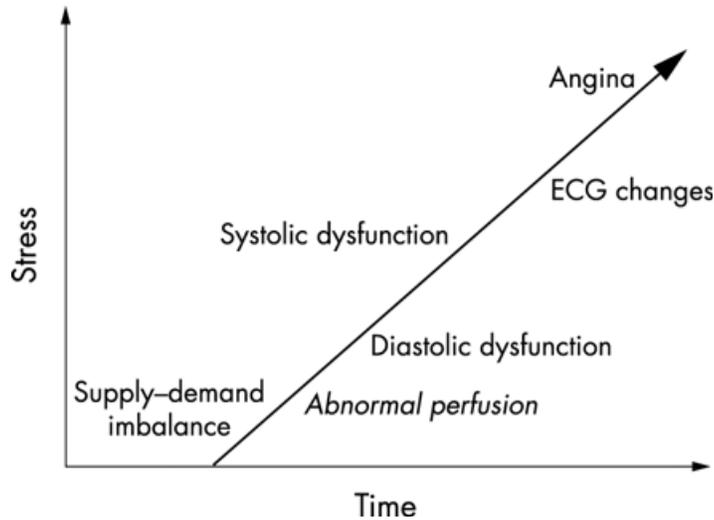
### **Cardiac function: mechanisms of cardiac contraction and relaxation**

The major function of cardiac myocytes is cardiac contraction and relaxation. The contractile proteins of the heart lie inside the myocytes and are energy dependent. The energy is derived from adenosine triphosphate (ATP) which is produced by the mitochondria. The contractile function also requires ions in the form of potassium, sodium and calcium. The sarcoplasmic reticulum (SR) plays a major role in maintaining the right concentration of intracellular calcium. Calcium release from the SR initiates myocardial contraction and when calcium is once again taken up into the SR relaxation occurs. The uptake of calcium into the SR requires energy. The contractile proteins consist of actin and myosin filaments. The calcium ions initiate contraction by interacting with troponin C to relieve the inhibition of troponin I. The actin and myosin filaments slide over each other resulting in shortening and which in turn causes the sarcomere to contract. This process is modulated by multiple mechanisms such as the beta adrenergic system (3).

The two basic events of the cardiac cycle are systole, the contraction phase, followed by diastole with relaxation and filling. Systole leads to ejection of blood out of the ventricles. The amount of blood delivered at each contraction, i.e. the stroke volume, depends on multiple physiological factors that affect the pre- and afterload of the heart. Diastole commences as calcium ions are taken up by the SR resulting in relaxation and a decline in LV pressures allowing for ventricular filling to begin. This is followed by the next systole.

The heart is supplied with arterial blood through the coronary arteries mainly during diastole. The arteries are covered on the inside by a thin layer of endothelium. The normal endothelium has haemostatic functions and regulates vascular tone through production of a variety of vasoactive humoral factors. These include nitric oxide which leads to vasodilatation, and endothelin which leads to vasoconstriction. Normally, the endothelium promotes its vasoregulatory functions in response to a variety of systemic, neurohumoral and mechanic stimuli. Atherosclerosis leads to endothelial dysfunction with an imbalance in the endothelium derived counteracting vasoactive factors. Coronary artery disease leads to narrowing of the vessels and therefore an inadequate blood supply to the heart, resulting in myocardial ischemia (3).

The myocardial response to ischemia, the ischemic cascade, begins with diastolic dysfunction and thereafter systolic dysfunction leading to elevated filling pressures, followed by ECG changes such as ST-depression and only thereafter by symptoms (Fig.1). This explains why many patients experience shortness of breath before they have chest pain (4).



**Figure 1.** The classical ischemic cascade. (Monaghan MJ, *Heart* 2003;**89**:1391)  
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One mechanism of myocardial protection during ischemia is so-called myocardial stunning when contractile proteins temporarily stop working after an episode of decreased blood supply to save energy. Repeated episodes of ischemia and myocardial stunning may lead to a so-called hibernating myocardium, a condition of chronic contractile dysfunction caused by coronary artery stenosis and which can be reversed by revascularization procedures such as coronary bypass grafting (CABG) with an improvement in regional and global contractile function (5).

The LV contraction is multidirectional – longitudinal, circumferential and with rotation of the heart along its long axis. Already in the 15th century Leonardo DaVinci described the rotational motion of the left ventricle. During exercise the LV cardiac output is increased by higher heart rates, an increased stroke volume and ejection fraction (EF). Beta adrenergic stimulation leads to increased calcium uptake by the SR and accelerated myocardial relaxation and the early diastolic recoil is enhanced leading to that the early LV diastolic pressures become lower during exercise than at rest (6, 7).

### **Coronary artery bypass grafting**

Surgical revascularization in coronary heart disease is one of the great success stories in medicine. The Frenchman Alexis Carrel (1872-1944) understood the association between angina pectoris and coronary stenosis and in 1902 he published a technique for end to end anastomoses of blood vessels. In 1910 he demonstrated that blood-vessels could be kept for long periods in cold storage before they were used as transplants in surgery. He was awarded the Nobel Prize 1912 for his work (8, 9). Carrel and the aviator Charles Lindbergh collaborated in 1935 to develop a primitive heart-lung machine intended to allow direct cardiac surgery but the project did not lead to a clinically useful device. John Gibbon developed a clinically useful cardiopulmonary bypass technology which was successfully tried on a patient in 1953. In 1964 the first CABG was performed by DeBakey and co-workers. The operation gained great popularity and became widespread in the late 1960s (10).

Since 1994 there has been a decline by 26 percent of isolated coronary artery operations in Sweden. This is probably due to the development of percutaneous coronary interventions (PCI). The annual number of CABG operations in Sweden during the year 2004 was 5,139 cases compared with 16,067 PCI (11).

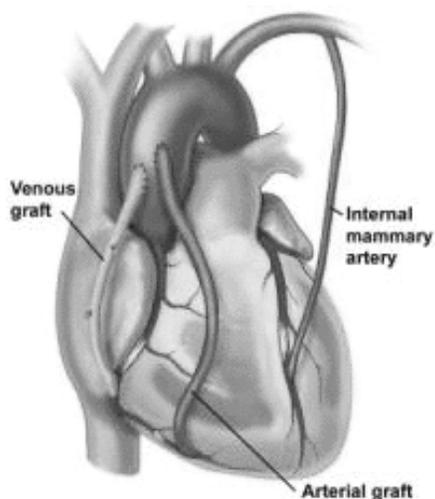
In CABG new conduits are fashioned to bypass the obstruction by the use of either reversed saphenous veins harvested from the legs or by using arterial conduits such as the internal mammary arteries and recently also gastroepiploic or radial arteries (Fig.2). CABG is highly effective in the relief of angina pectoris and improves quality of life. CABG improves exercise capacity and reduces mortality in patients with stenosis of the left main coronary artery or with triple vessel disease especially in those with impaired LV function. Eighty percent of patients are still free from angina at 5 years and 63 percent after 10 years (12, 13, 14).

The progression of atherosclerosis in native vessels and graft occlusions leads to ischemia, recurrence of angina and other cardiac events as well as repeat coronary reintervention. (12,15). It is obvious that all patients have to be on optimal medication before surgery e.g. aspirin and betablockers. Usually the patients are in cardiac arrest during the operation and the circulation is maintained by a heart and lung machine. To minimize perioperative damage and to protect the myocardium blood cardioplegia is usually used during the cardiac arrest. The saphenous vein is used mainly for distal branches of the right and circumflex coronary arteries and as well for sequential grafts of these vessels. The left internal mammary artery (LIMA) is preferred for grafting the left anterior descending artery. Intimal hyperplasia develops much more often in vein grafts than in the LIMA (10).

Graft occlusion: Early graft occlusion occurs in 8-12 percent of venous grafts and by 1 year 15-30 percent of vein grafts are occluded. After the first year the annual occlusion rate is 2 percent and after 6 years the occlusion rate rises to 4 percent. At 10 years approximately 50% of vein grafts have become occluded and in the remaining vein grafts significant atherosclerotic changes with significant stenoses are seen in 20-40%. Patency rates of LIMA grafts are superior with 95, 88, 83 percent at 1, 5, and 10 years, respectively (13, 14, 16). The occlusion of grafts is usually divided into three phases:

- The early phase (first month): trauma to the harvested vein during surgical preparation can denude the endothelium and thereby impair intrinsic fibrinolytic activity which predisposes for early thrombosis and occlusion of vein grafts.
- The intermediate phase (1 month to 1 year): intimal and medial thickening of the vessel due to an increase in connective tissue matrix.
- The late phase >1 year: degeneration of grafts and development of atherosclerosis.

Predictors of graft occlusion include small target vessel diameter and patient risk factors such as elevated LDL cholesterol, prior myocardial infarction and smoking. Smoking cessation is extremely important and several studies show that continued smoking increases mortality, recurrence of angina pectoris and repeated revascularization procedures (13, 14, 16, 17, 18). Early aspirin treatment within 48 hours after CABG improves graft patency and aggressive cholesterol lowering with statin treatment slows the progression of atherosclerotic vein-graft disease after CABG and results in fewer re-operations. (19, 20, 21)



**Fig.2** CABG using venous or arterial grafts.

## **Effects of CABG on left and right ventricular function**

### *Systolic function*

Most studies have used improvement of regional LV function to evaluate the effects of CABG on myocardial function. Few data point to any prognostic benefit of a regional myocardial improvement in contrast to the known prognostic impact of improved global LV function (22, 23). Investigations addressing the effects of CABG on global LV function are, however, limited (24, 25) and most have used echocardiography to evaluate the effects of CABG on LV ejection fraction (EF). This method is widely available but requires experienced investigators, especially when myocardial function is evaluated under stress. First-pass radionuclide angiography (FPRNA), is less investigator-dependent and may be used as a tool to evaluate left LVEF at rest as well as during stress.

### *Diastolic function*

In ischemic heart disease impairment in LV diastolic function precedes systolic dysfunction. Diastolic dysfunction is therefore a common finding in patients with coronary artery disease and may cause heart failure symptoms apart from its prognostic significance (26, 27, 28). Diastolic function may improve following coronary revascularization (29, 30, 31). However, most papers dealing with diastolic function before and after CABG include only small patient numbers with a short follow-up period. CABG by itself causes short-term reversible diastolic dysfunction (29, 32, 33). Cardiac catheterization is the standard technique for direct measurement of filling pressures and the rate of LV relaxation but is not suitable for widespread application and follow-up investigations. Conventional Doppler echocardiography can assess LV diastolic function by using transmitral flow velocity profiles. These parameters are, however, dependent on such factors as heart rate and preload (28, 34).

During the last few years, analyses of myocardial velocities using Doppler tissue imaging (DTI) have been made to assess LV diastolic function. The myocardial velocities during the different phases of diastole reflect LV relaxation and filling patterns. It has been postulated that DTI is less preload dependent in assessing diastolic function (35, 36). To our knowledge, the value of DTI for assessing LV diastolic function in patients with coronary artery disease before and after CABG has not been fully elucidated, and especially not in comparison with conventional Doppler.

### *Right ventricular function.*

Decreased RV function and paradoxical septal motion are a frequent observation after CABG. The underlying mechanism leading to the RV dysfunction in this patient group is still unknown. Suggested theories have include intraoperative ischemia, intraoperative myocardial damage, cardioplegia and pericardial disruption (37, 38, 39, 40, 41). Previous studies have shown that the RV dysfunction occurs perioperatively and remains decreased for about six months after CABG (42, 43). Reports on long-term follow-up examinations of RV function after CABG are lacking.

Nor has the relation between depressed RV function following CABG and exercise capacity been investigated. Furthermore, it is not known if the deterioration of the RV function is related to the state of coronary artery perfusion to the RV. Assessment of RV function is complex and there is no consensus about a non-invasive reference method for assessing RV function. One method currently in use is measurement of the tricuspid annular motion (TAM) (44, 45, 46).

### **The relationship between preoperative inflammatory parameters and CABG**

As mentioned before CABG is effective in relieving angina pectoris and, in certain subsets of patients it also prolongs life (12, 13, 15). However, the atherosclerotic process continues and thus limits the benefits of CABG. The progress of the atherosclerotic disease may lead to recurrent angina and other acute coronary syndromes (16, 18) and, by 10 years, nearly one third of the patients have required reintervention with CABG or PCI. The cause of progression of the disease is multifactorial and hyperlipidemia is one of the predictors of the long-term adverse outcome after CABG (17). Adequate lipid-lowering therapy leads to a significant reduction of the progression of atherosclerosis in vein grafts as well as in native coronary arteries after CABG (12, 19).

Inflammation has also been shown to be a major contributor to atherosclerosis and atherothrombotic complications(1, 2). Statin treatment not only lowers the levels of cholesterol but also the inflammatory markers C-reactive protein(CRP) and interleukin-6(IL-6) (47, 48, 49, 50). Furthermore, raised CRP and IL-6 levels have been shown to be predictors of cardiovascular events (51, 52, 53, 54) and according to the American Heart Association CRP levels of less than 1, 1-3 and >3 mg/L are associated with low, moderate, and high cardiovascular risks, respectively (55). IL-6, a major proinflammatory cytokine, is produced in a variety of tissues, including activated leucocytes, adipocytes and endothelial cells. IL-6 stimulates hepatic production of CRP. But CRP can also be produced locally such as in the

smooth muscle cells of atherosclerotic lesions in vein grafts as well as in human coronary artery smooth muscle cells (56, 57). Furthermore, CRP increases the production of IL-6 and endothelin (ET-1) from endothelial cells (58). Other inflammatory markers such as preprocedural elevated fibrinogen levels have also been shown to predict major adverse clinical events after PCI (59). Endothelins are a family of potent vasoconstrictor peptides with cell-growth promoting and mitogenic properties. These peptides are produced not only by endothelial cells but also by smooth muscle cells and macrophages. Plasma endothelin levels are raised in patients with significant atherosclerosis and correlate to the extent and severity of coronary artery disease (60, 61, 62). The relationship between preoperative inflammation and the outcome after CABG, especially early graft occlusion, has, however, not been addressed previously.

## AIMS OF THE THESIS

1. To prospectively evaluate *the effects of CABG on LV systolic function* at rest and during dobutamine stress using FPRNA and to assess the postoperative relationship between LV systolic function and stress-induced myocardial perfusion using SPECT, as well as to elucidate the relationship between postoperative LVEF, coronary graft patency, and work capacity as evaluated by an exercise test.
2. To prospectively evaluate *the effects of CABG on LV diastolic function* at rest and during dobutamine stress echocardiography, using the mitral annular velocity as assessed by pulsed-wave DTI before and after CABG.
3. To prospectively study *the effect of CABG on RV function* as measured by TAM, and to evaluate the relationship between the state of the right coronary artery (RCA) and grafts and RV function after CABG, as well as to assess the relationship between exercise performance and RV function after CABG.
4. To prospectively investigate the association between *preoperative inflammatory parameters* and early graft occlusion as well as late cardiovascular events after CABG.

## **PATIENTS AND METHODS**

### **Patients**

Ninety-nine patients accepted for CABG because of angina pectoris and significant coronary artery stenosis at angiography were included prospectively between May 1995 and February 2001 at the South Hospital in Stockholm.

During this period 764 patients underwent coronary angiography for stable angina pectoris and were referred for CABG. Their mean age was  $65\pm 8$  (Range 39-87) years. Seventy-nine percent were men and 21% were women. The majority, 70% had three-vessel and/or left main disease, 25% had two-vessel disease, and 5% had one-vessel disease. Comparing this patients to our study population their mean age were the same but there were fewer women (14% vs. 25%) and our study population had more frequently three-vessel disease.

Due to logistic reasons we did not include patients during the summer holiday period and because of the limited capacity to perform the non-invasive studies, only the first 2 patients who were accepted for CABG each week were included.

Exclusion criteria were:

1. History of recent myocardial infarction (4 weeks before preoperative angiography)
2. Atrial fibrillation,
3. Significant valvular heart disease
4. Previous CABG.

Baseline clinical, and coronary angiographic data are presented in table 1 and baseline medication in table 2.

**Table 1.** Baseline clinical and coronary angiographic characteristics of the 99 patients enrolled in the study. Findings are given as total numbers or the mean and standard deviation.

Variables	
Age (years)	65±9
Male/Female (n/n)	85/14
Systolic blood pressure (mm Hg)	141±23
Diastolic blood pressure (mm Hg)	83±9
BMI (kg/m <sup>2</sup> )	26.7±2.98
Diabetes (n) (%)	25 (25%)
Hypertension (n) (%)	39 (39%)
Smoker (n) (%)	20(20%)
Previous smoker (n) (%)	38(38%)
CCS	2,2±0,69
History of prior myocardial infraction (n) (%)	56 (57%)
Three-vessel and/or left main disease (n) (%)	81 (82%)
Two-vessel disease (n) (%)	16 (16%)
One-vessel disease (n) (%)	2 (2%)

BMI:Body mass index;

**Table 2:** Baseline medication of the 99 patients.

Medication	Percent
Betablockers (%)	89%
Calcium channel-inhibitors (%)	18%
Long-acting nitrates (%)	66%
Diuretics (%)	20%
ACE inhibitors/ARB (%)	31%
Statins (%)	77%
Aspirin (%)	97%
Warfarin (%)	2%

ACE:Angiotensin converting enzyme; ARB:Angiotensin receptor blockers

All patients underwent preoperative blood tests, exercise ECG testing, FPRNA, SPECT, echocardiography and a dobutamine stress test at the time of the initial coronary angiography.

All tests and coronary angiography were repeated 3 months after CABG and a third echocardiography was performed 12 months after CABG. The postoperative evaluation was performed 3 months after CABG as has been suggested to be optimal by different groups (63, 64). All patients were offered a clinical follow-up examination at 12 and 24 months (Fig.3).

**Figure 3.** Patient flow diagram

<b>Before CABG</b>	<b>(n)</b>	<b>3 months</b>	<b>(n)</b>	<b>1 year (n)</b>	<b>2 years(n)</b>	<b>5 years (n)</b>
↓		↓		↓	↓	↓
<b>Cl. exam.</b>	<b>(99)</b>	<b>Cl. exam.</b>	<b>(97)</b>	<b>Cl. exam. (90)</b>	<b>Cl. exam. (86)</b>	<b>Quest+MR(86+99)</b>
<b>Exercise test</b>	<b>(96)</b>	<b>Exercise test</b>	<b>(89)</b>			
<b>Cor.angio.</b>	<b>(99)</b>	<b>Cor.angio.</b>	<b>(81)</b>			
<b>Resting echo</b>	<b>(99)</b>	<b>Resting echo</b>	<b>(89)</b>	<b>Resting echo (86)</b>		
<b>DSE</b>	<b>(99)</b>	<b>DSE</b>	<b>(89)</b>			
<b>FPRNA</b>	<b>(99)</b>	<b>FPRNA</b>	<b>(89)</b>			
<b>SPECT</b>	<b>(99)</b>	<b>SPECT</b>	<b>(89)</b>			
<b>Blood tests</b>	<b>(99)</b>	<b>Blood tests</b>	<b>(89)</b>			

(n):number of patients; Cl.exam: clinical examination and data; Cor.angio: coronary angiography  
 echo:echocardiography; DSE: dobutamine stress echocardiography; FPRNA:first pass radionuclide angiography  
 SPECT: single photon emission computed tomography; Quest+MR: Questionnaires and medical records.

## **Methods**

### **Blood sampling and laboratory tests**

Blood samples were obtained from an antecubital vein without stasis using the vacutainer technique. After immediate preparation, all plasma samples were stored at -80°C until analysis. Leukocyte and platelet counts and serum levels of total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and fibrinogen were analyzed according to routine methods. Commercially available enzyme immunoassays were used for the determination of plasma concentrations of high-sensitivity C-reactive protein (hs CRP; Dade Behring Holding GmbH, Liederbach, Germany). Commercially available enzyme immunoassay was used for the determination of IL-6 (R&D systems, Abingdon, U.K.), ET-like immunoreactivity was analyzed by radioimmunoassay with the use of commercially available anti-sera (rabbit anti-ET-1 6901, Peninsula Laboratories)

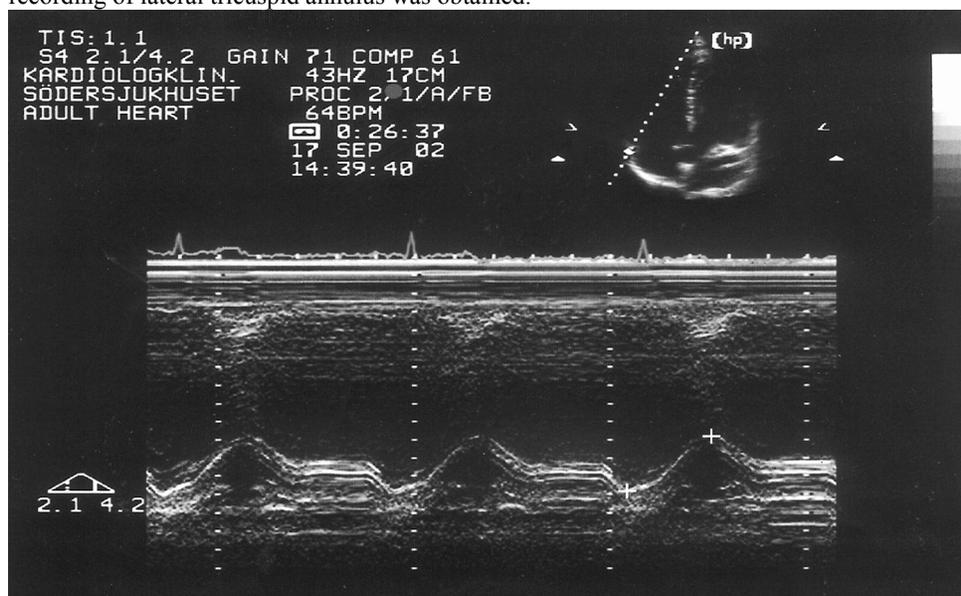
### **Echocardiography**

Commercially available echocardiographic equipment was used (Hewlett-Packard Sonos 5500 phased array system equipped with DTI technology, Andover, Mass). Recordings and calculations of different parameters were performed according to the recommendations of the American Society of Echocardiography (65). Global LV function was assessed using the magnitude of systolic mitral annular motion. In short, 2-D guided M-mode recordings of the mitral annular motion toward the cardiac apex in systole at 4 different LV sites, at the septal, anterior, lateral and inferior walls were recorded. The systolic motion from end-diastole according to ECG to the highest point of contraction during systole was recorded. A mean value for the above 4 sites was used to assess LV function (66). The echocardiographic examinations were performed in all patients at rest before CABG and 3 and 12 months after CABG.

RV function was assessed using the magnitude of TAM this was recorded at the RV free wall. From a 2-D guided apical 4-chamber view, the M-mode cursor was placed through the tricuspid annulus in such a way that the annulus moved along the M-mode cursor. The recording of TAM was performed on M-mode as shown in Fig.4. The total systolic displacement was measured from end diastole (beginning of QRS complex at the ECG) to the highest point of contraction using the leading edge of the echoes according to previous studies

(44). Paradoxical motion of the interventricular septum was analyzed visually or using M-mode echocardiography from the parasternal and apical views. A control group of 24 age-matched healthy subjects without a history of cardiac and pulmonary disease or systemic hypertension with normal findings at rest ECG and echocardiography was used for comparison.

**Figure 4.** Echocardiographic apical four-chamber view. Cursor line shows how M-mode recording of lateral tricuspid annulus was obtained.

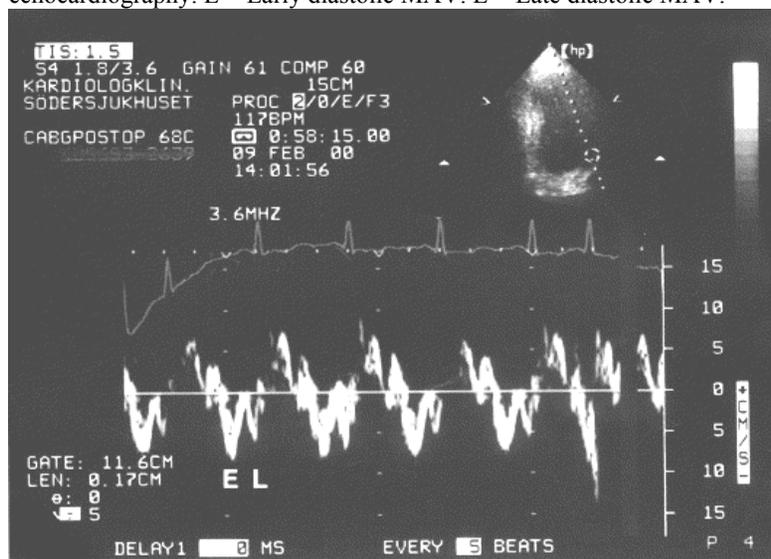


#### *Doppler tissue imaging*

Transmitral flow was recorded by pulsed wave Doppler with the sample volume placed between the mitral leaflet tips in an apical four-chamber view. Myocardial velocities of the LV were recorded at the mitral annulus using pulsed-wave DTI. A best-quality recording was made using a variable frequency phased array transducer (2.0–4.0 MHz), a low wall filter setting (50 Hz), a small sample volume and an optimal gain. The annular velocities were determined at 4 sites in the LV from the apical 4- and 2-chamber views as described previously (septal, lateral, anterior and inferior walls; and a mean value was obtained from 4 different sites, which was used for the assessment of LV function) (67). As shown in Figure 5. three major velocities were recorded at the annular sites: the peak major positive systolic velocity when the annulus moved towards the apex and 2 major negative velocities when the

annulus moved back towards the base (one during the early phase of diastole and another during the late phase of diastole). The velocities were recorded on line. A mean of 3 consecutive cycles was used for the calculations of all echo-Doppler parameters.

**Figure 5.** Recording of mitral annular velocities (MAV) at the anterior wall during stress echocardiography. E = Early diastolic MAV. L = Late diastolic MAV.



### Coronary angiography

Selective coronary angiography was performed not longer than one month before CABG. Postoperative coronary angiograms were performed 3 months after surgery. Pre- and postoperative coronary angiograms were interpreted independently by two experienced cardiologists without prior knowledge of other findings. On visual analysis, a 50% or more reduction of the luminal diameter in two orthogonal projections of a major coronary artery or one of its major branches or a bypass graft was considered to be significant for coronary artery disease. A graft was considered occluded if the entire vein graft was occluded at the origin or if the contrast failed to flow from the vein graft to the grafted artery.

### **Exercise ECG test**

A symptom-limited bicycle exercise stress test was performed before and 3 months after CABG. The protocol started with an initial workload of 30 W with 10 W increments every minute. The duration of exercise, maximal workload, watts/kg weight, and the reasons for stopping the exercise test were noted. The patients rated their level of exhaustion and symptoms on the 10-point Borg scale. End-points for exercise were exhaustion, grade 8 out of 10 of rated perceived exertion, chest pain grade 5 out of 10, severe arrhythmia, > 10 mm Hg drop in systolic blood pressure or >3 mm ST-segment depression on the electrocardiogram. The reasons for stopping the exercise test were divided into ischemic (chest pain, ECG changes, arrhythmia or abnormal blood pressure reaction) or non ischemic (exhaustion).

### **Dobutamine Stress**

After routine preparation for stress testing and insertion of an intravenous line, a resting ECG was obtained. Dobutamine was infused, starting at a dose of 5 µg/ kg/min, with a dose increases to 10, 20, 30, and 40 µg/kg/min every 3 minutes. If 85% of the maximum predicted heart rate had not been reached, up to 1 mg of atropine was injected intravenously. At the start of the study and at the end of each stage, ECG, blood pressure, and clinical signs were recorded. End-points of the test were the achievement of the peak dose, development of severe angina, or the occurrence of marked side effects. The latter included hypertension (systolic pressure >220 mmHg, diastolic pressure > 120 mmHg), hypotension (>20 mmHg fall of systolic pressure), severe dyspnea, or ventricular arrhythmias.

### **Dobutamine stress echocardiography**

A dobutamine stress test was used as described above. When the patients reached the end-points of the test (peak test), the infusion of dobutamine was stopped. The mitral annular velocities were first visualized on the screen at the end-point of the test. If the quality seemed satisfactory, the velocities were recorded in real time at different LV sites, as described before. The recording was started at the septum and then continued to lateral, inferior and anterior sites of the mitral annulus. If the early and late diastolic velocities were totally merged, visualization of the velocities was continued on the screen until separation of the waves was visible or a clear notch of the early velocity on the merged waves was noted (post-peak-stress echocardiography). The recording was then used for calculations. Dobutamine stress echocardiography was performed before and 3 months after CABG.

### Single photon emission computed tomography (SPECT): Acquisition Protocol

All patients underwent myocardial-perfusion-gated SPECT using a two-day Tc-99m-tetrofosmin acquisition protocol. The dobutamine stress study was performed on day 1. One minute before the end of the dobutamine infusion, depending on the patient's weight, 260-500 MBq Tc-99m-tetrofosmin (Nycomed, Amersham) was injected intravenously.

The rest study was performed on day 2. After 15 minutes of rest, 360-700 MBq Tc-99m-tetrofosmin was injected. The 8-frame gated SPECT imaging (with an initially automatically determined average RR interval based on the first five beats, a 40% allowable change, and a 1-beat PVC rejection field) was initiated 30 minutes after stress and 90 minutes after the injection at rest.

Acquisitions were performed as previously described(68) using a two-detector (Vertex, ADAC) camera to obtain 64 projections over a 180-degree noncircular arc extending from right anterior to left posterior oblique. A 20% window around the 140-keV energy peak of Tc-99m was used. All projection images were stored in a 64 x 64 x 16 matrix. The 8 projection sets were also summed up to generate an ungated set. Projection images were filtered using a 2D Butterworth filter order of 10 and a cut off frequency of 0.50 cycles/pixel. The pixel size was 0.64 cm x 0.64 cm. Images were constructed to form transaxial images using filtered back projection with a ramp filter. No scatter or attenuation correction was made.

Interpretation and Calculation: The gated perfusion SPECT was processed with an automatic reorientation program and the stress and rest images were interpreted based on the consensus of two experienced readers using a 16-segment model(69) (6 basal, 6 midventricular, and 4 apical segments) and a 4-point perfusion score for each segment: 0 point = normal perfusion; 1 point = mildly reduced; 2 points = moderately reduced; 3 points = severely reduced or absent. The 16 scores, one for each segment, were added up to give a summed stress score (SSS) and a summed rest score (SRS) and the difference between the two was calculated as a summed difference score (SDS). SPECT was performed simultaneously with the dobutamine stress echocardiography. Ischemia was defined as a SDS of 2 or more.(Table 3.)

**Table 3.** 16 segment score evaluation.

	<b>I normal</b>	<b>II ischemia</b>	<b>III scar</b>
Summed stress score	$\leq 1$	$\geq 2$	$\geq 2$
Summed rest score		$\leq 1$	$\geq 2$
Summed difference score		$\geq 2$	$\leq 1$

### **First-pass Radionuclide Angiography (FPRNA)**

Data were acquired immediately after the bolus injection of Tc-99m-tetrofosmin both at peak stress and at rest using a gamma camera (XT/C, General Electric, Milwaukee, WI, USA) linked to a General Electric Star 3200 computer. The view chosen was approximately left anterior oblique, 45 degrees, with a 5-degree caudal tilt. For acquisition, 25 msec per frame were chosen and the dataset was stored in a 64 x 64 matrix. Data were processed by two operators who were blinded to the echocardiography results, using commercially available software. In brief, the data were processed by drawing a region-of-interest (ROI) over both the left and right ventricles. The LV phase was selected on the generated coarse time activity curve and a new ROI was drawn over the LV. A cap-shaped background ROI – half of its area including lung tissue – was then drawn. One of the first cardiac cycles after the maximum count rate was selected from this final activity curve as the calculating beat.

### **Events**

Late cardiovascular events were defined as death or hospitalization for myocardial infarction, stroke, or a new intervention such as PCI or CABG. In the case of patients who suffered several events only the most serious event was recorded. The patients were followed for a mean of 5 (3-7) years. The patients received a questionnaire about cardiac events and hospitalizations and their medical records were scrutinized. The Swedish death register was used to check mortality.

## **Ethics**

The study was conducted according to the principles of the Helsinki Declaration, and all patients gave their informed written consent. The studies were approved by the Ethics Committee at the Karolinska Institutet.

## **Statistics**

The results are expressed as means and one standard deviation if normally distributed and as the median and interquartile range if nonparametrically distributed. Data with skewness values  $<-1$  or  $>1$  were considered to be nonparametrically distributed (eg.IL-6, CRP).

Comparisons of the results between groups were made using Student's unpaired t-test. Comparisons between parameters within the same group were made by using the paired t-test. Categorical variables were compared using the  $\chi^2$  test or Fishers exact test. P values less than 0.05 were considered statistically significant. If the parameters were not normally distributed they were tested using the Mann-Whitney U-test. Receiver-operating characteristic (ROC) curves were used to identify the prognostic content and the cut-off point for IL-6. Multiple logistic regression analyses were performed on variables showing a significant predictive value upon univariate analysis and in order to adjust for potential confounding factors and identify independent predictors. The nonparametric Wilcoxon-rank test was also used as an alternative test because the data are not to be normally distributed.

## RESULTS

Ninety-eight patients underwent CABG with cardiopulmonary bypass and one patient was operated using the off-pump technique. During and after the CABG, standard laboratory markers for myocardial infarction were obtained and only one patient was diagnosed with a small perioperative myocardial infarction. Patient stay at the operating hospital was  $8\pm 3$  days. Extra corporal circulation time was  $91\pm 32$  minutes and aorta occlusion time  $48\pm 17$  minutes. Fifty-five percent had antegrade cardioplegia and 45% had both antegrade and retrograde cardioplegia. Eighty-one percent of the patients were operated with blood cardioplegia and 19 % with crystalloid cardioplegia. Twenty-five percent of the patients had a documented episode of atrial fibrillation during the postoperative hospital stay. There were 5 early postoperative complications (2 late pneumothorax, 1 mediastinitis, 1 reoperation due to bleeding, 1 pulmonary embolism).

There were 23 late cardiovascular events among the 99 patients during a follow-up period of 5 (3-7) years after CABG (12 deaths, 4 myocardial infarctions, 5 patients requiring PTCA and 2 ischemic strokes).

### **Control coronary angiography 3 months after CABG:**

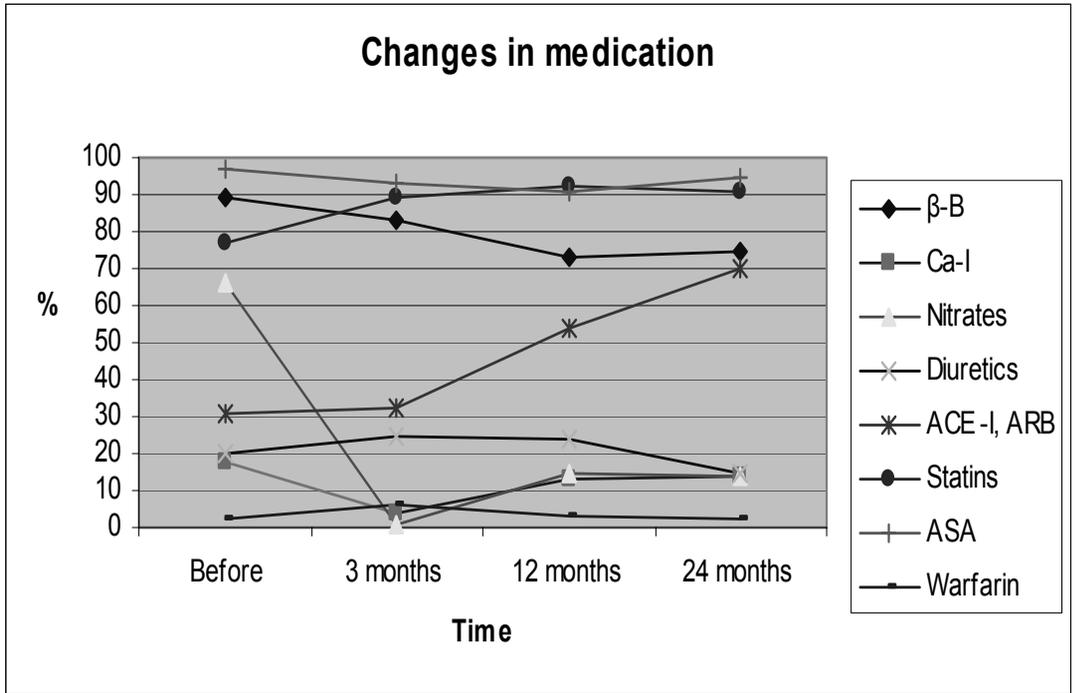
Eighty-one patients underwent repeat coronary angiography 3 months after CABG and were analyzed for graft occlusion. The reasons for not undergoing repeat angiography were death (n=3) and unwillingness to undergo another invasive procedure (n=15). There were no differences in baseline clinical, preoperative coronary angiographic data and medication between the 18 patients without a control coronary angiography and the 81 patients with a postoperative coronary angiography.

The postoperative angiography showed that 32 of 286 (11%) operated grafts were occluded 3 months after CABG, and 25 (31%) patients had one or more occluded grafts. Of a total of 78 grafted LIMA, 6 were occluded (7.7%) and of 208 vein grafts 26 were occluded (12.5%).

**Medication:**

Patient medication before, and at 3, 12 and 24 months after CABG is shown in fig.6

**Fig.6.** Patient medication over time before and after CABG.



beta-B:Betablockers; Ca-I:Calcium channel inhibitors; Nitrates:Longacting nitrates; ACE-I:Angiotensin converting enzyme inhibitors; ARB:Angiotensin receptor blockers; ASA:aspirin.

### **Study I: The effect of CABG on LV function and perfusion at rest and during stress.**

Of the 99 patients 79 had a preoperative LVEF<50% at rest measured by FPRNA but only 65 patients had complete SPECT and FPRNA studies both preoperatively and postoperatively, and were therefore enrolled in this part of the study.

The patients were evaluated with preoperative and postoperative FPRNA and SPECT at rest and during peak stress using dobutamine as the stress-producing agent. All patients underwent a symptom limited exercise ECG test preoperatively and postoperatively. Control coronary angiography was performed 3 months after CABG.

The patients were divided into two groups: group A consisted of 26 (40%) patients showing a 10% or more improvement of resting LVEF and group B consisted of 39 (60%) patients without an increased resting LVEF after CABG compared to preoperative values.

#### *Effects of CABG on Symptoms and Exercise Capacity*

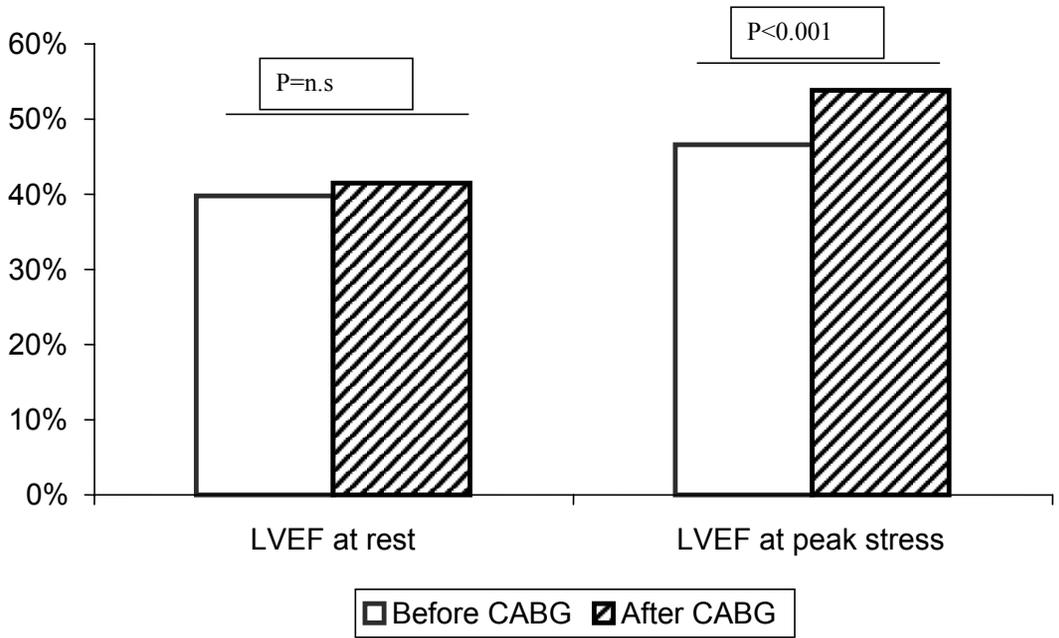
The patients reported a significant relief of angina symptoms at the 3-month follow-up as measured by the CCS classification (preoperative CCS 2.25±0.6 vs. 0.11 ±0.1 following CABG; P<0.001). The improvement of symptoms was the same in both groups. There was a 15% increase in work capacity (preoperative 129±39 W vs. 150±44 W after CABG; P<0.001), also without any differences between the groups. During the preoperative exercise test 64 % experienced angina while, in the postoperative study, only one patient in Group B experienced angina during the test.

#### *Effects of CABG on LVEF at Rest and under Peak Stress*

In the whole population, LVEF at rest evaluated by FPRNA did not improve significantly from the pre- to the postoperative examination (39.7±5% before to 41.4± % after CABG; n.s.), whereas LVEF during peak stress improved significantly by 18% (46.5±8% to 53.8±9%; P<0.001) after CABG. (Figure 7).

Group A had a preoperative LVEF at rest of 37.3±5.9 vs. 45.1±9 after CABG; P<0.001 and group B had a preoperative LVEF at rest of 40.5±5 vs. 40.1±6 after CABG; n.s. Both groups demonstrated a significant increase in LVEF under stress when comparing the pre and postoperative studies (group A LVEF 47.3±7.6 vs. 53.3.1±8.7; P<0.001 and group B LVEF 45.3±8.9 vs. 52.1±8.8; P<0.001). The relative increase in LVEF under peak stress postoperatively was of similar magnitude in both groups, 13% in group A versus 15% in group B.

**Figure 7:** Effect of CABG on left ventricular ejection fraction (LVEF) at rest and during stress. (n=65)



*Myocardial Perfusion at Rest and During Stress*

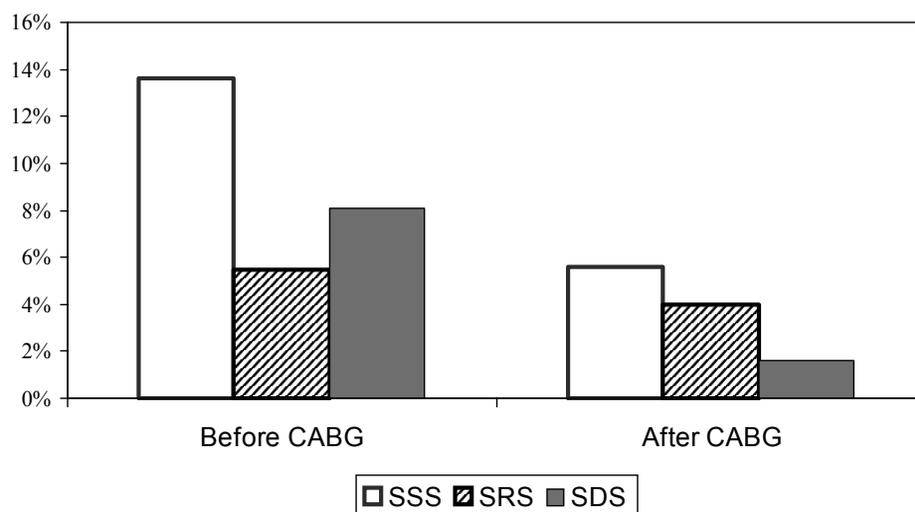
A significant reduction of the SSS, SRS, and SDS after CABG was observed in the patients. The quantitative resting and stress-induced perfusion abnormalities did not differ between Group A and Group B preoperatively. Perfusion defects both at rest and during dobutamine stress decreased significantly 3 months after CABG compared with preoperative studies; however, and as expected, the decrease was more pronounced during stress. The perfusion defects at rest (SRS) decreased by 27% (P<0.001) and, during peak dobutamine stress (SSS), they decreased by 59% (P<0.001). Data are presented in table 4 and fig.8.

**Table 4:** Comparison between Groups A and B regarding summed rest and stress scores before and after CABG quantified with myocardial perfusion SPECT.

		Group A (n = 26)	Group B (n = 39)	P
Before CABG	SRS	6.3±6	6.4±6	ns
	SSS	14.6±4	13.8±9	ns
After CABG	SRS	3.2±4	4.5±5	<0.01
	SSS	5.4±5	5.8±6	ns

SRS = summed rest score; SSS = summed stress score.

**Figure 8:** Bar graphs showing the effect of CABG on myocardial perfusion. Perfusion defects at rest (P=0.002) and during stress (P<0.001) and the difference between resting and peak defects (P<0.001).



SSS = summed stress score; SRS = summed rest score ; SDS = summed difference score.

### *Graft Patency*

A control coronary angiography was made 3 months postoperatively in 60 of the 65 patients, 5 patients being unwilling to have a control coronary angiography. All the operated grafts were patent in only 44 of the 60 patients (73.3%), and 16 (26.6%) had one or more occluded grafts. There was no difference in groups A and B regarding postoperative graft patency (group A 26% occluded grafts vs. group B 27% occluded grafts; n.s). There were no observed impact of graft occlusions on postoperative LVEF or work capacity.

**Study II: Improvement in diastolic LV function after CABG as assessed by Doppler tissue imaging (DTI).**

The Doppler tissue imaging technique first became available in our laboratory in February 1998. Study II therefore comprises only of 53 patients of the 99 patients. Patient baseline clinical data are shown in table 5.

**Table 5.** Baseline clinical, echocardiographic and coronary angiographic characteristics of the 53 patients.

Age	65 ± 9
Male/Female (n)	47/6
LVEDD (mm)	50 ± 5
Diabetes (n)(%)	10 (19%)
Hypertension (n)(%)	20 (38%)
History of prior myocardial infraction (n)(%)	28 (53%)
Three-vessel disease and/or left main (n)(%)	44 (83%)
Two-vessel disease (n)(%)	7 (13%)
One-vessel disease (n)(%)	2 (4%)

Findings are presented as total (n) and percent (%) or the mean and standard deviation.

*Echocardiographic parameters at rest.*

Using the conventional transmitral flow velocity waves, there were no significant changes when comparing diastolic parameters measured before CABG with findings obtained 3 and 12 months after CABG (trans-mitral early wave 0.65±0.17 vs. 0.68±0.19 vs. 0.70±0.18 cm/s; n.s)(trans-mitral atrial wave 0.67±0.17 vs. 0.59±0.18 vs. 0.67±0.18 cm/s; n.s). Compared to healthy subjects, patients had decreased systolic as well as diastolic mitral annular velocities as determined by DTI (systolic velocity = 9.5±1.1 vs. 6.3±1.2 cm/s; P<0.001; early diastolic velocity = 11.6±2.3 vs. 7.4±1.8 cm/s; P<0.001 and late diastolic velocity = 12.4±2.3 vs. 8.6±2.4 cm/s; P<0.001).

Repeated echocardiography using DTI before, 3 and 12 months after CABG, showed improvement in both systolic and diastolic LV function (Systolic velocity =  $6.3 \pm 1.2$  vs.  $6.6 \pm 1.3$  vs.  $6.9 \pm 1.3$  cm/s\*; \*P<0.05; early diastolic velocity =  $7.5 \pm 1.9$  vs.  $8.2 \pm 1.7$  vs.  $9.3 \pm 2.7$  cm/s; P<0.01; late diastolic velocity =  $8.6 \pm 2.4$  vs.  $8.0 \pm 2.5$  vs.  $8.8 \pm 2.2$  cm/s; n.s.)

#### *Subdivisions of patients according to SPECT.*

Patients were divided into 2 subgroups according to the results of SPECT 3 months after CABG: those with and those without residual reversible ischemia. There were 37 patients without signs of reversible ischemia. In these DTI showed a significant improvement in LV systolic and diastolic function when comparing preoperative with repeated DTI measurements 3 and 12 months after CABG (Systolic velocity =  $6.3 \pm 1.6$  vs.  $6.7 \pm 1.4$  vs.  $7.2 \pm 1.3$  cm/s; \*P<0.05; early diastolic velocity =  $7.4 \pm 2.0$  vs.  $8.2 \pm 1.6$  vs.  $9.3 \pm 2.6$  cm/s; \*P<0.05; \*\*P<0.01; late diastolic velocity =  $8.5 \pm 2.4$  vs.  $8.0 \pm 2.6$  vs.  $8.7 \pm 2.3$  cm/s; n.s.). The improvement in systolic function was only observed one year after CABG.

The other 16 patients with signs of residual reversible ischemia showed no improvement in systolic or diastolic function (Systolic velocity =  $6.5 \pm 1.3$  vs.  $6.4 \pm 1.2$  vs.  $6.7 \pm 1.4$  cm/s; n.s.; early diastolic velocity =  $7.3 \pm 2.2$  vs.  $7.8 \pm 2.0$  vs.  $8.4 \pm 2.6$  cm/s; n.s.; late diastolic velocity =  $9.1 \pm 2.5$  vs.  $8.2 \pm 2.6$  vs.  $9.2 \pm 2.3$  cm/s; n.s.)

#### *Stress echocardiography before and after CABG.*

Stress echocardiography findings could be analyzed in 47 patients (88%). Difficulties in the analysis were encountered in 6 patients during peak or post-peak stress due to unsatisfactory DTI signals, especially from the anterior wall of the LV. Before CABG there was a significant increase in the systolic mitral annular velocity (MAV) during peak stress echocardiography ( $6.4 \pm 1.3$  vs.  $8.7 \pm 2.5$ ; P<0.001), but no improvement in the early diastolic velocity was noted ( $7.6 \pm 1.9$  vs.  $8.0 \pm 2.2$ ; n.s.). After CABG, both the systolic and diastolic velocities showed significant improvement during the stress test. (Systolic MAV  $6.5 \pm 1.33$  vs.  $9.3 \pm 2.8$ ; P<0.001; early diastolic MAV  $8.1 \pm 1.8$  vs.  $10.3 \pm 2.2$ ; P<0.001).

### **Study III: Decreased RV function after CABG and its relation to exercise capacity.**

RV function measured by TAM was significantly reduced 3 months after CABG and remained so 1 year after CABG ( $22.4\pm 4.7\text{mm}$ ;  $14.5\pm 3.2\text{mm}$ ;  $14.7\pm 14.7\text{mm}$ ;  $P<0.001$ ). LV function measured from the mitral annular motion was unchanged 3 months and one year after CABG ( $12.0\pm 2.2\text{mm}$ ;  $11.7\pm 2.2\text{mm}$ ;  $10.4\pm 1.85\text{mm}$ ; n.s). Paradoxical septal movement was observed in 96% of patients 1 year after CABG.

#### *Subdivisions of patients according to right coronary artery stenosis and graft patency.*

Of the initial 99 patients, 87% had right coronary artery (RCA) disease whereas 13% had no stenosis of the RCA. Both groups experienced the same worsening of TAM postoperatively. In the group of 81 patients who had a postoperative coronary angiogram 3 months after CABG, the grafts to the RCA were patent in 89%. There was no difference in TAM 3 months and 1 year postoperatively between the patients with patent or occluded grafts to the RCA ( $14.2\text{ mm}$  vs.  $14.9\text{ mm}$ ; n.s. and  $14.3\text{ vs. }15.2\text{ mm}$ ; n.s.). In patients with preoperative RCA stenoses, 49% were proximal and 51 % were distal to the right ventricular artery. There was no difference in TAM between patients with proximal or distal RCA stenosis ( $21.6\text{ mm}$  vs.  $23.4\text{ mm}$ ; n.s), 3 months ( $14.3\text{ vs. }14.4\text{ mm}$ ; n.s) or 1 year ( $14.4\text{ vs. }15\text{ mm}$ ; n.s) after CABG.

#### *Exercise capacity and RV function.*

Eighty-six patients performed an exercise test before and after CABG. A cut-off value of at least 10 watts was arbitrarily taken to distinguish patients with and without improvement in exercise capacity when comparing pre and postoperative test. The exercise capacity was significantly improved compared to baseline in the whole group ( $126\pm 37\text{ Watts}$  vs.  $143\pm 43\text{ Watts}$ ;  $P<0.01$ ). Patients who improved their exercise capacity, group 1 ( $n=51$ ), were compared to those who showed no improvement or deterioration in exercise capacity, group 2 ( $n=35$ ), after CABG. Group 1 had more frequently ischemic stop criteria at their preoperative exercise test than to group 2 ( $70\%$  vs.  $29\%$ ;  $P<0.001$ ). There were no differences in the use of betablockers, calcium antagonists, digitalis or ACE inhibitors between the two groups. Nor did the state of the coronary arteries differ between the groups. Patients in group 1 showed a higher rate pressure product and higher work capacity after CABG. There was no difference in the TAM reduction between the groups. The echocardiographic and exercise test findings as well as the results of the coronary angiograms of the two groups are presented in Table 6.

**Table 6.** Echocardiographic, exercise and coronary angiographic data of patients with (group 1) and without (group 2) improved exercise capacity after CABG.

	Group 1 (n=51)		Group 2 (n=35)	
	Pre CABG	Post CABG	Pre CABG	Post CABG
Max watts	121±36	163±42 *	139±37	128±35*
MAM (mm)	12.7±2	11.7±2	11.6±4.7	11.1±3.5
TAM (mm)	22.7±4.5	14.4±3.8*	22±4.5	14.3±2.7*
Maximal heart rate (bpm)	121±36	163±42*	139±37	128±35
Max blood pressure (mm Hg)	175±21	194±27*	186±28	187±27
RPP	21693±5189	27231±6819*	24252± 6787	24802± 6819
Ischemic stop criteria (n)(%)	36 (70%)	1 (2%)	10 (29%)	0
Exhaustion stop criteria (n)(%)	15 (30%)	50 (98%)	25 (71%)	35 (100%)
3 VD a/o LM (n)(%)	40 (78%)		30 (86%)	
2 VD (n)(%)	9 (18%)		5 (14%)	
1 VD (n)(%)	2 (4%)		0	

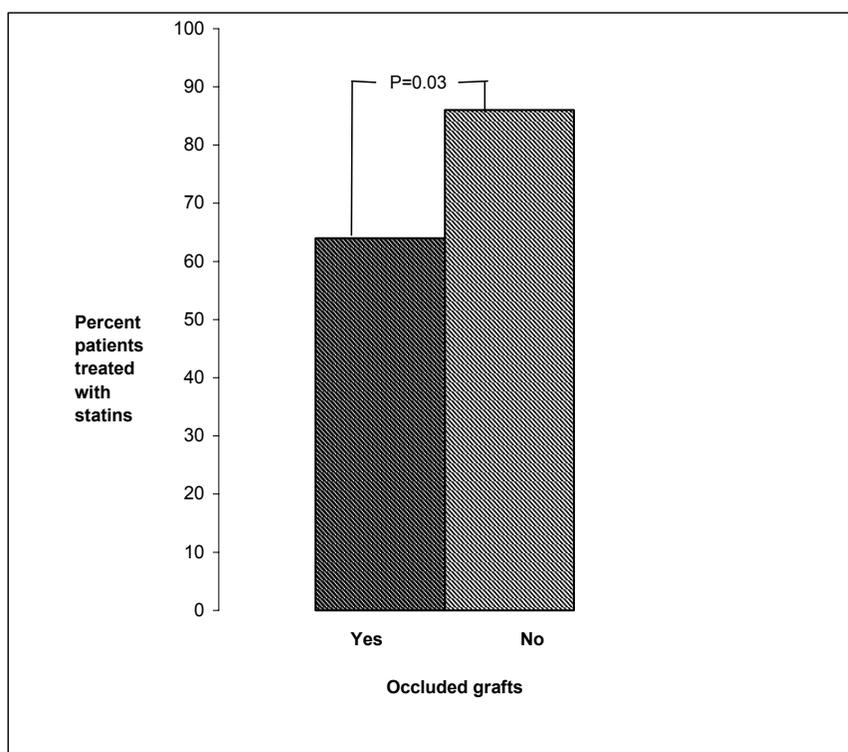
RPP - rate pressure product, MAM - mitral annular motion, TAM - tricuspid annular motion  
3VD a/o LM= 3-vessel disease and/or left main, 2 VD= 2-vessel disease, 1VD=1-vessel disease.

\*P<0,001. The P values were calculated within the same groups.

#### Study IV: Can preoperative inflammatory parameters predict early graft occlusion and late cardiovascular events after CABG?

Preoperative inflammatory parameters were significantly higher in patients who subsequently suffered early graft occlusion (n=25) compared with patients with open grafts (n=56): CRP (2.22 (1.11-4.47) vs. 1.23 (0.71-2.27) mg/L; P=0.03), IL-6 (2.88 (1.91-5.94) vs. 2.15 (1.54-3.14) pg/mL; P=0.006), fibrinogen (3.9±0.9 vs. 3.5±0.6 g/L, P=0.049) and age (68±8 vs. 64±8 years; P=0.04). In the multivariate analysis that included risk factors such as age, gender, diabetes, smoking, hypertension, and preoperative left ventricular ejection fraction only CRP and IL-6 independently predicted early graft occlusion. Fewer patients with graft occlusion received preoperative statin treatment (64% vs. 86%; P=0.03) as is shown in Fig 9.

**Fig 9.** The relationship between preoperative treatment with statins and graft occlusions.

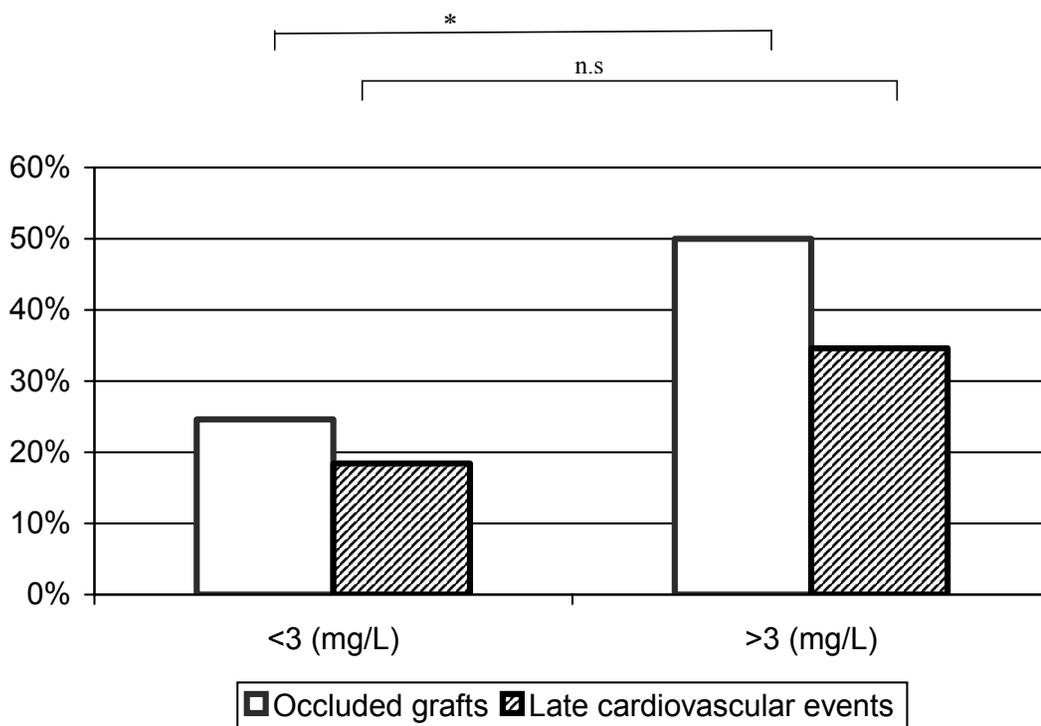


Patients with late cardiovascular events (n=23) compared to those without late cardiovascular events (n=76) were significantly older (69±10 vs. 63±9 years; P=0.004), and

they had higher levels of IL-6 (4.13 (1.83-5.87) vs. 2.08 (1.53-2.29) pg/mL,  $P=0.002$ ) and fibrinogen ( $4.0\pm 0,8$  vs.  $3.3\pm 0,5$  g/L;  $P=0.02$ ), whereas the other measured parameters did not differ significantly. No correlation was found between occluded grafts and late cardiovascular events. In a multivariate analysis of risk factors including age, gender, diabetes, smoking, hypertension, and preoperative left ventricular ejection fraction the only independent predictors of late cardiovascular events found were age and IL-6.

The results regarding CRP and IL-6, grouped according to cut-off points of 3 mg/L and 3,8 pg/mL respectively, are presented in Figs. 10 and 11 and show that the percentage of occluded grafts and late cardiovascular events are significantly higher in patients with IL-6  $>3,8$  pg/mL, but only significantly higher for occlusion and not for late cardiovascular events for CRP  $>3$  mg/L. The cut-off value of 3,8 pg/mL for IL6 was defined by ROC curve analysis.

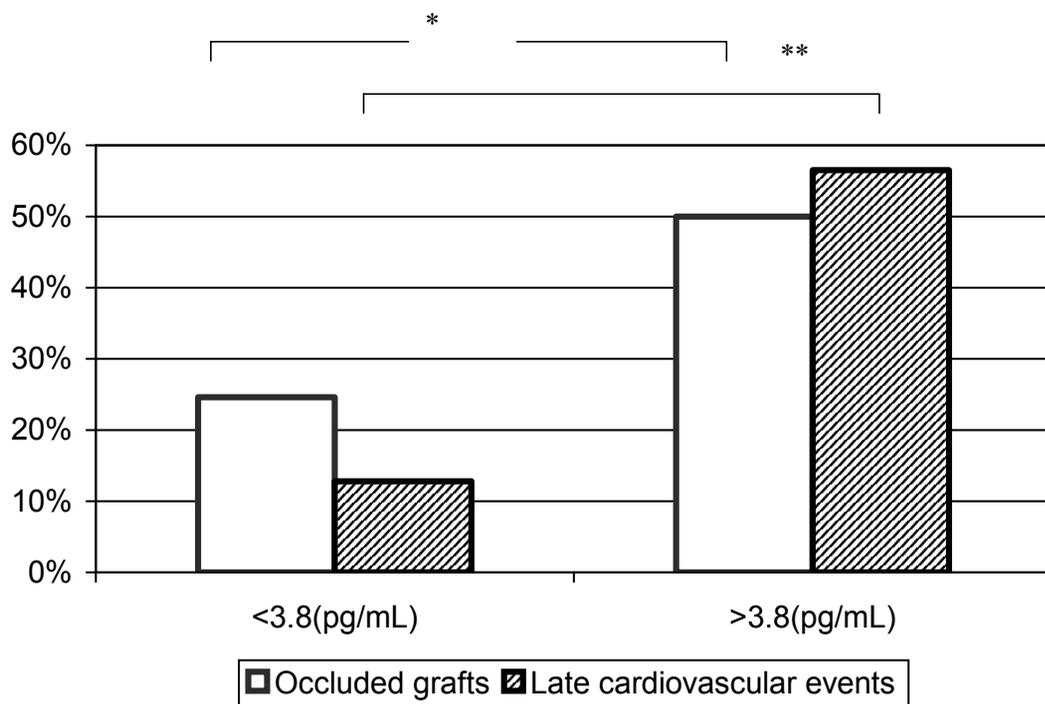
**Fig. 10.** C-reactive protein grouped according to a cut-off point of 3 mg/L and its relation to graft occlusions and late cardiovascular events.



\*= $P<0,05$ , n.s= non significant

**Fig. 11**

IL-6 grouped according to a cut-off point 3.8 pg/mL and its relation to graft occlusions and late cardiovascular events.



\* =P<0.05

\*\*=P<0.01

# GENERAL DISCUSSION

## **The effect of CABG on cardiac function**

### *1. CABG and systolic LV function.*

Our study demonstrates that CABG improves LVEF during stress but not at rest in the majority of patients with ischemic heart disease and moderate left ventricular dysfunction. There was also a significant improvement in myocardial perfusion which is more pronounced under stress than at rest. These findings are in accordance with one other recent investigation which report that that reversible scintigraphic perfusion defects before CABG are associated with a postoperative improvement in both perfusion and function but that an improvement in left ventricular function after CABG may not always occur under resting conditions but rather during stress(70).

There may be several possible explanations for improvement in LVEF during stress and the lack of improvement in resting conditions in our study.

- Systolic myocardial dysfunction in patients with chronic ischemic heart disease may be due to necrotic irreversibly damaged myocardial segments or to viable but hypoperfused segments that may recover after revascularization in the presence of stunning or hibernating myocardium. As demonstrated in previous studies, viable myocardium in at least 25% of the LV is required for CABG to improve global resting LVEF (71, 72). It is not known whether a limited amount of viable segments are unable to recover at rest, but still improve their function during stress.
- A prolonged conservative strategy with medical treatment in patients with chronic ischemic heart disease and dysfunctional myocardium may lead to deterioration of viable areas if present, and thereby limit the benefit from CABG at least as measured during resting conditions (73).
- The recovery of impaired but viable myocardium at rest may require a longer period of time than the evaluation period of 3 months in our study, especially in patients with more pronounced dysfunctional myocardium. In our study, there was a tendency to larger resting perfusion defects after CABG in patients not showing improvement in LVEF at rest. Indeed, previous reports have shown that the recovery of LV function may take up to one year in some patients (74, 75).

To our knowledge, the present investigation is unique in analyzing the relationship between

LVEF by means of both myocardial perfusion assessed by SPECT and the state of the coronary anatomy by repeated coronary angiography after CABG. There was no relationship between the functional recovery at rest and the patency of bypassed grafts, nor to the presence of myocardial ischemia as assessed by SPECT. Furthermore, our study shows that the benefits of CABG in patients with moderately impaired LV function are multiple: the relief of symptoms, an improvement of myocardial perfusion, especially under stress, improvement of LV function under stress, and an improvement in work capacity. Accordingly, the assessment of LV function at rest may not be fully adequate for an evaluation of the effects of CABG. In addition, an improvement in regional wall motion, as demonstrated in previous studies, does not signify an improvement in the global LVEF. Further large studies are needed to highlight the prognostic impact of CABG in patients who show LVEF improvement during dobutamine stress, but not at rest.

## *2. CABG and diastolic LV function*

Diastolic function has traditionally been measured by pulsed Doppler echocardiography of the transmitral flow, which has the disadvantage of being pre-load dependent (28, 34). If active relaxation is impaired, early mitral inflow will decrease. With worsening of diastolic dysfunction, left atrial pressures increase and the gradient increases between the left atrium and LV at the time of mitral valve opening. Because of rapid equilibration the duration of early ventricular filling will be short. With further deterioration, early filling will terminate abruptly due to the increase in LV stiffness and elevated end-diastolic pressures. It has long been recognised that LV diastolic function, as assessed by transmitral flow velocity profiles, is altered in patients with coronary artery disease.

DTI has recently been introduced to assess LV function and is easy to measure in almost all subjects (67, 76). Motion of the mitral annulus represents LV function along its long axis. LV diastolic dysfunction has also been reported in patients with coronary artery disease with the use of DTI (76, 77). The peak velocity of the mitral annulus during early diastole is usually considered to be a sensitive marker of diastolic function. A decrease in early diastolic mitral annular velocity is a sign of disturbed LV relaxation and can be secondary to coronary artery disease. Using conventional echo-Doppler parameters, several previous investigations have shown diverging results in measurements of both systolic and diastolic function after CABG (29, 30). These studies have, however, included rather small number of patients and most of them lacked a long term follow-up. One of these studies demonstrated an immediate improvement in diastolic function, as measured by colour M-

mode Doppler, after CABG independent of the use of extracorporeal circulation (78). On the other hand, the results of Shi et al. revealed an increase in diastolic dysfunction 48 hours after CABG with a return to preoperative conditions 6 months after CABG (79). Accordingly, with the use of DTI we have been able to show that CABG improves diastolic LV function whereas the conventional transmitral Doppler flow velocity profiles remained unchanged. We believe that DTI is probably a more sensitive method for assessing diastolic function. As compared with healthy subjects, and similar to the results of a previous study (80), a decreased early diastolic mitral annular velocity was noted in our patients in the preoperative evaluation. In the postoperative evaluation there was an improvement in LV diastolic function as assessed by DTI, especially in patients without residual LV ischemia measured by SPECT, reflecting that ischemia is one of the most common causes of diastolic dysfunction.

Previous investigators have postulated that the ratio between the conventionally measured transmitral early velocity ( $E$ ) and early diastolic velocity ( $e'$ ) as measured by DTI may reflect LV filling pressures (81, 82). In our study there was a tendency to an improvement in  $E/e'$ , without reaching significance. This is probably due to the unchanged transmitral early flow after CABG although there was a significant improvement in mitral annular diastolic velocity.

Some recently published papers have reported the usefulness of DTI during dobutamine stress for identifying patients with coronary artery disease (83, 84, 85, 86). Compared to the systolic velocity, there is less data of diastolic mitral annular or myocardial velocities during peak dobutamine stress (84, 85). The response of the early diastolic velocity during stress echocardiography was limited and was found to be similar in both healthy subjects and patients in those studies. In our study, during the preoperative dobutamine stress echocardiography, there was no improvement in early diastolic velocity although the systolic velocity increased significantly. This might indicate that diastolic function is a more sensitive sign of myocardial ischemia and may deteriorate in an earlier stage compared with systolic function during the ischemic cascade. On the other hand, our study shows a significant increase in the early diastolic mitral annular velocity at stress after CABG, indicating that this parameter can be used to demonstrate functional recovery after revascularization due to an improvement in myocardial perfusion.

The time course of improvement of diastolic LV function is not fully clarified. Our study showed that the improvement of diastolic function is likely to occur early, at 3 months after CABG, whereas, in some cases, recovery of diastolic function maybe delayed for up to 1 year.

### *3. CABG and the RV function.*

The usefulness of tricuspid annular motion (TAM) in assessing RV function has been confirmed in patients with acute and chronic ischemic heart disease, those with congestive heart failure as well as in patients after CABG by several authors (38,43,87,88,89). Kitano et al. in a follow-up study after CABG demonstrated that depressed RV function is still partly present after 6 months (38). In addition, a recent study comparing the effects of on-pump versus off-pump CABG on RV function showed no differences between the groups in preserving RV systolic and diastolic function as measured by DTI (90). In the present study TAM was used to assess RV systolic function. Our investigation has shown that RV function remains depressed and that septal motion remains paradoxical for as long as one year after CABG, suggesting that these postoperative findings might be permanent in the majority of the patients. Other investigators using DTI have also found that the tricuspid annular velocity and RV function are decreased after CABG (90, 91, 92). In addition, we have previously demonstrated that the systolic tricuspid annular velocity increases only moderately during dobutamine stress echocardiography 3 months after CABG (92).

It has been speculated that TAM depression may occur because of a non revascularized RV coronary branch from the right coronary artery (RCA) especially when grafts to a stenotic RCA are distal to a stenosis which limit coronary blood flow to the RV coronary branch. Schirmer et al have shown the RVEF to be higher postoperatively in patients with a revascularized RCA compared to patients without revascularization to the RCA (40). In our study TAM was equally depressed in both groups after CABG and we found no relationship between the location of the lesion in the RCA (proximal or distal to the RV artery branch), the state of the vein graft of the RCA, and the magnitude of RV functional impairment. The patients with an occluded graft of the RCA showed no difference in TAM compared to those with an open graft.

Other investigators have previously shown that exercise performance after CABG improves despite unchanged LV function at rest, but the significance of RV function was not addressed in these studies (93, 94). Our present study demonstrates that postoperative exercise tests are associated with a higher workload and rate-pressure product in spite of the depressed RV function at rest after CABG. Both the RV and LV function at rest were similar in patients with and without improvement in the postoperative exercise capacity. This finding reflects that exercise capacity may be related to the changes in both left and right ventricular performance during exercise rather than in resting cardiac function. Furthermore paradoxical

intraventricular septal motion may compensate for the decreased RV systolic function as assessed by TAM. We suggest that the septum is recruited to maintain RV stroke volume after CABG.

### **Inflammation prior to CABG. Its relation to early graft occlusion and late cardiovascular events.**

Despite antiplatelet treatment with aspirin, early graft occlusion following CABG remains a common finding with some 10-15% of grafts occluded one month after CABG (12, 13, 17).

Early saphenous vein graft failure is associated with an increased risk of long-term adverse clinical outcomes primarily because of a high rate of repeat revascularization (95).

In the present investigation, control coronary angiography showed that 11% of all grafts were occluded and that 31% of the patients had at least one occluded graft 3 months after CABG.

Occlusion in the first month after surgery is mainly due to a thrombotic occlusion but vessel-specific factors such as the diameter of the grafted vessel and the trauma related to the operative technique are probably also of importance. In contrast, late graft occlusion (>1 year after CABG) is due to intimal hyperplasia and progression of atherosclerosis (96).

Inflammatory mechanisms have been shown to play a key role in the progression of atherosclerosis and there are also data showing that inflammation and thrombosis are closely linked (97). Our present investigation demonstrates that elevated preoperative levels of CRP and IL-6 predict early graft occlusion after CABG. CRP causes monocytes to synthesize tissue factor and IL-6 seems also to have procoagulant properties (98). CRP induces plasminogen activator inhibitor-1, a marker of atherothrombosis, independently of IL-6 or ET-1 levels (99). Reactive thrombocytosis is partly influenced by inflammation and especially so in patients with coronary atherosclerosis with raised IL-6 levels (100). There are conflicting data on the association between preoperative IL-6 levels and restenosis as well as postoperative residual ischemia (59, 101). CRP lowers nitric oxide production and patients with elevated CRP levels therefore show impaired endothelial vasoreactivity, (102, 103, 104). Previous reports have shown that elevated levels of CRP before PCI predict recurrences of ischemic events and a worse prognosis (105, 106). Milazzo et al. found that preoperative CRP levels higher than 3 mg/L in patients with both unstable and stable angina were associated with an increased risk of recurrent ischemia one to six years after CABG (107). However the majority (71%) of their patients had unstable angina which effects CRP levels per se and these findings may not be applicable also to patients with stable angina. Moreover, a control coronary angiography was not performed to analyse the state of

the coronary arteries and grafts. Two other groups have found conflicting results concerning the significance of elevated preoperative CRP levels on the short-term postoperative outcome after CABG (108, 109). Long-term outcome was not addressed in these investigations. A recent study that included 843 patients undergoing CABG showed that CRP > 1.0 mg/dl was an independent predictor of long-term all-cause mortality after the operation but did not reach statistical significance concerning cardiac death (110). Fibrinogen is also a marker of inflammation and many prospective epidemiological studies have reported positive associations between the risk of coronary heart disease and elevated fibrinogen levels. In a recent meta-analysis of 154 211 participants in 31 prospective studies, a hazard ratio of 1.8 for coronary heart disease was found per 1-g/L increase in fibrinogen (111). In a prospective study on 220 patients elevated preoperative fibrinogen levels over 3.5 g/L were associated with a significantly increased 2-year mortality after CABG. This relationship was mainly due to an increase in the 30-day postoperative mortality (112). These investigations are in line with our present findings which show that elevated fibrinogen levels are related to both early occlusions of grafts and late cardiovascular events. Elevated ET-1 levels have been reported to be independent predictors of a more rapid progression of coronary artery atherosclerosis as measured by coronary angiography (60). ET-1 does, however, not seem to affect coagulation (113). This may explain why ET-1 failed to predict early graft occlusion in our patients.

Medication may have affected the results of our study and this is particularly relevant to statin treatment which is known to have anti-inflammatory properties (114). Interestingly, patients on preoperative statin treatment had a significantly lower percentage of early graft occlusions than patients without such treatment. We also found that patients with occluded vein grafts had lower preoperative levels of total and LDL cholesterol which probably explains why fewer patients in this group received statin treatment. This is in line with previous investigations which have demonstrated that statin therapy reduces the risk of cardiac events as well as the need for revascularization irrespective of cholesterol levels and that this effect may be due to the anti-inflammatory effects of statins rather than their lipid-lowering properties (49, 50, 51, 52, 115). Those of our patients who received statins had significantly lower CRP levels and insignificantly lower IL-6 levels. Our observations therefore suggest that the use of statin treatment irrespective of lipid levels before CABG may be beneficial, as has been suggested also by others (116, 117, 118). This indication applies especially to patients with raised inflammatory parameters. Collard et al. reported that preoperative statin therapy was independently associated with a reduction of early cardiac death after elective CABG and that discontinuation of statin therapy after surgery was

associated with an increase in late cardiac mortality (119). Initiation of statin treatment before CABG may therefore be considered in patients with elevated preoperative CRP levels. These suggestions, however, require confirmation by further trials before full implementation.

Elevated IL-6 levels constitute a stronger independent predictor of the long term risk of ischemic heart disease than raised CRP levels (120, 121). This is in line with our findings which show that IL-6 is an independent predictor of 5-year cardiovascular events. CRP seems to share this property without, however, reaching statistical significance. As these two markers of inflammation are closely linked, this divergence may be due to patient sample size.

## CONCLUSION

- I.** In patients with coronary artery disease and moderate impairment of LV function, CABG improves LVEF mainly under stress without improving LVEF at rest. Despite a lack of resting LVEF improvement, CABG relieves symptoms, improves myocardial perfusion, and improves the work capacity of these patients. Moreover, there was no relationship between graft occlusion, stress-induced myocardial ischemia and the absence of improvement in resting LVEF after CABG.
- II.** DTI is a useful method for assessing diastolic function at rest and under stress. Mitral annulus velocity assessed by DTI reveals an improvement in diastolic LV function at rest and during stress after CABG that conventional Doppler echocardiography does not detect. The improvement was seen only in patients without postoperative signs of reversible ischemia.
- III.** One year after CABG, RV function measured by TAM remains depressed and septal motion remains paradoxical, suggesting that these postoperative findings may be permanent in most patients. These findings were independent of the state of the RCA and operated grafts. In spite of a reduced TAM, exercise performance improved 3 months after CABG. Decreased TAM following CABG is probably of no clinical significance.
- IV.** Raised preoperative IL-6 levels are predictors of both early graft occlusion and late cardiovascular events after CABG. Elevated preoperative CRP levels can predict early graft occlusion after CABG.

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