Coronary revascularisation in young adults

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Abstract

Objective: To evaluate the long-term outcome of coronary artery bypass surgery (CABG) in patients <40 years old and to determine factors predictive of adverse outcomes. Methods: Retrospective review of data on 220 patients who underwent isolated CABG at Green Lane Hospital, New Zealand from 1970 to 1992. Results: The actuarial survival after surgery was 91, 74 and 50% at 5, 10 and 15 years, respectively. Recurrence of ischaemic symptoms occurred at a median time of 72 months, and only 20% of patients remained asymptomatic 10 years after CABG. Univariate analysis of potentially adverse surgical factors showed that patients who had prolonged bypass time (≥100 min, \( P < 0.007 \)) had increased late mortality. There were two distinct operative eras with respect to the use of IMA conduits (4% pre 1985, 87% post 1984) The relationship between IMA conduits use and survival was significant on time independent analysis (\( P < 0.02 \)), but was not using the log-rank test. Preoperative clinical characteristics associated with increased late mortality were impaired left ventricular function (end-systolic volume (ESV) ≥80 ml, \( P = 0.008 \); ejection fraction <40%, \( P = 0.0005 \)), and lack of aspirin use either pre- or post-operatively (\( P < 0.0001 \)). Multivariate analysis indicated that reduced ejection fraction (\( P = 0.04 \)) and prolonged bypass time (\( P = 0.05 \)) was associated with an increased risk of late death. Aspirin therapy (\( P = 0.001 \)) was associated with decreased late mortality. Cumulative events rate of reintervention and mortality was reduced in female patients (\( P = 0.0009 \)). At review, 45% of patients had total cholesterol ≤6.5 mmol/l. Conclusion: To avoid the early recurrence of symptoms, the need for reintervention and late mortality, young patients should receive IMA conduits, cardisplegia as myocardial protection, aspirin and therapy to modify/ameliorate their risk factors including dyslipidaemia, diabetes and left ventricular dysfunction. © 1997 Elsevier Science B.V.

Keywords: Bypass time; Cardioplegia; Cardiac volume; IMA; Aspirin

1. Introduction

Coronary artery bypass graft surgery (CABG) relieves angina and improves long term outcome in patients with severe coronary artery disease or left ventricular dysfunction [1]. The long term efficacy of CABG has been limited by progression of disease leading to occlusion of both native vessels and saphenous vein grafts [2]. Aspirin [3] reduces the occlusion of saphenous vein grafts, and disease progression may be inhibited by the use of lipid-modifying therapy [4]. Randomised controlled trials have not specifically examined the survival benefit of CABG in young patients, though the European trial suggested a greater benefit from surgery in older patients [5]. Compared with older patients, young surgical patients have been reported to have a higher frequency of risk factors such as smoking and dyslipidaemia which may lead to accelerated atherosclerosis especially in saphenous vein grafts [6,9,10], though surgery was initially effective in relieving symptoms [6–9]. The increased frequency of
risk factors for early saphenous vein graft occlusion in young patients has lead to the increased use of angioplasty as the revascularisation procedure, particularly in single vessel disease. More recently, angioplasty has been shown to have similar efficacy as revascularisation procedures for double and triple vessel disease in suitable patients [11]. However, in spite of the efficacy of angioplasty, many patients still require surgical revascularisation. Identification of potentially modifiable surgical factors which may contribute to an adverse outcome is desirable.

Oclusion of saphenous vein grafts has prompted the use of internal mammary arteries as the conduits of choice [12]. Several studies have shown the superiority of mammary grafts over saphenous vein grafts in maintaining patency and improving the 10 year survival rate [12–15]. Loop et al. [12] found that patients who had vein grafts had 1.61 times greater risk of death throughout the 10 years compared with those who received internal mammary artery conduits. In the John Hopkins series, [7] it has been recently reported that the era of operation may affect reintervention free survival, suggesting that other aspects of surgical technique influence outcome. Whether the recent introduction of blood cardioplegia influenced this result is unknown.

In this study of young patients (<40 years old) who underwent a first isolated CABG operation, we examined the factors which may predispose to adverse late outcomes including death, reintervention (angioplasty, CABG or transplantation) and on the recurrence of ischaemic events (myocardial infarction or angina).

2. Materials and methods

We retrospectively evaluated the risk factors potentially affecting adverse late outcome in 220 adult coronary patients aged <40 years who underwent first isolated CABG surgery at Green Lane Hospital during the period from 1970 to 1992. The end points examined were death, a further ischaemic event (recurrence of angina, myocardial infarction) or the need for further cardiac intervention (CABG, angioplasty or cardiac transplantation).

Pre- and perioperative data were obtained by review of the hospital case notes. The preoperative variables examined were: gender, diabetes (either on insulin and/or fasting blood glucose ≥ 6.5 mmol/l), hypertension (on antihypertensive therapy or blood pressure ≥ 150/95), a positive family history of premature coronary artery disease (women < 60 and men ≤ 50 year old), smoking history (smoker [current or stopped ≤ 1 year], ex-smoker [stopped 1–10 years], non-smoker [stopped > 10 years or never smoked]), aspirin use (either preoperative or commenced within 1 month or ≤ 1 month post-operatively) class of angina (Canadian Cardiovascular Society), hypercholesterolaemia (> 5.2 mmol/l), previous Q-wave myocardial infarction (MI), left ventricular end-diastolic pressure (LVEDP), left ventricular end systolic volume (ESV), left main and left anterior descending coronary (LAD) stenosis of ≥ 50% luminal diameter reduction and myocardial score [16]. Intraoperative variables examined were: cardiopulmonary bypass and aortic cross-clamp times, the number of proximal and distal anastomoses of grafts and the completeness of revascularisation. Revascularisation was considered incomplete if ≥ 10% of the myocardium was supplied by an artery with a stenosis ≥ 50% which was not grafted. The use of internal mammary artery (IMA) conduits and cardioplegia was also recorded. Perioperative infarction was defined as the development of new Q-waves and/or elevation of aspartate aminotransferase (≥ 100 U/ml) [17,18].

Late review was conducted by clinic review and/or by detailed questionnaires mailed to patients and their physicians as previously described [18,19] and there after by cold pursuit. Post-operative smoking history (defined as smoking regularly for at least 1 month), the use of aspirin and lipid modifying therapy data were also recorded.

Statistical analysis using the log-rank test was used to test the univariate associations. Multivariate analysis was performed using Cox proportional hazards analysis in two stages. Initially, all potential factors were included in the model. Factors with $P > 0.5$ were initially removed and other factors with least significance were also removed so that there was approximately one factor per ten end-point events in the final model. To enhance the multivariate model and to avoid problems with missing data, ejection fraction was substituted for ESV and lipid therapy was also omitted from the final model. Patient survival and intervention-free periods were expressed as actuarial analysis using the Kaplan–Meier method. Statistical significance was taken as a $P$ value < 0.05.

3. Results

3.1. Patient demographics

Isolated CABG was performed on 220 patients (84% male) aged 36 ± 3.1 years. The patients characteristics are shown in Table 1. The majority of patients (80%) underwent CABG for severe angina (class III or higher). Ninety percent of patients had total cholesterol levels > 5.2 mmol/l (200 mg/dl) and 37% had a total cholesterol level > 7.8 mmol/l (300 mg/dl). Only 21% of the patients had never smoked. A positive family history of premature coronary heart disease was present in 40% of the cases while diabetes and hypertension were present in 5.1% and 17.4% of cases, respectively.
Most patients (75%) had normal or mildly impaired left ventricular function (ejection fraction ≥ 50%); the mean ejection fraction for the group being 58 ± 13%. Sixty one percent of patients had end systolic volume (ESV) < 80 ml; the mean ESV was 79 ± 47 ml. Eighty eight percent of patients had significant left anterior descending stenosis and 12% had ≥ 50% left main coronary stenosis. Sixty four percent of patients had severe coronary artery disease [6] as determined by a myocardial score of ≥ 10 units (the approximate equivalent of severe triple vessel disease).

### 3.2. Surgical results

There were no operative deaths. Four patients (1.8%) died within 30 days of surgery, all of whom had prolonged bypass times ≥ 100 min (mean bypass time of 191 min). Two of these four were from a group of 11 patients who had emergency CABG. Perioperative myocardial infarction was observed in 21 patients (9.5%).

The mean cardiopulmonary bypass and aortic cross clamp time was 101 ± 40 and 54 ± 25 min, respectively. Myocardial protection was performed using intermittent aortic cross clamping with ventricular fibrillation in 128 cases (58%). Cardioplegia was used in 92 patients (42%); all patients except one received crystalloid.

The mean number of grafts per patient was 2.5. Forty eight patients received internal mammary artery (IMA) conduits with no patient receiving bilateral IMAs. Only 4% of patients received IMA conduits prior to 1985, whereas 87% received IMAs post 1984. 22% (42/190) had incomplete revascularisation.

### Table 1

Baseline characteristics

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>220</td>
</tr>
<tr>
<td>Mean age (years)*</td>
<td>36.4 ± 3.1</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>84.1 (185)</td>
</tr>
<tr>
<td>Family history of premature CAD, % (n)</td>
<td>40.3 (85/211)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>17.4 (38/218)</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>5.1 (11/215)</td>
</tr>
<tr>
<td>Smoking [current or stopped &lt;1 year], % (n)</td>
<td>61.3 (133/217)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)*</td>
<td>7.3 ± 1.8</td>
</tr>
<tr>
<td>Angina class ≥ III, % (n)</td>
<td>68.7 (149)</td>
</tr>
<tr>
<td>Ejection fraction (%)*</td>
<td>58.2 ± 13.4</td>
</tr>
<tr>
<td>ESV (ml)*</td>
<td>79.0 ± 47.4</td>
</tr>
<tr>
<td>LVEDP (mm)*</td>
<td>14.1 ± 6.6</td>
</tr>
<tr>
<td>Left main stenosis (%)</td>
<td>12.3</td>
</tr>
<tr>
<td>Myocardial score ≥ 10 units (%)</td>
<td>64.2</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end-diastolic pressure; ESV, end-systolic volume; and n, number; coronary artery disease = CAD; angina class = Canadian cardiovascular society class of angina.

* Mean ± S.D.

### 3.3. Long-term follow-up

#### 3.3.1. (a) Survival

Nine patients could not be traced after the perioperative period and a further 17 patients had less than 2 years follow-up. The overall survival at 5, 10 and 15 years after surgery was 91, 74 and 50%, respectively (Fig. 1). Mean duration of follow-up was 8.5 ± 5.3 years. Univariate analysis identified several factors, which adversely influenced outcome (Table 2). End systolic volume ≥ 80 ml, ejection fraction < 40% and bypass time ≥ 100 min were associated with a higher late mortality. Pre- and postoperative use of aspirin increased survival. Multivariate analysis (Table 3) showed that a prolonged bypass time and decreased ejection fraction were associated with decreased late survival, while the use of aspirin enhanced survival. When time independent multivariate analysis was performed, IMA conduits were significantly associated with enhanced survival (P = 0.02).

#### 3.3.2. (b) Reintervention

Seventy one patients (32%) underwent reinterventions (60 reoperative CABG, nine angioplasty and two orthotopic cardiac transplants). From the cumulative Kaplan–Meier curves, 52% of the patients required reintervention within 10 years of their initial surgery (Fig. 1). On univariate analysis (Table 2) factors associated with increased frequency of reintervention were male sex and lack of aspirin use. Multivariate analysis with Cox proportional hazards showed that female gender (P = 0.0009) and higher myocardial score (P = 0.04) had a reduced cumulative reintervention and mortality rate. When reoperative CABG was undertaken, there was an associated 8.3% (5/60) mortality.

#### 3.3.3. (c) Recurrence of symptoms

The median time to recurrence of ischaemic symptoms, reintervention or late death was 72 months with only 20% patients being event-free at 10 years (Fig. 1). Table 2 shows that prolonged bypass time ≥ 100 min and lack of use of aspirin preoperatively were all associated with an earlier return of symptoms. However, when these factors were analysed by Cox proportional hazards method, higher myocardial score (0.006) and the use of aspirin (P = 0.02) was associated with lower cumulative recurrence of symptoms, reintervention and death.

#### 3.3.4. (d) Control of risk factors

At review, in spite of 37% of patients taking lipid-modifying therapy, 45% of patients (59/132) had total cholesterol levels > 6.5 mmol/l. Also 45% of the patients (101/183) did not take aspirin post-operatively. At some time postoperatively, 28% of patients admitted to smoking.
Fig. 1. Kaplan–Meier survival curves of patients aged <40 years following coronary artery bypass surgery. The percentage of patients free from recurrent ischaemia (▼), reintervention (■) and death (●) at yearly post-operative intervals are shown. The number of patients at 0, 5, 10 and 15 years post-operatively are as shown. Age and sex-matched controls from the general population are shown as a dotted line.

4. Discussion

In this study we have reported the surgical experience and late outcome of CABG from one centre in patients aged <40 years. In the era since 1970, there have been many advances in surgical technique including the use of IMA conduits and improved myocardial preservation especially during prolonged procedures [20]. Angioplasty has reduced the need for surgery for less extensive disease, [18] implying that less low risk surgery is undertaken.

There was a total of 67 late deaths (30%) in this cohort. The actuarial curve indicates overall survival of 91, 74, 50% at 5, 10 and 15 years, respectively, which was comparable with other cohorts of young patients. There was 76% 10 year survival in Johns Hopkins series [7] (201 patients), and 85% 10 years in Cleveland clinic series [6] (107 patients). In a series from Prague, Czechoslovakia [8] of 128 patients the 10 year survival was 60%, though whether this represents a poorer outcome cannot be determined from the reported data.

Table 2
Univariate analysis of factors potentially associated with late mortality, reintervention and recurrence of symptoms

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Reintervention</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.02</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td>0.93</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Left main stenosis</td>
<td>0.40</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.18</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>ESV</td>
<td>0.97</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.61</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>No aspirin</td>
<td>0.0005</td>
<td>0.002</td>
<td>0.007</td>
</tr>
<tr>
<td>Cardioplegia</td>
<td>0.89</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Bypass time</td>
<td>0.57</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Aortic cross-clamp time</td>
<td>0.63</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>No IMA</td>
<td>0.97</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

ESV, end-systolic volume; and IMA, internal mammary artery.

Table 3
Analysis of factors potentially associated with increased late mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3.20</td>
<td>0.07</td>
</tr>
<tr>
<td>No aspirin</td>
<td>10.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>4.30</td>
<td>0.03</td>
</tr>
<tr>
<td>No IMA</td>
<td>1.67</td>
<td>0.20</td>
</tr>
<tr>
<td>Myocardial score</td>
<td>0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Bypass time</td>
<td>3.69</td>
<td>0.05</td>
</tr>
</tbody>
</table>

IMA, internal mammary artery.
4.1. Factors affecting survival after coronary artery bypass grafting

4.1.1. Perfusion time

In our series, prolonged bypass time of ≥ 100 min was associated with increased mortality (44% compared with 17%), increased reintervention and frequency of recurrence of ischaemic symptoms. In a large cohort of patients of all ages reported from Adelaide, Australia [21] the mortality was 10.3% when the bypass time was ≥ 100 min and an overall mortality of 0.63% when the mean bypass time was 48 min. Prolonged bypass time may reflect other factors not included in the analysis such as the quality of the vessels available for grafting, obesity (with increased epicardial fat), and unsatisfactory conduits. Thus prolonged bypass times may not be a 'modifiable' factor.

4.1.2. Internal mammary artery

Over the last 20 years, there has been increasing use of internal mammary arteries (IMA) as the preferred conduits for coronary artery bypass grafting. Several short [7,13] and long term follow-up [12,14] studies have shown the superiority of IMA over saphenous vein grafts. IMA reduces the requirement for further revascularisation procedures, [19] extends the time to recurrence of ischaemic symptoms [12] and these conduits are associated with superior patency rate of around 90% at up to 10 years post-surgery [1]. An IMA graft to the anterior descending coronary artery improves the 10 year survival compared with a saphenous vein graft [14,15]. Approximately 20% of patients received IMA conduits, almost entirely after 1984. While the use of IMA conduits was significantly associated with increased survival (P < 0.02) using time-independent multivariate analysis, IMA conduit use were not significant by log-rank test.

4.1.3. Myocardial protection

In our series we found that perioperative myocardial infarction was not associated with increased late mortality. The lack of a late effect of perioperative infarction in our study may be due to either the small number of post-operative deaths or a rather conservative diagnostic criteria for perioperative myocardial infarction of new Q-waves and/or an elevated AST ≥ 100 U/ml. The 9.5% perioperative MI rate is comparable with the 7% in the Zehr et al. [7] study, though the perioperative MI was diagnosed only on the basis of new Q-wave changes in the latter series.

Cardioplegia was used in 42% of this group of young patients undergoing CABG surgery. Its usage was found not to have any significant relation to perioperative myocardial infarction. We have shown, however, that the introduction of blood cardioplegia to our institution has resulted in a reduction in perioperative AST levels in the entire cohort of CABG patients [22].

In the John Hopkins series [7] year of operation was associated with outcome. Marked changes in practice, including the introduction of angioscopy for less extensive disease have markedly affected the nature of our patient population. Because of these differences a later era of operation adversely affected prognosis which was also related to the early perioperative hazard. As the era of operation distorted the multivariate analysis it was excluded.

4.1.4. Ventricular function

Hamer et al. [23] examined the effect of end systolic volume and long term survival following CABG. Patients with an ejection fraction ≤ 40% the 10 year survival was only 40%. On their multivariate analysis, end systolic volume index was the only independent predictor of survival after CABG. A similar trend was seen in the study by White et al. [24] which showed decreased survival in patients following myocardial infarction with ejection fraction below 50% or end systolic volume above 100 ml. Our study confirmed the findings of our colleagues studies, [23,24] with an increased mortality for patients with increased ventricular volumes; in the multivariate analysis ejection fraction was only included because the data set was more complete. As angiotensin converting enzyme inhibitors limit increases in left ventricular volume, [25] patients with evidence of left ventricular impairment or dilatation should receive these agents prior to and after surgery.

4.1.5. Antiplatelet therapy

A large number of patients in our cohort did not receive aspirin (88/205) before CABG. Most of these patients were in the 1970s to early 1980s when aspirin was not used regularly. Aspirin use in our cohort reduces late mortality rate by 65%, decreases reintervention and recurrences of ischaemic symptoms. Aspirin improves vein graft patency in the years after coronary bypass surgery [3] as early graft occlusion is mainly due to thrombosis whereas later occlusion is often secondary to progressive atherosclerosis. The occlusion rate at 3 years of grafts patent at 1 year was not significantly improved by aspirin [26]. However, during this post-operative period the occlusion rate of saphenous vein grafts is low. Aspirin also has important effects in native arteries necessitating its continuing use [27].

4.1.6. Risk factors for coronary heart disease

Surprisingly, hypercholesterolaemia (> 5.2 mmol/l) was not associated with increased long-term mortality, perhaps because many patients had severe hypercholesterolaemia. Missing data (from the 1970s) precluded the use of total cholesterol or lipid modifying therapy in the multivariate model. Patients, 45%, had a total cholesterol level > 6.5 mmol/l at the time of review but
only 20% of patients received HMG-CoA reductase inhibitors with limited duration of therapy. Potentially more of these patients could have benefited from these agents [4].

In this study we found that a family history of premature coronary heart disease was not a predictor of late mortality. In the study of Kelly et al. [9], their young coronary patients were more likely to have a positive family history, hypercholesterolemia and to be smokers compared with their control group. It is probable that these patients have more aggressive atherosclerotic disease. Several risk factors including dyslipidaemia and procoagulant disorders may be associated with disease progression in these patients. Furthermore, vein graft patency is decreased in patients with hypercholesterolemia and diabetes which are commonly seen in young patients with coronary artery disease.

Smoking history, diabetes, and hypertension did not affect the long term outcome in this cohort. Female gender was shown in our study to have lower late mortality and reintervention. In the series of Lytle et al. [6] and Zehr et al. [7], smoking history, female sex and hypertension did not affect late mortality but diabetes was a significant predictor of mortality.

Of note, measured by myocardial score, the extent of coronary artery disease, negatively correlated with symptom recurrence and reintervention. This may imply that patients with less extensive disease may have developed progressive disease in non-bypassed vessels, suggesting that percutaneous revascularisation may be the preferable option in these patients.

In suitable patients, coronary angioplasty may provide excellent long-term survival and may defer the need for surgery. The study of Buffet et al. [28] on 132 patients gives a 10 year survival of 96% and 58% were free of events at 10 years. Preliminary data from our group [29] also suggests excellent angioplasty procedural results but a high frequency of late revascularisation because of progressive disease.

5. Conclusion

When coronary surgery is needed in young patients, IMA conduits should be used. It is desirable to optimise myocardial protection and attempt to limit bypass times. With the progressive nature of the atherosclerotic disease process in the native coronary vessels and the accelerated process in the grafts, close attention to compliance with aspirin treatment and the modification of the risk factors is of utmost importance.

References


