Cerebral Lesions in Patients Undergoing Coronary Artery Bypass Grafting in Relation to Asymptomatic Carotid and Vertebral Artery Stenosis

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Objectives: Carotid artery stenosis (CAS) and vertebral artery stenosis (VAS) are associated with cerebral infarction after coronary artery bypass surgery (CABG). It remains unclear whether this association is causal. We investigated the associations between neurologically asymptomatic CAS and VAS and the occurrence of subclinical cerebral lesions after CABG verified by magnetic resonance imaging.

Methods: CABG patients were included and CAS and VAS were identified by magnetic resonance angiography. Cerebral magnetic resonance imaging was performed to identify new post-operative subclinical cerebral lesions. The associations between CAS/VAS post-operative cerebral lesions were investigated.

Results: Forty-six patients were included in the study. 13% had significant CAS and 11% had significant VAS. Thirty-five percent had new cerebral infarction postoperatively. We found a significant association between the presence of cerebral vessel stenosis and acute cerebral infarction (67% vs. 27%, \( p = 0.047 \)). However none of the patients with stenosis had isolated cerebral lesions in the ipsilateral vascular territory.

Conclusion: Asymptomatic CAS and VAS is common in CABG patients and is associated with an increased risk of postoperative cerebral infarction. Our study suggests that asymptomatic CAS and VAS primarily are risk markers rather than causal factors for cerebral infarction after CABG.

Keywords: Carotid stenosis, cerebral infarction

Introduction

Ischemic stroke remains one of the most feared complications to cardiac surgery. The risk of developing stroke after cardiac surgery is somewhere between 2% and 6%.1–4 It is well known that many patients undergoing coronary artery bypass grafting (CABG) have stenosis of their internal carotid arteries due to atherosclerosis, and it is evident that both the presence and severity of this disease increase the risk of stroke.5,6

The natural history of asymptomatic, carotid stenosis under best medical treatment is poorly understood, and it remains unclear whether asymptomatic carotid stenosis primarily is an etiological factor for stroke or simply a marker of increased risk.7–9 This makes the treatment of patients with asymptomatic, significant carotid artery stenosis undergoing cardiac surgery a controversial issue, often attracting polarised opinions.7,10–13 The differing interpretations have led to varying guidelines regarding whether to screen CABG patients for carotid stenosis and in turn whether to treat asymptomatic patients with carotid endarterectomy, carotid artery stenting or simply best medical treatment.14–17

Symptomatic vertebral artery stenosis is a major predictor of recurrent ischemic stroke in the posterior circulation.18 In addition asymptomatic patients with vertebral artery stenosis are reported to have a higher risk of ischemic stroke than patients without this disease, however, investigation and treatment of vertebral artery territory stroke has received much less attention than that of stroke in the carotid territory.19 The consequence of vertebral artery stenosis among CABG patients is unknown.
The purpose of this study was to examine the prevalence of acute subclinical cerebral infarction as well as the prevalence of significant, asymptomatic carotid and vertebral artery stenosis in a population undergoing CABG. In addition this study sought to establish whether the presence of asymptomatic carotid and vertebral artery stenosis primarily is useful for risk prediction or for establishing causality for acute subclinical cerebral infarction after CABG.

Material and Methods

The study population was derived from all patients undergoing CABG at our hospital from February to August 2012. The participants were recruited on the day of admission. Inclusion criteria were indication for CABG and age above 18 years. Exclusion criteria were stroke or transient ischemic attack (TIA) within the past 6 months in order to rule out patients with symptomatic carotid or vertebral artery stenosis. Other exclusion criteria were indication for carotid endarterectomy (CEA), simultaneous valve intervention and contraindications to magnetic resonance imaging (MRI) such as implanted cardiac pacemakers. In addition patients with claustrophobia and severe nausea were excluded. All participants provided written informed consent and the study was approved by the National Committee on Health Research Ethics, reference H-4-2011-092.

The study design was cross-sectional. Contrast enhanced magnetic resonance angiography (CE-MRA) was performed between three and seven days after surgery in order to assess the prevalence of carotid and vertebral artery stenosis in the population. Concomitant to the CE-MRA the participants underwent cerebral magnetic resonance diffusion-weighted imaging (DWI) between three and seven days after surgery, which was used to assess the occurrence of peri- or postoperative acute infarction in the population.

The MRI studies were obtained with a 3.0-Tesla (Siemens Verio) whole-body scanner using a standardized protocol. Comparison of CE-MRA and DWI was used to identify associations between carotid and vertebral artery stenosis and subclinical cerebral infarction in the individual patients.

Contrast-enhanced magnetic resonance angiography

CE-MRA is established as an accurate non-invasive method for measuring degrees of carotid stenosis.\(^{20,21}\) 15 ml of Gadolinium was used as the contrast agent. Two patients had allergy to Gadolinium contrast and had Time-of-Flight MRA sequences instead of CE-MRA (Fig. 1). The CE-MRA images were blinded and presented the principal investigator minimum a month after completion of the scans. The degree of carotid artery stenosis was assessed by measurements of the smallest transverse diameter at the level of the stenosis compared to the diameter of the distal uninvolved vessel where the arterial walls are parallel.

\[
\text{Stenosis} = \frac{\text{diameter of distal uninvolved artery} - \text{smallest transverse diameter}}{\text{diameter of distal uninvolved artery}} \times 100\%
\]

Non-significant stenosis was defined as a stenosis diameter of <50% and significant stenosis was defined as stenosis diameter >50%.\(^{22,23}\) Vertebral artery stenosis was assessed in a similar fashion.

Cerebral magnetic resonance diffusion-weighted imaging

Cerebral DWI is established as a highly accurate modality for identifying regions of cerebral ischemia and for distinguishing the acute from the non-acute cerebral infarction. Acute infarction can be distinguished from non-acute infarction for up to 10 days.\(^{24,25}\) The DWI scans were used to establish the presence and volume of existing infarcts and to distinguish acute from non-acute cerebral infarction among the participants. The DWI scans were obtained on the same scanner as the CE-MRA. The DWI images from the cerebral MRIs were interpreted by one of the principal investigators blinded to the results of the CE-MRA studies. The images were analysed for the presence, number and volume of acute DWI lesions. Acute lesions smaller than 0.2 cm\(^3\) were reported as <0.2 cm\(^3\) due to the limited spatial resolution of MRI. Acute lesion volumes greater than 0.2 cm\(^3\) were reported in their actual size. (Fig. 1)

Surgical Procedures

Cardiopulmonary bypass was established by aortic cannulation and a two-stage venous cannula in the right atrium. Patients were fully heparinised (activated clotting time >480 s). Cardiac arrest was achieved with cold blood cardioplegia and extracorporeal circulation was performed under normothermia. Surgical access to the heart was gained through a median sternotomy in all of the patients. The left internal mammary artery and great saphenous vein were harvested. If veins were of poor quality a radial artery from the non-dominant hand was used. The left internal mammary artery was anastomosed whenever indicated to the left anterior descending coronary artery.

Standard anaesthetic techniques were used and intraoperative monitoring was in accordance with guidelines. The surgical volume of patients and their clinical outcome are comparable to other high-volume heart centres. Standard guidelines for anti-coagulation therapy were used. Before elective CABG anti-coagulation therapy was...
Asymptomatic Carotid Stenosis in CABG-Patients

Categorical variables were presented as percentages and comparison between participants and non-participants was analyzed with the $\chi^2$ statistic. If the expected cell count was $< 5$ the Fisher’s exact test was used. Continuous variables were presented as mean $\pm$ standard deviation if normally distributed.

**Results**

**Baseline characteristics**

A total of 298 patients underwent CABG during the inclusion period. Of these patients 46 were included as participants in the study. The participants were compared to the non-participants in order to evaluate possible selection bias in this non-consecutive series. However, the groups were well balanced. (Table 1) Five patients (9%) suffered from preoperative atrial fibrillation. Additional baseline data for the participants are presented in Table 2.

**Statistical Analysis**

Statistical analyses were performed using the SAS Enterprise Guide statistical software version 4.3. A nominal level of 5% statistical significance (two tailed) was assumed throughout.

If the patient suffered from unstable angina or had stenosis of the left mainstem, acetylsalicylic acid and low-molecular-weight heparin was continued until the evening before CABG. In case of treatment with fondaparinux this was paused 48 h before CABG. Treatment with warfarin due to atrial fibrillation was paused 3 days prior to CABG. During surgery 3.5 mg/kg of unfractionated heparin was given before cardiopulmonary bypass was initiated resulting in an activated clotting time above 480 s. After cardiopulmonary bypass was finished protamine sulfate was given until the activated clotting time was below 125 s. In the postoperative period of immobilization 4000 international units of enoxaparin was given once daily. Lifelong postoperative treatment with acetylsalicylic acid as well as patients’ previous anti-coagulation therapy was restarted on the second day after CABG.
Table 1  Baseline characteristics of participating vs. non-participating patients

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Non-participants</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender (%)</td>
<td>91.3</td>
<td>82.9</td>
<td>0.150</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.0 ± 9.0</td>
<td>67.5 ± 9.8</td>
<td>0.765</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>73.9</td>
<td>83.6</td>
<td>0.115</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>82.2</td>
<td>72.0</td>
<td>0.152</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>58.5</td>
<td>58.4</td>
<td>0.987</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>60.9</td>
<td>58.2</td>
<td>0.732</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22.2</td>
<td>27.5</td>
<td>0.406</td>
</tr>
<tr>
<td>Renal Failure (%)</td>
<td>4.4</td>
<td>6.4</td>
<td>0.257</td>
</tr>
<tr>
<td>NYHA Class 0–2 (%)</td>
<td>84.2</td>
<td>72.7</td>
<td></td>
</tr>
<tr>
<td>NYHA Class &gt;2 (%)</td>
<td>15.8</td>
<td>27.3</td>
<td>0.412</td>
</tr>
<tr>
<td>CCS Class 0–2 (%)</td>
<td>70.7</td>
<td>73.1</td>
<td></td>
</tr>
<tr>
<td>CCS Class &gt;2 (%)</td>
<td>29.3</td>
<td>26.9</td>
<td>0.086</td>
</tr>
<tr>
<td>Previous Stroke or TIA (%)</td>
<td>6.5</td>
<td>13.6</td>
<td>0.185</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>54.4</td>
<td>52.8</td>
<td>0.820</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction; TIA: Transient ischemic attack; NYHA: New York Heart Association functional classification; CCS: Canadian Cardiovascular Society grading of angina pectoris

Table 2  Baseline characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referal diagnosis</td>
<td>Stable angina</td>
</tr>
<tr>
<td></td>
<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>NSTEMI</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Instilto</td>
</tr>
<tr>
<td>Preoperative atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Number of coronary lesions</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Coronary vessel disease</td>
<td>1-VD</td>
</tr>
<tr>
<td></td>
<td>2-VD</td>
</tr>
<tr>
<td></td>
<td>3-VD</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;49</td>
</tr>
<tr>
<td></td>
<td>30–49</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
</tr>
<tr>
<td>Left main stem disease</td>
<td></td>
</tr>
</tbody>
</table>

VD: Vessel disease

Patient outcomes
Postoperatively one participant (no. 94) suffered a clinical stroke (day 0) with light paresis of the upper left extremity. Description of the cerebral MRI-scan for this patient can be viewed in Table 3. The paresis was resolving on day 2. There was no development of neurological symptoms among the other participants.

CE-MRA
A total of 11 out of 46 participants (24%) had signs of carotid artery plaque (i.e., all carotid stenoses visible on CE-MRA). Three of the participants had bilaterally distributed plaques. Six participants (13%) had significant carotid artery stenosis (i.e., carotid stenosis diameter >50%), and five participants (11%) had significant vertebral artery stenosis.

DWI
16 out of 46 participants (35%) had evidence of acute cerebral infarction ranging from <0.2 cm³ to 3.7 cm³ (Fig. 1). Twelve of the participants with acute cerebral infarction (25%) had multiple lesions, and in 10 participants (22%), the multiple lesions occurred in more than one vascular territory. Eight of the participants with multiple lesions had bilaterally distributed lesions (Table 3).
unchanged since 200226,27) which is highly clinically rele-

mic circulatory arrest. One patient (2%) suffered a clini-

during or shortly after on-pump CABG with normo ther-

subclinical cerebral infarctions (range, 1 to 12 lesions)

three CABG patients (33%) developed DWI-verifi ed acute

Discussion

In this study population, which was very similar to the

background population of consecutively operated CABG

patients (Table 1), we found that approximately one in

three CABG patients (33%) developed DWI-verified acute

subclinical cerebral infarctions (range, 1 to 12 lesions)

during or shortly after on-pump CABG with normo ther-

circulatory arrest. One patient (2%) suffered a clini-
cal stroke. The rate of subclinical infarction remains

unchanged since 200226,27) which is highly clinically rele-

vant since subclinical infarctions are associated with cog-
nitive decline.28)

Two in three patients (67%) with either asymptomatic

significant carotid or vertebral artery stenosis developed

subclinical cerebral infarction compared to only a quarter

of the patients (27%) without stenoses. This confirms that

stenosis of the cerebral vessels is an important risk factor

for cerebral infarction after CABG. On the other hand

two in three patients with subclinical cerebral infarction

(63%) did not have either carotid artery or vertebral artery

stenosis, confirming that many other factors contribute to

the development of cerebral infarction after CABG.

More than one third of the patients (39%) had peri- or

postoperative atrial fi brillation during their admission.

However, the incidence of cerebral infarction was identi-
cal in the group with versus without atrial fi brillation

(33% vs. 36%, p = 0.869). This suggests that peri- or

postoperative atrial fi brillation is not a risk factor for

cerebral infarction after CABG. The reason for this fi nd-
ing can well be, that patients during admission are treated

rapidly as soon as atrial fi brillation is diagnosed, and that

thrombus thus does not form in the atrium (Table 4).

Among patients with stenosis of the cerebral vessels

and acute cerebral infarction, none had isolated cerebral

lesions in the vascular territory of the ipsilateral stenotic

artery, which should have been the case, had the carotid

stenosis been the etiological factor for the infarction. The

only patient with isolated infarction in the carotid

circulation did not have vertebral artery stenosis.

Finally, in the fi ve patients with multiple cerebral

lesions, where one of the infarct locations could be caused

by emboli from the stenotic artery (termed ‘partial’ in

Table 3) all had additional cerebral lesions with no asso-

ciation between the location of the stenotic artery and

the vascular territory. Thus, asymptomatic carotid and

vertebral artery stenosis primarily seem to be markers for

increased infarction risk rather than ethological factors

(Table 3).

There are a number of limitations to this study. Pri-

marily, the study was slightly underpowered, yielding a

strong yet insignifi cant trend regarding the association of

isolated asymptomatic carotid stenosis and post-operative

cerebral infarction. Never the less this study is the larg-
est of its kind. The inclusion of the participants was

Table 3 Overview of Participants with DWI identified acute cerebral infarcts

<table>
<thead>
<tr>
<th>Participant no.</th>
<th>No. of infarcts</th>
<th>Total infarct volume (cm³)</th>
<th>Vascular territories</th>
<th>Right/Left side</th>
<th>Carotid Stenosis</th>
<th>Vertebral Stenosis</th>
<th>Corresponding Stenosis/Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>1</td>
<td>&lt;0.2</td>
<td>Posterior</td>
<td>Left</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>194</td>
<td>1</td>
<td>0.3</td>
<td>Posterior</td>
<td>Left</td>
<td>Right</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>224</td>
<td>1</td>
<td>&lt;0.2</td>
<td>Medial</td>
<td>Left</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>244</td>
<td>1</td>
<td>&lt;0.2</td>
<td>Posterior</td>
<td>Right</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>240</td>
<td>2</td>
<td>0.2</td>
<td>Anterior, Posterior</td>
<td>Right</td>
<td>None</td>
<td>Right</td>
<td>Partial</td>
</tr>
<tr>
<td>297</td>
<td>2</td>
<td>&lt;0.2</td>
<td>Posterior</td>
<td>Right</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>265</td>
<td>2</td>
<td>&lt;0.2</td>
<td>Medial, Posterior</td>
<td>Both</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>268</td>
<td>2</td>
<td>3.7</td>
<td>Posterior</td>
<td>Right</td>
<td>None</td>
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<td>No</td>
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<td>79</td>
<td>3</td>
<td>0.8</td>
<td>Posterior</td>
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<td>None</td>
<td>No</td>
</tr>
<tr>
<td>238</td>
<td>3</td>
<td>&lt;0.2</td>
<td>Medial, Posterior</td>
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<td>None</td>
<td>Left</td>
<td>Partial</td>
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<tr>
<td>58</td>
<td>7</td>
<td>0.7</td>
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<td>Both</td>
<td>Occlusion, Right</td>
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<td>Partial</td>
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<tr>
<td>298</td>
<td>8</td>
<td>2.5</td>
<td>All territories</td>
<td>Both</td>
<td>Right</td>
<td>Occlusion, Left</td>
<td>Partial</td>
</tr>
<tr>
<td>206</td>
<td>10</td>
<td>0.3</td>
<td>All territories</td>
<td>Both</td>
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<td>None</td>
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</tr>
<tr>
<td>94</td>
<td>12</td>
<td>2.1</td>
<td>All territories</td>
<td>Both</td>
<td>None</td>
<td>None</td>
<td>Partial</td>
</tr>
</tbody>
</table>

DWI: Cerebral magnetic resonance diffusion-weighted imaging; *: Patient suffered a clinical stroke
non-consecutive; however the baseline characteristics were similar between participants and all CABG patients. The CE-MRA scans were performed postoperatively. Preferably, all CE-MRA scans should have been completed before surgery and DWI scans after surgery. However, since carotid plaque morphology does not change significantly over a one year period, the impact is small.29)

**Conclusion**

Development of subclinical cerebral infarction after on-pump CABG is frequent and occurs in approximately one third of patients. Asymptomatic, significant carotid artery stenosis is present in 13% of CABG patients. Carotid and vertebral artery stenoses are associated with an increased risk of subclinical cerebral infarction after CABG surgery. However, the lack of connection between the location of the cerebral vessel disease and subsequent post-operative cerebral infarction suggests that the atherosclerotic burden in the arteries supplying the brain primarily is useful for risk prediction rather than establishing causality.

**Disclosure statement**

All authors have no conflicts of interest.

**References**


