Early and late prognostic significance of remote and reversible preoperative neurological events in patients undergoing coronary artery bypass grafting

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Abstract

Objectives: Preoperative neurological event with functional impairment is high risk for operative morbidity and mortality after coronary artery bypass grafting (CABG). However, data regarding the influence of remote and reversible neurological events on early and late survival are lacking.

Methods: The clinical profile and operative outcome of 5542 patients who underwent first-time CABG from 01 April 1999 through 30 June 2008 were analysed. Late survival data were 100% complete. The relationship between preoperative neurological event and survival (early and late) was investigated using multivariate logistic regression and survival analyses. Results: Mean age was 65.2 ± 9.2 years, and 494 patients (8.9%) had remote reversible neurological events preoperatively. There were 129 (2.3%) operative and 595 (10.7%) late deaths after a mean follow-up of 4.9 ± 2.7 years. Reversible neurological events had strong univariate (odds ratio (OR) 2.80, 95% confidence interval (CI) 1.82—4.33, p < 0.0001) and multivariate associations (OR 2.14, 95% CI 1.34—3.41, p = 0.001) with operative mortality. Although reversible neurological events exhibited a powerful univariate relationship with late deaths (hazard ratio (HR) 1.66, 95% CI 1.30—2.12, p < 0.0001), this was not maintained after controlling for other factors in multivariable analysis (HR 1.24, 95% CI 0.97—1.59, p = 0.08). Neurological complications, more frequent in patients with preoperative events, were implicated in 25% of operative deaths in patients with preoperative neurological events. The respective 5- and 10-year survival rates for patients with reversible neurological events (86% and 68%) were substantially lower than others (91% and 80%, p < 0.0001).

Conclusions: Remote reversible neurological events increase the risk of fatal and non-fatal postoperative neurological complications. Rigorous measures to improve cerebral protection are warranted in these patients.

Keywords: Preoperative neurological event; Coronary artery bypass grafting outcomes (morbidity; mortality); Survival

1. Introduction

Severe neurological dysfunction with functional impairment is considered a significant risk factor for operative mortality in patients undergoing coronary artery bypass grafting (CABG) [1,2], but the prognostic implication of remote episodes of reversible neurological events is not clear. Paradoxically, patients who have had stroke previously without residual functional debility are more often seen in cardiac surgery practice. It is pertinent, therefore, to investigate the impact of remote and reversible preoperative neurological event on early and late outcomes of CABG.

Several studies have demonstrated a strong correlation between preoperative stroke or pre-existing cerebrovascular disease and postoperative neurological complications after on-pump and off-pump CABG [3—12]. In doing so, some of the studies have indirectly implicated preoperative neurological event as a potential cause of operative mortality. However, data showing a direct association between remote and reversible preoperative neurological event and survival (early and late) after CABG are lacking. The objectives of this study, therefore, were to: (1) report the prevalence of remote and reversible preoperative neurological event among patients undergoing CABG and (2) determine its direct influence on early and late postoperative survival.

2. Materials and methods

We prospectively collect and store clinical data in the cardiothoracic surgery database of our university teaching hospital, which is managed by dedicated trained staff that
regularly update and validate entries. After obtaining approval for this study and a waiver for patient consent from the Medical and Ethics committee of our institution, we identified all patients who underwent isolated first-time CABG from 1 April 1999 through 30 June 2008 and retrieved their preoperative characteristics, intra-operative details and postoperative complications. Autopsy reports and death certificates for operative deaths were reviewed and follow-up survival data were obtained for all surviving patients (100%) in February 2009 using the National Health Service Strategic Tracing Service.

A remote and reversible preoperative neurological event was defined as a history of cerebrovascular accident or transient ischaemic attack more than 2 weeks before surgery that was followed by a full recovery before the time of surgery. Patients were excluded if they had residual neurological deficit or progressive neurological disease such as Alzheimer’s and Parkinson’s disease (n = 82). During the study period, patients with a history of neurological event and/or carotid bruit on clinical evaluation were further investigated by carotid Doppler scanning and subsequent review by vascular surgeons. Where indicated, carotid endarterectomy was performed, mostly as a separate procedure before CABG or occasionally as concomitant operation. Those who underwent concomitant carotid endarterectomy (n = 28) were not included in this study.

At CABG, the mean arterial pressure was maintained at or greater than 60 mmHg on cardiopulmonary bypass for patients with preoperative neurological event.

2.1. Data analysis

The primary endpoints were operative and long-term survival. Two tiers of statistical analyses were performed. First, we treated the whole study population as a single group and explored the influence of preoperative neurological event on operative and late mortality. We performed separate univariate screening to identify the potential risk of preoperative neurological event for operative and late mortality. Remote and reversible preoperative neurological event and other variables that exhibited strong associations with operative mortality were included in stepwise, multifactorial logistic regression analysis to determine their independent effect. Similarly, the late prognostic impact of remote and reversible preoperative neurological event was determined using Cox proportional hazards model constructed with potential risk factors, including remote and reversible preoperative neurological event. The second analysis was a matched cohort comparison. For this, we performed a 1:2 matching of patients with preoperative neurological event to a control group without a history of neurological event. Matching was done using the Greedy method [13] for age, sex and left ventricular ejection fraction.

Discrete variables are reported as percentages and compared in the matched group comparison using chi-square test, and continuous variables are reported as mean ± standard deviation (SD) and compared using Student’s t-tests. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows (SPSS Inc. 2005, Chicago, IL, USA), and a two-sided p < 0.05 was considered significant.

3. Results

3.1. Baseline and operative characteristics

The clinical profile of the study population is displayed in Table 1. The mean age of the 5542 patients was 65.2 ± 9.2 years, and 1175 (21.2%) were female. A total of 494 patients (8.9%) had remote and reversible preoperative neurological event. The vast majority of patients had multivessel disease with good left ventricular function. Most of the patients (93.1%) received between two and six bypass grafts during surgery with cardiopulmonary bypass (92.6%) and cross-clamp fibrillatory arrest (59.1%). The mean number of occluded coronaries was 2.7 ± 6 and the mean number of grafts was 2.7 ± 8. The predominant revascularisation strategy was left internal mammary artery (95.6%) to the left anterior descending artery and vein grafts to other targets.

Possible causes of preoperative neurological event were ischaemic in 104 patients, haemorrhagic (subarachnoid and subdural) in seven and unknown in 383. Ischaemic events were related to carotid artery stenosis (n = 64; 15 were unoperated and 49 underwent carotid endarterectomy) and pre-existing atrial fibrillation (n = 40).

3.2. The risk of remote and reversible preoperative neurological event

Postoperative neurological complication was more frequent among patients with preoperative neurological event (5.1% vs 1.6% for other patients, p < 0.0001). Operative mortality was remarkably higher among patients with preoperative neurological event (n = 27, 5.5%) compared with other patients (n = 102, 2.0%, p < 0.0001). Preoperative

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%) (n = 5542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1175 (21.2)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>65.2 ± 9.2</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>Angina class III/IV</td>
<td>2336 (42.2)</td>
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<tr>
<td>Cardiac morbidity</td>
<td></td>
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<tr>
<td>Coronary artery disease</td>
<td></td>
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<tr>
<td>Two-vessel</td>
<td>1319 (23.8)</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>3893 (70.2)</td>
</tr>
<tr>
<td>Left main stem</td>
<td>1692 (30.5)</td>
</tr>
<tr>
<td>Ejection fraction &gt;0.50</td>
<td></td>
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<tr>
<td>Prior myocardial infarction</td>
<td>2131 (38.4)</td>
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<tr>
<td>Prior heart failure</td>
<td>782 (14.1)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
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<tr>
<td>Prior reversible neurological event</td>
<td>494 (8.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1093 (19.7)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>93 (1.6)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>535 (9.7)</td>
</tr>
<tr>
<td>Operative data</td>
<td></td>
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<tr>
<td>Off-pump</td>
<td>412 (7.4)</td>
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<tr>
<td>Operative outcome</td>
<td></td>
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<tr>
<td>Neurological events</td>
<td></td>
</tr>
<tr>
<td>Reversible</td>
<td>66 (1.2)</td>
</tr>
<tr>
<td>Permanent</td>
<td>39 (0.7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>129 (2.3)</td>
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</tbody>
</table>
neurological event exhibited strong univariate (odds ratio (OR) 2.80, 95% confidence interval (CI) 1.82—4.33) and multivariate associations (OR 2.14, 95% CI 1.34—3.41) with operative mortality (see Table 2). After controlling for the effect of other factors, preoperative neurological event increased the risk of operative mortality by 114%.

Analysis of the causes of death for 105 out of 129 patients (81.4%) revealed the predominant single-system causes of operative death as cardiac (60%), respiratory (15%) and neurological (5%). Multisystem causes included neurological causes in 5% of operative deaths. For patients with preoperative neurological event, postoperative neurological complications contributed to 25% of operative mortality, compared with 9% for other patients. Patients without preoperative neurological event who suffered postoperative neurological complications had higher operative mortality (7.5%) compared with those who did not have postoperative neurological complication (1.9%, p < 0.0001).

All-cause mortality during a mean follow-up of 4.9 ± 2.7 (maximum 10 years) years was 10.7% (n = 595). Patients with preoperative neurological events experienced greater rates of late mortality (n = 76, 16.3% vs n = 519, 10.5%, p < 0.0001). Patients who did not have preoperative neurological event but developed postoperative neurological complication had higher rates of late mortality (29.3%) compared with those who did not have postoperative neurological complication (10.2%, p < 0.0001). Preoperative neurological event had a strong univariate association with late death (hazard ratio (HR) 1.66, 95% CI 1.30—2.11) but, after controlling for other factors in a multivariate model, this association was not maintained (HR 1.24, 95% CI 0.97—1.59, p = 0.08) as shown in Table 3.

The 5- and 10-year survival rates (Fig. 1) for patients with remote and reversible preoperative neurological events (86% and 68%) were substantially inferior to other patients (91% and 80%, p < 0.0001).
4. Discussion

Remote and reversible neurological event is not infrequent in patients presenting for CABG. The present study, like other reports [6], shows that about 9% of patients undergoing CABG have a history of reversible neurological event, which adversely affects operative outcomes directly and indirectly. Patients with preoperative neurological event had increased incidence of postoperative morbidity, longer hospital stays, operative mortality and late deaths.

4.1. Direct impact of preoperative neurological event

An important finding, worthy of note, is the powerful independent effect of preoperative neurological event on early operative outcomes. By increasing the mortality risk of CABG by 114%, preoperative neurological event exerted a stronger influence on operative outcome than age and moderate left ventricular dysfunction (ejection fraction 0.30—0.50). Perhaps preoperative neurological event is an indicator of increased neurological vulnerability often due to cerebrovascular disease. Our data suggests that preoperative neurological event predisposes to fatal postoperative neurological complications as reflected by a relatively high proportion of deaths due to neurological causes in this patient cohort. This finding is consistent with extensively published association between pre- and postoperative neurological events [4—6]. In these series there was up to 10-fold increase in operative mortality in those who developed postoperative neurological complications. The significant adverse effect of preoperative neurological event on postoperative morbidity and mortality justifies a consistent and focussed management strategy to minimise the incidence of postoperative neurological dysfunction, particularly in these high-risk group of patients.

4.2. Other effects of preoperative neurological event

In addition to a high incidence of postoperative neurological dysfunction, patients with preoperative neurological event also suffered from high rates of cardiac, respiratory and renal complications, which led to longer hospital stays. Apart from the influence of preoperative neurological event, a high prevalence of co-morbidities such as diabetes, renal insufficiency and peripheral vascular disease in patients with preoperative neurological events also contributed to the high
postoperative morbidity. Similarly, there was a greater rate of late mortality in patients with preoperative neurological event due to the negative prognostic impact of these co-morbidities rather than preoperative neurological event itself. Although preoperative neurological event did not have a primary role in significantly reducing long-term survival, the bipartite relationship of postoperative neurological dysfunction with preoperative neurological event, on the one hand, and with late mortality on the other, suggests a secondary contribution from preoperative neurological event. Our finding of significant increase in late mortality for patients with postoperative cerebrovascular dysfunction corroborates the report of Salazar et al. [14], which reported considerably reduced survival at 1 and 5 years of 67% and 47%, respectively, in postoperative stroke patients after CABG. Again, this stresses the importance of cerebral protective measures during CABG for this cohort of patients.

4.3. Clinical implications

Patients with preoperative neurological event undergoing CABG should be considered high risk even if they do not have residual functional deficit, and a comprehensive strategy to mitigate postoperative morbidity and mortality is warranted for this group of patients. In spite of the putative advantages of off-pump CABG in this group of patients [15], there is still controversy about its benefit in reducing neurological complications [16,17]. It can be argued, however, that a thoughtful management of the ascending aorta rather than the avoidance of cardiopulmonary bypass is the principal measure leading to reduced postoperative neurological event. For example, ‘no aorta touch technique’ [18], epicardial scanning [19,20] and intra-operative trans-oesophageal echocardiography [21] have been associated with reduced postoperative stroke rates and should be part of a multimodality approach that is customised to each patient. Whereas routine use of cerebral imaging as recommended by some authors [22] is controversial, increasing evidence is accruing in support of regular use of carotid ultrasound scanning and intra-operative monitoring of cerebral oxygenation [23,24], especially in high-risk patients.

4.4. Limitations

Cerebral imaging was not carried out to investigate the extent of cerebral involvement in patients with preoperative neurological events. As patients with small cerebral infarcts could be asymptomatic [22], this study may have under-reported the prevalence of preoperative neurological disease in CABG patients. In addition, routine Doppler scanning for carotid artery disease was not standard practice during the study period, so the frequencies reported in this study do not include asymptomatic disease. However, all patients with symptomatic carotid artery disease were jointly managed with vascular surgeons.

5. Conclusion

Remote and reversible preoperative neurological event, not uncommon in patients undergoing CABG, increased the risk for fatal and non-fatal postoperative neurological morbidity, and all-cause operative mortality. Preoperative neurological event was an independent predictor for operative mortality but not for late death, even though patients with preoperative neurological event had a high rate of late mortality, which compromised their long-term survival. Perhaps effective strategies to prevent postoperative neurological complications might improve the outcome of CABG in patients with preoperative neurological event.

References

In our institution we are now piloting the use of cerebral oximetry in patients to explore extracranial arteries before CABG. What is your opinion of this?

First, for example, in our institution we systematically perform echo Doppler morbidities which could have influenced the results by themselves.

remote and reversible preoperative neurological events to CABG. Is it emboli from atherosclerotic plaque or is it atrial fibrillation emboli?

Firstly, in a retrospective study like this, we know that events such as TIA can be underestimated. I have some interrogation concerning the proportion of each cause of remote reversible neurological dysfunction. Is it emboli from atherosclerotic plaque or is it atrial fibrillation emboli?

Second, it would be interesting to know the mean or median time from remote and reversible preoperative neurological events to CABG.

Thirdly, I suggest that your matched population analysis should be interpreted cautiously. The two groups have a different proportion of co-morbidities which could have influenced the results by themselves.

To conclude, I would like to ask you if you have changed your daily practice. We did not look at preoperative atrial fibrillation specifically in this study, but our experience (and we have done a lot of work with preoperative atrial fibrillation) is that 9% to 10% of patients undergoing CABG have preoperative atrial fibrillation. Whether we need to develop a strategy against the left atrial appendage in patients undergoing coronary artery bypass grafting is not clear. However in our practice we perform concomitant atrial fibrillation ablation at the time of surgery.

Dr G. Fourniel: My second question concerns your operative strategy. Have you changed it in favour of extending arterial grafts to prevent aortic manipulation?

Dr Ngaage: I do agree that the single most important strategy to reduce embolic stroke is thoughtful manipulation or care of the aorta. We still do most of our procedures on-pump, and we haven’t changed our practice yet. But, as I said, we are piloting cerebral oximetry and will see whether we will be able to include that in our overall strategy.

Dr S. Salzberg (Zurich, Switzerland): My question is grafting onto the aortic arch. I would like to ask whether you are using cerebral oximetry to detect cerebral oxygen desaturation during surgery? Could you make comment on how many of these patients did have atrial fibrillation and, if so, in the future how would you address this atrial fibrillation and, in particular, the left atrial appendage?

Dr Ngaage: We did not look at preoperative atrial fibrillation specifically in this study, but our experience (and we have done a lot of work with preoperative atrial fibrillation) is that 9% to 10% of patients undergoing CABG have preoperative atrial fibrillation. Whether we need to develop a strategy against the left atrial appendage in patients undergoing coronary artery bypass grafting is not clear. However in our practice we perform concomitant atrial fibrillation ablation at the time of surgery.

Dr I. Saeed (London, UK): I would just like to ask whether you looked at the postoperative neurological event rate and its association with preoperative neurological event rate? And, secondly, I may have missed it on your slide, but did you look at the interaction between carotid disease and preoperative neurological event?

Dr Ngaage: I believe you asked something about carotid disease. I didn’t hear the rest. We do not routinely scan the carotid arteries except for patients who have had recent neurological events who have not already been investigated. For patients with significant carotid disease we do perform concomitant endarterectomy or sequential carotid endarterectomy.

Dr Saeed: My question is, basically is this just a surrogate for something we already know, which is preoperative carotid artery disease? Is a reversible preoperative neurological event just another surrogate for preoperative carotid artery disease?

Dr Ngaage: Possibly, yes, it could be a sign of carotid artery disease, but not all the patients had carotid artery disease.