Importance of cerebral artery risk evaluation before off-pump coronary artery bypass grafting to avoid perioperative stroke

Kiyoshi Doi*, Hitoshi Yaku

Department of Cardiovascular Surgery, Koto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi, Hirokoji, Kamikyo-ku, Kyoto 602-8566, Japan

Received 10 November 2009; received in revised form 27 February 2010; accepted 8 March 2010

Abstract

Objective: Cerebrovascular atherosclerotic disease is a widely known risk factor for stroke after conventional coronary artery bypass grafting (CABG). The aim of this study is to evaluate the incidence of stroke in patients with significant cerebrovascular disease after off-pump CABG.

Methods: In this retrospective study, 611 patients, who underwent off-pump CABG, were divided into high-risk (n = 196) and low-risk groups (n = 415) for perioperative stroke using preoperative brain magnetic resonance angiography/imaging and cervical Doppler sonography, and the incidence of stroke in the two groups was compared. Results: No ‘intra-operative’ stroke was observed. However, seven patients (3.6%) in the high-risk group and one patient (0.2%) in the low-risk group developed ‘delayed stroke’ between the day of surgery and postoperative day 18 (mean postoperative day 8.8). The predominant aetiology of delayed stroke was thrombo-embolism. Assignment to the high-risk group had a significant association with the occurrence of delayed stroke (p = 0.011). The person-time incidence rate of stroke in the high-risk group was much higher within 1 month (3.57) after CABG than beyond 1 month (0.14). Conclusions: Patients with significant cerebrovascular disease did not develop intra-operative stroke after off-pump CABG. However, these patients were likely to suffer from delayed stroke within 30 days of surgery.

Keywords: Coronary artery bypass grafting; Off-pump; Cerebrovascular disease; Stroke

1. Introduction

The aetiology of stroke after coronary artery bypass grafting (CABG) is complex and multifactorial, and it may include systemic inflammatory response, cerebral embolism and cerebral hypoperfusion. Intra-operative release of atherosclerotic emboli associated with aortic cannulation and cross-clamping is believed to be the most important risk factor [1]. Because off-pump CABG can decrease aortic manipulation, this technique has been expected to reduce the incidence of stroke. However, some meta-analyses have failed to demonstrate a significant benefit of off-pump CABG in reducing the rate of perioperative stroke [2,3].

Most previous studies defined stroke as an event occurring over the course of the entire hospital stay and have not focussed on the timing of stroke. More than half of the strokes occurred after the patients fully recovered from the effect of anaesthesia without any neurological deficit [4,5]. The causes of these ‘delayed strokes’ also seem to be multifactorial, and few studies have specifically addressed the incidence and aetiology of delayed stroke after off-pump CABG.

In addition to cerebral emboli derived from aortic atherosclerosis, patients undergoing CABG are likely to have severe atherosclerosis of the carotid/cranial arteries. The presence of cerebrovascular disease is also a widely accepted risk factor for stroke [6]. The aim of this study was to examine the impact of cerebrovascular disease on the incidence and timing of stroke after off-pump CABG.

2. Materials and methods

2.1. Study group

Between January 1997 and December 2008, 707 patients underwent off-pump CABG in our institution. Among them, 611 patients, who underwent a preoperative screening examination involving brain magnetic resonance imaging (MRI), brain magnetic resonance angiography (MRA) and cervical Doppler ultrasonography, were enrolled in this retrospective study. The 611 patients were divided by neurologists into two groups (high-risk and low-risk) on the basis of the presence or absence of carotid or intracranial artery stenosis and past history of stroke according to an algorithm shown in Fig. 1.

2.2. Surgical techniques

In almost all cases, off-pump CABG was performed through a median sternotomy. Proximal anastomoses of free conduits...
(saphenous vein and radial artery) were placed on the ascending aorta using less invasive anastomotic devices such as Aortic connector (St. Jude Medical Inc., St Paul, MN, USA), Heartstring (Guidant, Indianapolis, IN, USA), and Enclose (Novare Surgical Systems, Cupertino, CA, USA) rather than using a partial aortic clamp. When intra-operative epi-aortic ultrasonography revealed significant atherosclerotic disease, an aortic no-touch technique was applied using the free conduits as Y or I extensions on the in situ internal thoracic artery graft (composite graft).

2.3. Perioperative anti-platelet/anticoagulation protocol

The intake of all anti-platelet agents, including aspirin, was suspended 7 days before surgery, except in patients with unstable angina and tight left main disease. Subcutaneous heparin was administered until the day before surgery. During CABG, intravenous heparin was administrated to achieve an activated clotting time of greater than 300 s, and it was neutralised at the end of the procedure with protamine sulphate. The administration of aspirin was reinitiated on the day after surgery. Warfarin treatment was also initiated in patients, who had received a vein graft.

2.4. Definitions

Stroke was defined as a new neurological deficit lasting for more than 24 h. If the neurological deficit was present when the patient emerged from anaesthesia, the stroke was defined as ‘intra-operative stroke’. ‘Delayed stroke’ was defined as a stroke occurring after the patient fully recovered from the effect of anaesthesia without neurological deficit and if it occurred within 1 month of surgery. Stroke was diagnosed by neurologists and confirmed by brain MRI or computed tomography (CT). Renal failure was defined as a serum creatinine level of greater than 1.5 mg dl$^{-1}$ or the requirement for haemodialysis. Low cardiac output syndrome (LOS) was defined as the use of postoperative inotropic support for more than 48 h. Perioperative myocardial infarction (PMI) was diagnosed if the level of serum creatine kinase MB isoenzyme was more than 100 IU l$^{-1}$.

The occurrence of stroke (stroke rate) was expressed as a person-time incidence rate [7]. Incidence per 100 person-months, $r$, is defined by the following equation: $r = (N/D) \times 100$, where $N$ is the number of strokes occurring during the observation period and $D$ is person-time units (months).

2.5. Statistical analysis

Numerical variables are presented as the mean ± standard deviation for each patient group and compared using the Mann—Whitney test. Categorical variables are given as percentages and compared using the chi-square and Fisher’s exact tests where appropriate. Event-free ratio analysis was performed with the Kaplan—Meier method, and statistical significance was calculated with the log-rank test. Univariate analysis, expressed as odds ratio with 95% confidence interval limits and $p$ values, was used to evaluate the effect of preoperative and postoperative variables on the occurrence of neurologic complications. Statistical significance was accepted at $p < 0.05$. Analyses were performed using the SPSS statistical software (version17.0; SPSS Inc., Chicago, IL, USA).

3. Results

Of the 611 patients who underwent the risk assessment for perioperative stroke before surgery, 196 patients (32%) were considered to be at high risk for stroke. None of these patients had experienced a recent episode of cerebrovascular accident (CVA), nor did any of them require previous or concomitant carotid artery intervention. The remaining 415 patients (68%) were considered to be at low risk for perioperative stroke. The preoperative characteristics of the groups are summarised in Table 1. Patients in the high-risk group were older, had a higher prevalence of diabetes and renal failure and a greater average number of diseased coronary vessels. In 423 cases out of the entire 611, off-pump CABG cases, the anastomotic devices were available. Of those, 241 cases used free conduits, and 15.8% of them required aortic no-touch technique after assessment using epi-aortic ultrasonography.

Table 2 lists the observed postoperative results. No intra-operative stroke occurred in either group. However, seven patients (3.6%) in the high-risk group developed delayed stroke after an initially uncomplicated neurologic course, in
comparison to only one patient (0.2%) in the low-risk group ($p = 0.002$). Transient ischaemic attacks (TIA) were observed in 2.6% of patients in the high-risk group and 1.2% of those in the low-risk group ($p = 0.30$).

Delayed stroke occurred between the day of surgery and postoperative day 18 (mean postoperative day 8.8) as shown in Table 3. One delayed stroke occurred after postoperative coronary angiography, and five of these occurred distal to the high-grade cerebrovascular stenosis. According to the univariate analysis, designation in the high-risk group was significantly associated with the occurrence of delayed stroke ($p = 0.011$) (Table 4). However, there was no significant association between age, male gender, preoperative/postoperative renal failure, diabetes mellitus, preoperative left ventricular ejection fraction, low cardiac output syndrome, perioperative myocardial infarction, episode of postoperative atrial fibrillation, postoperative coronary angiography and occurrence of delayed stroke.

Fig. 2 shows the relationship between the probability of remaining free from stroke and the amount of time after off-pump CABG in the two groups. The probability in the high-risk group decreased rapidly during the very early postoperative period, and this was followed by a more gradual decline over the next several years. The person-time incidence rate of stroke (stroke rate) in the high-risk group was much higher within 1 month (3.57) after CABG than that at later than 1 month (0.14) after a mean follow-up of 2.3 years (Table 5). A similar reduction in the stroke rate was also observed in the low-risk group, although it was less remarkable.
Atherosclerosis is a systemic disorder occurring throughout the vascular tree. Therefore, patients undergoing CABG are likely to develop severe atherosclerosis in the carotid/cranial arteries. The presence of significant cerebrovascular disease is believed to increase the risk of stroke after CABG.

Perioperative strokes associated with cerebrovascular disease can be divided into two principal aetiological mechanisms: hypoperfusion and thrombo-embolism. Hypoperfusion strokes arise from haemodynamic compromise distal to the carotid/cranial artery stenosis, and have been associated with the patients’ capacity for cerebral autoregulation, which may be impaired by cardiopulmonary bypass [8]. Thrombo-embolic strokes are caused by thrombus formation at the site of the ulcerated atherosclerotic plaque on the carotid/cranial arteries [9].

Recent studies have shown that the use of the off-pump technique combined with minimal manipulation of the aorta can reduce the incidence of intra-operative stroke to almost zero [10–12]. These reports are in agreement with the findings of our study and, furthermore, there were no cases of intra-operative stroke after off-pump CABG even in patients with significant cerebrovascular disease (high-risk group). This result suggests that avoidance of cardiopulmonary bypass may preserve the capacity of cerebral autoregulation and, as a result, reduce the incidence of stroke associated with intra-operative hypoperfusion.

Eight patients in our study (1.3%) developed delayed stroke after off-pump CABG. Currently, the aetiological mechanism of delayed stroke is still unclear; atrial fibrillation and low ventricular ejection fraction have been suggested to contribute to its occurrence [4,12]. In our study, the presence of significant cerebrovascular disease (high-risk group) seemed to be a risk factor for delayed stroke (Table 4). However, there was no significant association between preoperative low left ventricular ejection fraction, episode of postoperative atrial fibrillation and occurrence of delayed stroke. Most of these infarctions occurred distal to the significant stenosis, and thrombo-embolism was the predominant aetiology.

Another important aspect of delayed stroke is that the incidence rates are not constant over time. Peel et al. reported that the incidence of delayed stroke increased rapidly after the day of off-pump CABG, reached a peak on postoperative day 4, and then decreased exponentially [13]. In our study, the incidence rate of stroke (stroke rate) in the high-risk group was much higher within 1 month (3.57) of off-pump CABG than that beyond 1 month (0.14) (Table 5).

One possible explanation for these phenomena is the increase in coagulability during the early postoperative period. According to a study by Parolari et al., activation of the coagulation–fibrinolytic system and endothelial cell damage increased at 4 and 8 postoperative days, returning to baseline levels 30 days after off-pump CABG [14]. Platelet activation has also been reported to gradually decrease until day 30, with a sudden increase in aggregation on day 2 [15]. Furthermore, the inhibition of platelet aggregation by aspirin seems to be compromised within a few days after off-pump CABG [16]. In our study, the predominant aetiology of delayed stroke was thrombo-embolism rather than hypoperfusion. Presumably, an increase in coagulability may accelerate the formation of thrombi at atherosclerotic lesions in carotid/cranial arteries. Therefore, high-risk patients may require aggressive anticoagulation/anti-platelet therapy for at least 30 days after off-pump CABG.

Our results raise the question whether patients in the high-risk group require either synchronous or staged carotid revascularisation plus off-pump CABG to prevent delayed stroke. According to a systematic review of patients undergoing staged/synchronous carotid endarterectomy and CABG, the incidence of stroke was around 4%, regardless of the timing of the procedure [17]. Guzman et al. reported that 6.1% of patients developed stroke from the time of prophylactic carotid stenting to 30 days after the CABG procedure [18]. Delayed strokes are usually associated with a better neurologic prognosis than intra-operative strokes [5]. In our study, seven patients (3.6%) in the high-risk group developed delayed stroke, and five of them recovered fully. Patients in the high-risk group were neurologically asymptomatic before surgery, and some of them had significant stenosis in the intracranial arteries rather than in the carotid arteries. Therefore, further investigation is required to elucidate, which patient in the high-risk group will benefit from the prophylactic carotid procedures.

Several limitations of this study needed to be addressed. This study was a retrospective non-randomised observational study. The number of study patients was relatively small (n = 611), and only eight delayed strokes were observed. This does not allow multivariate analysis to evaluate the independent effect of variables on the occurrence of delayed stroke. Imaging modalities (MRI/MRA, CT, angiography and ultrasonography) could make a diagnosis of thrombo-embolic stroke, and most of the delayed strokes occurred distal to the significant carotid/cranial artery stenosis. Although the thrombus was potentially derived from the heart, echocardiography could not reveal an intracardiac thrombus at the time of delayed strokes. We also did not investigate the haematologic variables of patients undergoing off-pump CABG. Therefore, further assessment would be required to confirm our hypothesis.

In conclusion, no intra-operative stroke was observed after off-pump CABG even in patients with significant cerebrovascular disease. However, these patients were likely to develop delayed stroke within 30 days of surgery.

4. Discussion

Table 5

<table>
<thead>
<tr>
<th>Stroke rate after off-pump CABG.</th>
<th>Stroke rate &lt;1 month</th>
<th>Stroke rate ≥1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk group</td>
<td>3.75 (7/196)</td>
<td>0.14 (10/189)</td>
</tr>
<tr>
<td>Low-risk group</td>
<td>0.24 (1/415)</td>
<td>0.05 (10/414)</td>
</tr>
</tbody>
</table>

The incidence rates are not constant over time. Peel et al. reported that the incidence of delayed stroke increased rapidly after the day of off-pump CABG, reached a peak on postoperative day 4, and then decreased exponentially [13]. In our study, the incidence rate of stroke (stroke rate) in the high-risk group was much higher within 1 month (3.57) of off-pump CABG than that beyond 1 month (0.14) (Table 5).

One possible explanation for these phenomena is the increase in coagulability during the early postoperative period. According to a study by Parolari et al., activation of the coagulation–fibrinolytic system and endothelial cell damage increased at 4 and 8 postoperative days, returning to baseline levels 30 days after off-pump CABG [14]. Platelet activation has also been reported to gradually decrease until day 30, with a sudden increase in aggregation on day 2 [15]. Furthermore, the inhibition of platelet aggregation by aspirin seems to be compromised within a few days after off-pump CABG [16]. In our study, the predominant aetiology of delayed stroke was thrombo-embolism rather than hypoperfusion. Presumably, an increase in coagulability may accelerate the formation of thrombi at atherosclerotic lesions in carotid/cranial arteries. Therefore, high-risk patients may require aggressive anticoagulation/anti-platelet therapy for at least 30 days after off-pump CABG.

Our results raise the question whether patients in the high-risk group require either synchronous or staged carotid revascularisation plus off-pump CABG to prevent delayed stroke. According to a systematic review of patients undergoing staged/synchronous carotid endarterectomy and CABG, the incidence of stroke was around 4%, regardless of the timing of the procedure [17]. Guzman et al. reported that 6.1% of patients developed stroke from the time of prophylactic carotid stenting to 30 days after the CABG procedure [18]. Delayed strokes are usually associated with a better neurologic prognosis than intra-operative strokes [5]. In our study, seven patients (3.6%) in the high-risk group developed delayed stroke, and five of them recovered fully. Patients in the high-risk group were neurologically asymptomatic before surgery, and some of them had significant stenosis in the intracranial arteries rather than in the carotid arteries. Therefore, further investigation is required to elucidate, which patient in the high-risk group will benefit from the prophylactic carotid procedures.

Several limitations of this study needed to be addressed. This study was a retrospective non-randomised observational study. The number of study patients was relatively small (n = 611), and only eight delayed strokes were observed. This does not allow multivariate analysis to evaluate the independent effect of variables on the occurrence of delayed stroke. Imaging modalities (MRI/MRA, CT, angiography and ultrasonography) could make a diagnosis of thrombo-embolic stroke, and most of the delayed strokes occurred distal to the significant carotid/cranial artery stenosis. Although the thrombus was potentially derived from the heart, echocardiography could not reveal an intracardiac thrombus at the time of delayed strokes. We also did not investigate the haematologic variables of patients undergoing off-pump CABG. Therefore, further assessment would be required to confirm our hypothesis.

In conclusion, no intra-operative stroke was observed after off-pump CABG even in patients with significant cerebrovascular disease. However, these patients were likely to develop delayed stroke within 30 days of surgery.

References


