Distribution of Perioperative Stroke in Cardiac Surgery
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Running title: Distribution of Perioperative Stroke

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.13793
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ABSTRACT

Background
Recent literature suggests that a cardiac origin in ischemic stroke is more frequent than previously assumed. However, it is not always clear which patients benefit from additional cardiac investigations if obvious cardiac pathology is absent.

Methods
We performed a single-center retrospective observational study in 7454 consecutive patients admitted to the ICU after cardiac surgery in the period 2006-2015 and who had postoperative brain imaging. Cerebral imaging was studied for the occurrence of stroke including subtype and involved vascular territory. We assumed that all perioperative thromboembolic strokes are of cardiac origin. Data obtained from a hospital cohort of consecutive patients who received a diagnosis of ischemic stroke was used for comparison.

Results
Thromboembolic stroke occurred in 135 cardiac surgery patients in which in 56 (41%) the posterior cerebral circulation was involved. In the control group 100 out of 503 strokes (20%) were located in the posterior cerebral circulation. The relative risk for a posterior location for stroke after cardiac surgery compared to patients with ischemic stroke without prior cardiac surgery was 2.09; 95%CI 1.60-2.72.

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Conclusions

Thromboembolic stroke after cardiac surgery occurs twice as much in the posterior cerebral circulation compared to ischemic strokes in the general population. If confirmed in general stroke cohorts, the consequence of this finding may be that in patients with an ischemic stroke that involves the posterior cerebral circulation the chance of a cardiac origin is increased and therefore might trigger additional cardiac investigations like long-term heart rhythm monitoring or echocardiography.

INTRODUCTION

The distribution pattern of thromboembolic stroke is in part related to its etiology. Embolic ischemic stroke originating from atherosclerotic plaques of the carotid bifurcation is located in the anterior cerebral circulation whereas those from plaques in the subclavian or vertebral arteries in the posterior cerebral circulation. Intracardiac thrombi or a ruptured atheroma in the aortic arch may result in thromboembolic stroke in multiple vascular territories. The location may thus provide a clue for the embolic origin of thromboembolic stroke. In general, the anterior circulation is involved in almost three-quarters of all thromboembolic strokes. Of these, occlusion of the middle cerebral artery or its branches is the most common type, accounting for approximately 90% of anterior circulation infarcts.

Strokes in the posterior cerebral circulation are much less common. Possible causes of posterior strokes are atherosclerotic disease of the basilar, vertebral or subclavian arteries, or cardioembolism. Mechanisms from which cardioembolism can occur include atrial fibrillation, valvular pathology or replacement, a mural thrombus associated with myocardial infarction, dilated cardiomyopathy, or ventricular aneurysm.
Recent literature suggests that stroke from a cardiac origin is more frequent than previously assumed.\textsuperscript{6,7} However, it is unclear which patients benefit from additional cardiac investigations if a clear cardiac pathology, e.g. atrial fibrillation, endocarditis, or valve disease is absent. The mainstay of clinical diagnosis is the presence of a potential major cardiac source of embolism in the absence of significant arterial disease. Diagnosing this type of emboli becomes more difficult when cardiac and arterial disease coexist.\textsuperscript{8,9} About 20-30\% of all ischemic strokes remain cryptogenic after standard evaluation.\textsuperscript{10} It would be helpful to determine a distinguished pattern that could guide clinicians towards a potential cardiac etiology.

A possible approach to increase the chance of finding a cardiac etiology is to look for differences in the affected cerebral arterial territories between cardioembolic stroke and non-cardioembolic stroke. For that reason we studied thromboembolic stroke after cardiac surgery that was assumed to be of cardiac origin in all cases. Ischemic stroke after cardiac surgery has an incidence of about 2\%.\textsuperscript{11,12} We hypothesised that thromboembolic stroke after cardiac surgery was more often localized in the posterior cerebral circulation compared to patients hospitalized with ischemic stroke without prior cardiac surgery. This theory was based on findings of a cohort study in stroke patients in which a multiple ischemic lesion pattern in the posterior circulation was associated with the presence of a patent foramen ovale (PFO).\textsuperscript{13}

**METHODS**

*Study design and inclusion criteria*

Ethical approval was obtained at April 8th 2014 from the Medical Ethics Committee of the University Medical Center Groningen and known under number METc 2014/154. The
Medical Ethics Committee waived the need for patient consent. We performed a retrospective observational study including all consecutive patients who were admitted to the ICU at the University Medical Center Groningen after cardiac surgery during November 2006 until November 2015. Patients who had postoperative brain imaging (CT or MRI) during their hospital stay following cardiac surgery were selected by means of radiological codes used to invoice healthcare consumption in our hospital and included in this study. Type of cardiac surgery (e.g. CABG or valve procedure) was based on corresponding cardiac surgery codes. *In order to complete the specific relevant data belonging to the selected patients, information from the electronic patient dossiers were used.*

All patients had at least one brain imaging or follow-up brain imaging one day or more after cardiac surgery. At first images were rated without prior knowledge of the clinical symptoms as described in the patients file and radiological reports. The brain images were rated independent by the first (RP) and senior author (WMvdB) to distinguish between hemorrhagic, thromboembolic, air embolism, or hemodynamic stroke with or without involvement of typical watershed areas and to determine if the clinical symptoms that triggered brain imaging correlated with the site and age of the lesion and then compared with the original radiological reports. Differentiation between an ‘old’ infarct, e.g. existing prior to surgery, and an acute infarct was based both on findings on brain imaging and the occurrence of clinical symptoms that triggered brain imaging. In case of discrepancies the findings were discussed until consensus was reached.

We categorized stroke localisation based on the modified Oxfordshire method that classifies the infarcts based on their anatomic distribution into four groups: total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI), and lacunar infarcts (LACI).\(^\text{14}\) Besides the Oxfordshire criteria we defined hemodynamic stroke as infarction on brain imaging typically located in the watershed areas.
or global ischemia. These patients were excluded from the analyses. *Small (<2 cm) infarcts that occurred perioperatively that may fulfill the criteria for lacunar stroke were considered thromboembolic stroke in this setting if clinical signs and location of these small ischemic lesions were consonant.* Patients with infarcts in multiple territories that involved the posterior cerebral circulation were considered posterior circulation infarct patients in the primary analysis. *Air emboli were reported as a separate subtype of stroke. If brain imaging did not show any pathological findings other diseases were considered as an explanation, for example global hypoperfusion during surgery, metabolic disturbances, toxic/sedative effects of anaesthetics, or an inexplicable delirium. When both findings on brain imaging and clinical symptoms were not compatible with the diagnosis of stroke, the event was categorized as no stroke.*

*Patients who had brain imaging for other reasons than suspected stroke, e.g. because of (mild) traumatic brain injury during admission, or had brain imaging or neurological symptoms prior to cardiac surgery were excluded.*

*Multiple infarcts were defined as the presence of more than one lesion on brain imaging even if they were located in the same vascular territory and thus may originate from one embolus.*

**Control group**

In the control group, information about stroke distribution was obtained from a consecutive observational prospective cohort from our hospital in the period 2010 until 2015 totalling 503 unique patients with ischemic stroke. In-hospital stroke and thus peri-operative stroke was not included in this cohort so there is no overlap with the study group.
Work-up for these patients was according to a standardized protocol that included a non-contrast brain CT and an ECG. Almost every patient received a CT/MRI angiography including neck vasculature except if patients were in such a poor clinical condition that further treatment was not considered. In case of atrial fibrillation a cardiac etiology for stroke was assumed even in presence of atherosclerosis. On indication (e.g. young stroke, cardiac history, multiple strokes) an echocardiography was performed. In case of valve insufficiency in absence of any other clear cause for stroke or thrombus on echocardiography cardioembolic stroke was also assumed. If a PFO was found in absence of any other clear cause cardioembolic stroke was considered as probable. Stroke localisation was determined according to the methods described in the study population by a vascular neurologist. Stroke type was determined according to the TOAST criteria.

Statistical analyses

To study if the distribution pattern after thromboembolic stroke from a cardiac cause differs from ischemic stroke in the control group Pearson chi-square test was used yielding a crude relative risk with corresponding 95% confidence intervals (CI).

As a cardiac source is associated with a larger risk of multiple thromboembolic infarcts we also compared the incidence of multiple infarcts after cardiac surgery compared to the control group with the same test and also calculated the relative risk for patients with multiple strokes that included the posterior circulation after cardiac surgery compared to the control population.
RESULTS

Of the 7454 patients who underwent cardiac surgery in the study period 463 (6.2%) had postoperative brain imaging and were used for further data complementation. Of these 463 patients 172 patients had brain imaging for other reasons than suspected stroke and 110 patients had no stroke leaving 181 patients (2.3%) with confirmed stroke that were relevant for this study [Table 1]. In 135 (76%) patients the stroke etiology was determined to be thromboembolic, including 8 with lesions <2 cm [Table 2]. Hemodynamic stroke was the presumed cause in 38 (21%) patients. In two-third this was based on involvement of watershed areas and in the remaining on global ischemia. ICH occurred in 5 patients (2%) mainly in presence of coagulation disorders. Air embolism occurred in 3 patients (1%), one each during CABG, valvular, and aorta surgery. The median interval between cardiac surgery and detection of clinical symptoms was 2 days for both ‘all strokes’ and ‘thromboembolic stroke’.

Of the 135 thromboembolic stroke patients, 79 patients (59%) had a stroke restricted to the anterior circulation, in 42 patients (31%) stroke was restricted to the posterior circulation, while in 14 patients (10%) ischemic areas were found in both the anterior and posterior cerebral circulation [Table 3]. That means that in total 56 patients (41%) had a thromboembolic stroke that involved the posterior circulation [Figure 1].

The cohort of ischemic stroke patients not associated with cardiac surgery that was used as control group consisted of 503 patients. Presumed stroke etiology was cardioembolic in 19%, atherosclerotic in 46%, and other or undetermined in 35% of patients. In 100 of them (20%) the posterior cerebral circulation was involved. The relative risk for posterior stroke after cardiac surgery compared to controls was 2.09; 95%CI 1.60-2.72 [Table 4].
Of the 135 patients with thromboembolic stroke after cardiac surgery 27 (20%) had multiple infarcts compared to 44/503 (9%) in the control group: relative risk 2.29; 95% CI 1.47-3.55.

When both analyses are combined 24 (18%) patients out of 135 had multiple thromboembolic infarcts that included the posterior circulation after cardiac surgery compared to 13 (3%) out of 503 in the control group: relative risk 6.88; 95% CI 3.60-13.15.

DISCUSSION

The major finding of this study is that thromboembolic stroke in the setting of cardiac surgery is more likely to affect the posterior circulation than in a cohort outside the setting of cardiac surgery. As our assumption that all perioperative thromboembolic strokes are of cardiac origin is correct, posterior localization is an indication for a cardiac source of thromboembolic stroke. The relative risk for posterior localization almost equals that for multiple infarction that was already postulated to be associated with a cardiac etiology.

Approximately 40% of cerebral blood flow goes to each internal carotic artery and only 20% goes to the posterior circulation. Therefore arithmetically, a fifth of cardiac emboli should end up within the posterior circulation. This number is in line with that from a large cohort study in 538 patients where 28% had a stroke in the posterior circulation.\(^\text{15}\) One-fifth was exactly the percentage of posterior strokes found in our control population, but we did not perform an extended cardiological investigation to confirm or rule out a cardiac source for embolism in all these patients. This might lead to an underestimation of determining stroke origin in cohort studies as the numbers depend on the extent of additional research. In the New England Medical Center posterior circulation registry a cardiac source of embolism was

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reported in 24%. In contrast, the Hallym stroke registry reported that only 11% of 591 Korean patients with posterior circulation strokes had potential cardiac sources of embolism.

However, in our study in which all thromboembolic strokes were assumed to be of cardiac origin the posterior circulation was involved in more than 40% of the patients, suggesting that by an unexplained mechanism more cardiac emboli may end up within the posterior circulation than would be expected based on the cerebral blood flow distribution. Our findings could suggest that thromboembolic stroke in the posterior circulation have an increased risk of being of cardioembolic origin. This may lower the threshold for additional cardiac diagnostic studies like echocardiography or Holter ECGs.

Our findings are in line with a cohort study in stroke patients in which patients with carotid stenosis, other apparent stroke causes such as dissection or vasculitis, or an apparent embolic source were excluded. They found that multiple ischemic lesion patterns in the posterior circulation were associated with the presence of a PFO. Based on a 99mTc-MAA Brain SPECT study this may be caused by an increased blood flow in the posterior circulation compared to that in the anterior circulation in right-to-left shunting during a Valsalva maneuver. However, PFO related stroke may not be a good model for cardioembolism in general, but to our knowledge there are no studies on well-established cardioembolic causes and stroke distribution.

Multiple stroke is associated with a cardioembolic source. The possibility of a cardiac source in case of multiple infarcts is strengthened based on the results of our study in which
one-fifth of patients with peri-operative stroke after cardiac surgery had multiple infarcts compared to 9% in the control population. The combination of multiple infarcts and involvement of the posterior circulation was almost 7 times higher compared to the control population.

Several limitations of our study must be addressed. Computer tomography is actually known to have a limited sensitivity when it comes to detecting acute cerebral ischemia, especially in the fossa posterior and perioperative lesions may be quite small in some patients and may therefore easily be missed. As a result in some patients with clinically suspected stroke the CT images did not reveal a stroke as certain cause. However, all patients underwent brain CT one day or later after cardiac surgery, which might increase the sensitivity of finding ischemic changes on brain CT if these occurred intraoperatively. Another reason for underestimation of the actual stroke rate after cardiac surgery is that only 11 of the 291 patients who had a brain CT and were supplementary examined with MRI. Furthermore, we restricted the search to patients after cardiac surgery who had brain imaging. Patients with a fatal stroke may not have had brain imaging and could have been undetected by our search strategy. Although this may be considered a limitation in estimating actual stroke rate after cardiac surgery it does not influence our primary analysis that involves stroke localization. The key element of our analysis was that we assume that all perioperative infarcts were attributed to cardiogenic embolism. Our post cardiac surgery stroke patients didn’t had a systematic screening by means of CT angiography or carotid duplex to rule out atherosclerotic plaques as an alternative explanation for the assumed cardiac origin of the embolus. Only 43 of the 135 patients (31%) with thromboembolic stroke after cardiac surgery had diagnostic work-up by means of a duplex and in 3 (2%) patients a MR-angiography was also performed revealing 11 patients with carotid stenosis (>70%) and 4 patients with

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vertebral artery stenosis. However, all 4 patients with vertebral artery stenosis had an anterior
circulation stroke.

At last, we did not have angiographic imaging data from all patients to confirm an occlusion
of the affected vascular territory. On the other hand we did use a well validated stroke
subtype classification (Oxfordshire) to differentiate stroke location. However, differentiation
between thromboembolic and hemodynamic stroke may be challenging in some patients as
low cerebral perfusion may cause cortical infarcts which may appear embolic in origin.
Although clinical information was also taken into account for determination, brain imaging
could have been misleading and as a result some patients that should have been excluded
because of a non-thromboembolic stroke may have been unjustly included in the analyses.

Information about the patients' clinical condition and the moment symptoms became
recognizable is essential to determine whether a stroke actually did occur during or after
cardiac surgery. The median of two days between surgery and the neurological event was
prolonged in cases where patients remained sedated for an extended period of time. This
obscures the detection of focal symptoms and the actual onset of stroke development.
However, some patients deteriorate several days after surgery due to late stroke onset, for
instance as a complication of atrial fibrillation, but also due to a more gradual development of
the ischemic area. All these patients were included in the analyses and considered to have a
stroke from a cardiac origin.

It is unclear if a post cardiac surgery stroke is a valid model for spontaneous cardio-embolic
stroke in community, which is mainly caused by paroxysmal atrial fibrillation, as post-
operative stroke may result from several causes, including aortic cross clamping or surgical
manipulation, cerebral hypoperfusion, concomitant cardiac pathology (e.g. intra-cardiac

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thrombus, low ejection fraction, valve disease, atrial septal defect) as well as atrial fibrillation.

To address our hypothesis that ischemic stroke in the posterior cerebral circulation in a community cohort increases the chance of a cardiac origin confirmation of our findings is therefore warranted.

CONCLUSION

There is a difference in the distribution pattern between thromboembolic stroke after cardiac surgery and thromboembolic stroke occurring in the community. Translated to the general population this may implicate that ischemic stroke located in the posterior cerebral circulation doubles the chance of a cardiac origin. This chance is further increased in presence of multiple strokes. If our findings are confirmed in general stroke cohorts, ischemic stroke located in the posterior cerebral circulation, may lower the threshold for initiating additional cardiac diagnostic studies in order to point towards a cardiac source in these patients.

REFERENCES


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distribution through patent foramen ovale demonstrated by 99mTc-MAA brain

MD, Patronas N, Latour L, Warach S et al. Magnetic Resonance Imaging and
Computed Tomography in Emergency Assessment of Patients With Suspected Acute

Table 1. Baseline characteristics of the patients with stroke after cardiac surgery (study
group; n=181) and the observational cohort of patients with ischemic stroke (controls; n=503)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (n=181)</th>
<th>Control group (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Female sex</td>
<td>66 (37%)</td>
<td>201 (40%)</td>
</tr>
<tr>
<td>Type of cardiac surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>101 (56%)</td>
<td></td>
</tr>
<tr>
<td>Valve surgery</td>
<td>98 (54%)</td>
<td></td>
</tr>
<tr>
<td>Aorta surgery</td>
<td>39 (26%)</td>
<td></td>
</tr>
<tr>
<td>Rethoracotomy</td>
<td>29 (16%)</td>
<td></td>
</tr>
<tr>
<td>Cardio-pulmonary bypass during surgery</td>
<td>145 (80%)</td>
<td></td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>104 (58%)</td>
<td>60 (12%)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>31 (17%)</td>
<td>106 (21%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>48 (27%)</td>
<td>91 (18%)</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>Condition</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90 (50%)</td>
<td>206 (41%)</td>
</tr>
<tr>
<td>Hypercholesterolemia/ lipidemia</td>
<td>22 (12%)</td>
<td>181 (36%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>19 (11%)</td>
<td>35 (7%)</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>15 (8%)</td>
<td>141 (28%)</td>
</tr>
<tr>
<td>Recent history of smoking</td>
<td>10 (6%)</td>
<td>151 (30%)</td>
</tr>
</tbody>
</table>

1. Latest surgery prior to stroke

Table 2. Stroke subtypes in all 181 patients with stroke after cardiac surgery

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic stroke</td>
<td>135 (76%)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Air embolism</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>38 (21%)</td>
</tr>
</tbody>
</table>

Table 3. Stroke localization and number of infarcts in patients with cardioembolic stroke (n=135)

<table>
<thead>
<tr>
<th>Localization</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior circulation</td>
<td>79 (59%)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>42 (31%)</td>
</tr>
<tr>
<td>Both anterior/posterior</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Number of infarcts</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>108 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Table 4. Posterior stroke and multiple strokes after cardiac surgery compared with observational cohort (controls)

<table>
<thead>
<tr>
<th></th>
<th>Thromboembolic stroke after cardiac surgery (n=135)</th>
<th>Ischemic stroke controls (n=503)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior stroke</td>
<td>56 (41%)</td>
<td>100 (20%)</td>
<td>2.09 (1.60-2.27)</td>
</tr>
<tr>
<td>Multiple strokes</td>
<td>27 (20%)</td>
<td>44 (9%)</td>
<td>2.29 (1.47-3.55)</td>
</tr>
<tr>
<td>Localization multiple strokes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>3 (11%)</td>
<td>31 (70%)</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>10 (37%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Anterior/Posterior</td>
<td>14 (52%)</td>
<td>11 (25%)</td>
<td></td>
</tr>
<tr>
<td>Posterior &amp; multiple</td>
<td>24 (18%)</td>
<td>13 (3%)</td>
<td>6.88 (3.60-13.15)</td>
</tr>
</tbody>
</table>
Figure 1. Flowchart of the study population (posterior stroke in gray)

Cardiac surgery group