Persistent but reversible coronary microvascular dysfunction after bypass grafting

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The first coronary artery bypass grafting (CABG) was carried out by René Favaloro in 1967 (16). Vein grafts were used initially, but soon a number of arterial conduits were also employed, and by the 1980s use of the left internal mammary artery (LIMA), as an in situ graft to the left anterior descending coronary artery (LAD), had gained considerable popularity. The use of the LIMA became standard procedure when studies showed a 40% reduction in mortality in patients in whom the LIMA was grafted to the LAD compared with patients who underwent standard vein grafting (9, 23).

Although the efficacy of CABG in relieving symptoms and improving prognosis is well established, other uncertainties remain. Previous studies using Doppler guide wires to measure flow velocity have demonstrated that the flow capacity of LIMA grafts is low immediately postoperatively and higher 6–12 mo later (1), but little information is available on the intervening time course of this recovery. The effect of CABG at the tissue level has not been systematically investigated, despite previous studies suggesting that the early postoperative impairment of blood flow is due to injury to the microvasculature rather than dysfunction of the conduit itself (17). Previous methods employed to measure coronary blood flow have included the use of Doppler wires (17), quantitative coronary arteriography (33), and myocardial scintigraphy (29). All these techniques suffer from fundamental limitations (14), in that the former two measure epicardial artery flow velocity, and not true tissue perfusion, whereas the latter provides only semiquantitative data and cannot be used to quantify myocardial blood flow (MBF). The above limitations are overcome by positron emission tomography (PET), which can provide repeated, noninvasive measures of absolute MBF in selected regions of the heart (14).

In the present study, we used a combination of venous and arterial conduits to assess the effect of revascularization by CABG on regional MBF (measured with PET and H215O), coronary vasodilator reserve (CVR), and minimal coronary resistance (MCR) in patients with triple-vessel disease. To evaluate the time course of recovery, patients were studied at baseline and then 1 and 6 mo after revascularization.

**METHODS**

**Study Population**

Normal controls. Two groups of gender- and age-matched normal volunteers were studied. The first group of 14 sub-

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Subjects (57 ± 13 yr of age, not significant vs. patients) served as controls for the MBF data; the second group of 9 subjects (59 ± 12 yr of age, not significant vs. patients) served as controls for the left ventricular volume data. None of the subjects had a history of cardiac diseases, and they had normal physical examination and resting electrocardiogram and a negative exercise stress test at high workload.

Patients. Eight patients (1 woman and 7 men, mean age 66.5 ± 5.4 yr) with three-vessel coronary artery disease and good left ventricular systolic function who were due to undergo CABG entered the study. All patients were considered to have good caliber distal arteries, allowing uncomplicated grafting of a bypass conduit. None of the patients had evidence of left ventricular hypertrophy on the basis of the electrocardiogram and left ventriculography. None had evidence of previous infarction. The baseline hemodynamic and angiographic data are reported in Table 1.

The baseline ejection fraction (EF) in patients was 53 ± 8%, which was significantly lower than in controls (64 ± 7%, P = 0.001). Mean end-systolic volume (ESV) was higher in patients (61 ± 22 vs. 43 ± 13 ml, P < 0.05); end-diastolic volume (EDV) was not significantly different (127 ± 30 and 118 ± 18 ml in patients and controls, respectively). The cardiac output (CO) of patients was significantly lower (3.75 ± 0.82 vs. 4.98 ± 0.89 l/min, P < 0.005) than in controls. The values obtained for controls compared well with those previously published using the same technique (6).

The protocol of the study was approved by the Research Ethics Committee of the Hammersmith Hospital. Radiation exposure was licensed by the United Kingdom Administration of Radioactive Substances Advisory Committee. All subjects gave informed, written consent before each study.

Study Protocol

All patients underwent a PET study during the month before and at 1 and 6 mo after CABG to measure MBF and ventricular volumes.

CABG. The surgical procedure, carried out by the same surgeon in all cases, involved the use of the LIMA, the gastroepiploic artery, and at least one saphenous vein graft in each patient. The LIMA was grafted onto the LAD artery, the gastroepiploic artery onto the posterior descending artery, and the saphenous vein(s) to the circumflex artery. Patient 6 underwent a repeat bypass using the right basilic vein.

PET. PET scans were performed using an ECAT 931-08/12 multislice positron scanner (CTI/Siemens, Knoxville, TN), as described previously (2, 19). A brief summary of the scanning protocol follows. Subjects lay supine in the scanner, and a 5-min rectilinear transmission scan was recorded to facilitate positioning of the left ventricle within the field of view by exposure of a circular ring source of 68Ge. Subsequently, a 20-min transmission scan was performed to correct all emission scans for tissue attenuation.

After the transmission scan, a gated blood pool scan was performed by inhalation of C15O2, delivered at a rate of 500 ml/min with 3 MBq·ml−1·min−1 activity for 4 min. The inhaled C15O rapidly forms [15O]carboxyhemoglobin, which is used to label the intravascular blood pool. The scanning procedure has been described previously (5). After a 10-min period (corresponding to ~5 half-lives of 15O) to allow for decay, C15O2 was administered for 3.5 min with 4 MBq/ml activity at a rate of 500 ml/min. The C15O2 is immediately converted, by carbonic anhydrase in the lung, to H215O, which is used to measure MBF. MBF was measured at rest and during pharmacologically induced hyperemia (intravenous dipyridamole infusion at 0.56 mg/kg for 4 min), as previously described (2). Blood pressure and heart rate were recorded automatically by Dinamap (Critikon, Tampa, FL) at 1-min intervals during dipyridamole infusion, and the 12-lead electrocardiograph was recorded every minute by a Marquette electrocardiograph (Marquette Electronics, Milwaukeee, WI).

PET Data Analysis

Briefly, the sinograms were corrected for attenuation and reconstructed on a SUN SPARC workstation employing a standard filter backprojection reconstruction algorithm. Im-

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<th>Table 1. Patient characteristics</th>
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ISMN, isosorbide mononitrate; LAD, left anterior descending coronary artery; Cx, circumflex artery; RCA, right coronary artery; LMS, left mainstem artery; OM1, first obtuse marginal coronary artery; D1, first diagonal coronary artery.
To compare patients and controls, ANOVA was followed by a t-test. The Bonferroni method was used to calculate the patients' results at the different study times using Scheffe's test. The statistical analysis was assumed to be the myocardial territory subtended by the anterior ROI was assumed to be subtended by the LAD and inferior myocardium were defined separately, and regions of interest (ROIs) were identified within each sector. Resting (baseline) MBF was calculated using a single-compartment model including corrections for spillover and the partial volume effect, as previously reported (2, 19). Four equally spaced sectors corresponding to the anterior, septal, lateral, and inferior myocardium (6) were resliced in the short axis and further analyzed by Analyze (Mayo Foundation) (34) and Pro-Matlab (Mathworks) software. The gated C15O sinograms were reprocessed employing an iterative reconstruction algorithm as elaborated by Boyd et al. (5). Left ventricular volumes were determined on a plane-by-plane, gate-by-gate basis. This approach allowed the calculation of global EF (EDV / ESV/EDV), absolute ventricular volumes, stroke volume, and CO.

MBF was calculated using a single-compartment model that includes corrections for spillover and the partial volume effect, as previously reported (2, 19). Four equally spaced sectors corresponding to the anterior, septal, lateral, and inferior myocardium were defined separately, and regions of interest (ROIs) were identified within each sector. Resting (baseline) MBF (MBF$_{bas}$) was corrected (cMBF$_{bas}$) for the resting rate-pressure product (RPP) of each patient, according to the following formula: cMBF$_{bas}$ = MBF$_{bas}$ × 10$^6$/RPP. CVR is defined as the quotient of mean arterial blood pressure and MBF hyp.

In relating the MBF results to the epicardial arteries, the MCR was derived by calculating the quotient of mean arterial blood pressure and MBF hyp. MCR was 47.58 ± 5.65 mmHg·min·g$^{-1}$·ml$^{-1}$ in controls. This was less than the value in patients preoperatively (59.37 ± 14.56 mmHg·min·g$^{-1}$·ml$^{-1}$, P = 0.02) but was not different from either of the postoperative measurements (Table 3). MCR was 47.58 ± 5.65 mmHg·min·g$^{-1}$·ml$^{-1}$ in controls. This was less than the value in patients preoperatively (59.37 ± 14.56 mmHg·min·g$^{-1}$·ml$^{-1}$, P = 0.02) but higher than the value obtained at 6 mo (35.76 ± 10.12 mmHg·min·g$^{-1}$·ml$^{-1}$, P = 0.003).

In patients, MBF$_{hyp}$ and CVR increased progressively but did not reach statistical significance until 6 mo after surgery (Table 3, Fig. 2). After correction of MBF$_{bas}$ for the RPP, both CVRs measured after CABG (1.7 ± 0.55 and 2.4 ± 0.28 at 1 and 6 mo, respectively) were different from baseline (1.00 ± 0.24, P < 0.05 and P < 0.001 vs. 1 and 6 mo, respectively), and there was no difference from the pooled data analysis.
also a statistically significant difference between the two postoperative CVRs \((P < 0.05; \text{Fig. 2})\). MCR tended to be lower 1 mo after CABG but became significantly different from baseline only at 6 mo (Fig. 3).

**Regional Results**

Comparison with controls demonstrated that preoperative MBF_{hyp} in patients was reduced in the anterior and inferior ROIs \((P = 0.002\) and \(P = 0.03\), respectively) but was comparable to controls by 1 mo after surgery. There was no difference in MBF_{hyp} in the lateral ROI between controls and patients at any time point.

MBF_{hyp} and CVR rose in all three regions over the period of the study, although the increase was not statistically significant in the lateral ROI (Table 4). Comparison among regions demonstrated that preoperative hyperemic flow in the lateral territory was greater than that in the other two regions \((P < 0.01\) vs. anterior ROI and \(P < 0.05\) vs. inferior ROI) but that there was a statistically significant difference in CVR only between the anterior and lateral ROIs \((P < 0.01)\).

There were no differences among territories in flow rates or CVR at 1 mo. At 6 mo after surgery, MBF_{bas} was again higher in the lateral ROI than in the other regions \((P < 0.05\) vs. anterior ROI and \(P < 0.01\) vs. inferior ROI) and MBF_{hyp} was significantly higher in this ROI than in the anterior ROI \((P < 0.05)\). CVR was significantly higher in the inferior than in the anterior ROI \((P < 0.05)\). Correction for RPP did not have any notable impact on these results.

**DISCUSSION**

The principal finding of the present study is that, in patients undergoing bypass surgery, CVR increases gradually after revascularization, achieving normal values 6 mo after the intervention. This normalization of CVR is due to a progressive decrease of MCR after surgery. Finally, the present study indicates that, up to 6 mo after CABG, there are no significant differences between arterial and venous grafts in terms of MBF_{hyp} and CVR. We previously showed that measurement of CVR by means of PET with H_2^{15}O is reproducible (20), and the changes observed after CABG are well above

![Fig. 2. Whole heart CVR for each patient before and 1 and 6 mo after bypass surgery. CVR was calculated as MBF_{hyp}/cMBF_{bas}, where MBF_{hyp} is hyperemic myocardial blood flow and cMBF_{bas} is corrected baseline myocardial blood flow. There is progressive improvement of CVR up to 6 mo.](image)

![Fig. 3. Scatter plot, with means indicated by horizontal bars, of minimal coronary resistance (MCR) at each time point. At 6 mo, MCR is significantly lower than the preoperative level. NS, not significant.](image)
shown to improve cardioplegia, cooling, or handling of the heart during operative impairment has been attributed to the use of Myocardial blood flow: regional results

Table 4. Myocardial blood flow: regional results

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<th>CVR</th>
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Values are ml·min<sup>−1</sup>·g<sup>−1</sup>. *P < 0.01 vs. preoperative; †P < 0.05 vs. preoperative; ‡P < 0.001 vs. preoperative and < 0.05 vs. 1 mo.

the repeatability coefficient for CVR. This rules out the possibility that the observed changes in CVR are due to methodological constraints.

In the absence of significant epicardial stenoses, CVR provides an indication of the functional integrity of the coronary microcirculation; therefore, our data suggest the presence of microvascular dysfunction soon after CABG. A number of factors can influence microvascular function, including ventricular hypertrophy, prior myocardial infarction, prolonged hypertension, drug treatment, and recent cardiopulmonary bypass (30). The first three factors were excluded in the present study by using appropriate criteria for patient selection. There were inevitable modifications in the drug regimens of patients after their operations (Table 1). In most cases, one or more of a β-blocker, a calcium-channel blocker, or nitrates were withdrawn. Although none of these classes of drugs has a significant effect on CVR (18, 36, 43), a washout period of 72 h was allowed before each PET scan to minimize any potentially confounding effect.

A number of investigators have demonstrated a reduced CVR associated with a bypass graft in the immediate (<24 h) postoperative period (1, 17) that was shown to improve ≥6 mo later. This very early postoperative impairment has been attributed to the use of cardioplegia, cooling, or handling of the heart during surgery (17). However, it is unlikely that these mechanisms continue to have an effect 1 mo after the operation. Supporting this assertion is the observation by Uren et al. (40) that CVR in the region subtended by the dilated artery is still depressed 1 wk after a successful percutaneous transluminal coronary angioplasty. The latter observation is consistent with an increased resistance at the microvascular level, which seems to be due to sympathetically mediated vasoconstriction, as recently demonstrated by Rimoldi et al. (34). The potential confounding factors present early after bypass surgery clearly do not apply after percutaneous transluminal coronary angioplasty. Therefore, we hypothesize that the slow recovery of CVR observed after CABG is consistent with a persistent microvascular dysfunction probably associated with chronic coronary artery disease (14).

A number of different factors may be involved in the pathogenesis of this microvascular dysfunction. These can be divided into three broad categories: 1) remodeling of the vessel wall, 2) abnormal intramyocardial pressure (higher extravascular resistance), and 3) active vasoconstriction or loss of vasodilator capacity (8). Structural remodeling of the coronary microcirculation includes changes in the arteriolar wall and a relative reduction in the total number of vessels. This has been best documented in hypertensive patients in
whom medial thickening of intramural coronary arteries has been seen, resulting in increased intravascular resistance and reduced CVR (38). Although we excluded patients with arterial hypertension, it is possible that there may be a structural abnormality underlying at least some of the dysfunction we observed, such as that detected in rats exposed to a reperfusion injury (13).

Elevated diastolic intraventricular pressure would result in a rise in intramyocardial pressure and increase the extravascular component of coronary resistance. Although we did not measure intramyocardial pressures, all our patients had normal systolic function, and no significant change in the measured hemodynamic variables was observed at the different time points.

Endothelial dysfunction resulting in the loss of vasodilating capacity has been reported in animals and patients with coronary artery disease (27, 42, 46) and is thought to be due to free radical-mediated injury (3, 22, 25). Neurohumoral factors have also been shown to affect the vasomotor function of the coronary microcirculation (12, 21, 28), but there is little evidence to suggest that they have a role in the posts ischemic state. In addition, small coronary arterioles receive autonomic innervation, and their diameter may be altered by stimulation of these nerves (11, 34).

Postischemic impairment of the coronary microvasculature (microvascular stunning) has been demonstrated in animal experiments by Bolli et al. (4) as a distinct phenomenon from the better-characterized postischemic myocardial contractile dysfunction known as myocardial stunning (7). This postischemic microvascular dysfunction has been described in a number of settings and variously termed capillary non-reflow (15), microvascular stunning (4), microvascular incompetence (26), low flow (32), and slow coronary flow (24). The pathogenesis of this condition remains uncertain.

Finally, our study shows that CVR rises over the same period in all three regions of the heart independently of the graft used. There has been controversy regarding the ability of different grafts to provide adequate blood flow during peak myocardial demand (31, 39). Our data suggest that there is little difference in CVR between territories subtended by saphenous veins and arterial grafts. In addition, we show that CVR in the grafted territories rises to the same level as that in controls. Early studies examining the flow capacity of bypass grafts suggested that maximal flow capacity within these grafts was reduced relative to normal controls (43). Many of these investigations were carried out using techniques that either did not allow accurate estimation of high flows or achieved submaximal coronary vasodilatation (43). Studies employing appropriate methods have since shown, as we have, that flow reserve is normalized with the use of arterial (1) and venous grafts (45).

A limitation of our study is the absence of data to exclude alterations in the dimensions or physiological responses of graft conduits over time that may influence the observed changes in blood flow to tissue perfused by these grafts. Gurné et al. (17) demonstrated that the CVR was lower at ~1 wk than at 18 mo after surgery. They showed that the bypass conduits behaved in a similar fashion in response to the vasodilators papaverine and isosorbide dinitrate at both time points, suggesting that the early dysfunction must have been in vessels further downstream. Dipyridamole causes selective dilatation of resistive vessels in the microcirculation rather than epicardial arteries (37). We are not aware of data demonstrating its effect on bypass grafts, but whether it dilates these or not, inasmuch as the bulk of the overall coronary vascular resistance resides in small arterioles (10), dilatation of the grafts would not be expected to have a significant influence on MBFhyp without a simultaneous response from the microcirculation.

It may be argued that dipyridamole was not the ideal agent to use in this study, inasmuch as it does not always induce maximal MBF, and a number of patients may be less responsive to it (44). However, its efficacy and reproducibility in a wide range of investigations made it an attractive agent to use, and papaverine, which has a more reliable maximally vasodilating effect, would have required intracoronary administration. In addition, the fact that patients served as their own controls should have overcome most problems of limited response to the drug. Exercise would offer a physiological stimulus, but the need to minimize patient movement during the PET acquisition and to standardize the test conditions between subjects and between studies made us disinclined to stress our patients in this way.

Another important limitation of the study is clearly the small number of patients enrolled. However, the fact that they serve as their own controls and the consistency of the data point to the results having considerable significance.

REFERENCES


