ORIGINAL ARTICLE

Distribution of perioperative stroke in cardiac surgery

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Background and purpose: The recent literature suggests that a cardiac origin in ischaemic 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: A single-center retrospective observational study was performed with 7454 consecutive patients admitted to the intensive care unit 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. It was assumed that all perioperative thromboembolic strokes are of cardiac origin. Data obtained from a hospital cohort of consecutive patients who received a diagnosis of ischaemic stroke were used for comparison.

Results: Thromboembolic stroke occurred in 135 cardiac surgery patients in 56 (41%) of whom 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 ischaemic stroke without prior cardiac surgery was 2.09; 95% confidence interval 1.60–2.72.

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

Introduction

The distribution pattern of thromboembolic stroke is in part related to its etiology [1]. Embolic ischaemic stroke originating from atherosclerotic plaques of the carotid bifurcation is located in the anterior cerebral circulation whereas strokes from plaques in the subclavian or vertebral arteries are located 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 [2,3].

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 [4,5].

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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.

The recent literature suggests that stroke from a cardiac origin is more frequent than previously assumed [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 embolism becomes more difficult when cardiac and arterial disease coexist [8,9]. About 20%–30% of all ischaemic strokes remain cryptogenic after standard evaluation [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 thromboembolic stroke after cardiac surgery that was assumed to be of cardiac origin in all cases was studied. Ischaemic stroke after cardiac surgery has an incidence of about 2% [11,12]. It was hypothesized that thromboembolic stroke after cardiac surgery was more often localized in the posterior cerebral circulation compared to patients hospitalized with ischaemic stroke without prior cardiac surgery. This theory was based on findings of a cohort study in stroke patients in which a multiple ischaemic lesion pattern in the posterior circulation was associated with the presence of a patent foramen ovale (PFO) [13].

Methods

Study design and inclusion criteria

Ethical approval was obtained on 8 April 2014 from the Medical Ethics Committee of the University Medical Center Groningen under number METc 2014/154. The Medical Ethics Committee waived the need for patient consent. A retrospective observational study was performed including all consecutive patients who were admitted to the intensive care unit at the University Medical Center Groningen after cardiac surgery between November 2006 and November 2015. Patients who had postoperative brain imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] during their hospital stay following cardiac surgery were selected by means of radiological codes used to invoice healthcare consumption in our hospital and were included in this study. Type of cardiac surgery [e.g. coronary artery bypass graft (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 was used.

All patients had at least one brain imaging or follow-up brain imaging 1 day or more after cardiac surgery. At first, images were rated without prior knowledge of the clinical symptoms as described in the patient's file and radiological reports. The brain images were rated independently by the first author (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; then the ratings were 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 the case of discrepancies, the findings were discussed until consensus was reached.

Stroke localization was categorized based on the modified Oxfordshire method that classifies the infarcts based on their anatomical distribution into four groups: total anterior circulation infarcts, partial anterior circulation infarcts, posterior circulation infarcts and lacunar infarcts [14]. Besides the Oxfordshire criteria, hemodynamic stroke was defined as infarction on brain imaging typically located in the watershed areas or global ischaemia. These patients were excluded from the analyses. Small (<2 cm) infarcts that occurred perioperatively that may fulfil the criteria for lacunar stroke were considered thromboembolic stroke in this setting if the clinical signs and location of these small ischaemic 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, e.g. global hypoperfusion during surgery, metabolic disturbances, toxic/sedative effects of anesthetics 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 2010–2015 totaling 503 unique patients with ischaemic stroke. In-hospital stroke and thus perioperative stroke was not included in this cohort so there is no overlap with the study group.

The work-up for these patients was according to a standardized protocol that included a non-contrast brain CT and an electrocardiogram. 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 the case of atrial fibrillation, a cardiac etiology for stroke was assumed even in the presence of atherosclerosis. On indication (e.g. young stroke, cardiac history, multiple strokes), an echocardiography was performed. In the case of valve insufficiency in the absence of any other clear cause for stroke or thrombus on echocardiography, cardioembolic stroke was again assumed. If a PFO was found in the absence of any other clear cause, cardioembolic stroke was considered as probable. Stroke localization was determined according to the methods described for 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 ischaemic stroke in the control group the Pearson chi-squared test was used yielding a crude relative risk with corresponding 95% confidence interval (CI).

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

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 who were relevant for this study (Table 1). In 135 (76%) patients, the stroke etiology was determined to be thromboembolic, including eight with lesions <2 cm (Table 2). Hemodynamic stroke was the presumed cause in 38 (21%) patients. In two-thirds, this was based on involvement of watershed areas and in the remaining on global ischaemia. Intracerebral hemorrhage occurred in five patients (2%) mainly in the presence of coagulation disorders. Air embolism occurred in three 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

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

Variable	Study group ($n = 181$) N (%)	Control group ($n = 503$) N (%)
Mean age (years)	68	68
Female sex	66 (37%)	201 (40%)
Type of cardiac surgery		
CABG	101 (56%)	
Valve surgery	98 (54%)	
Aorta surgery	39 (26%)	
Rethoracotomy[a]	29 (16%)	
Cardio-pulmonary bypass during surgery	145 (80%)	
History of ischaemic heart disease	104 (58%)	60 (12%)
History of stroke	31 (17%)	106 (21%)
Diabetes mellitus	48 (27%)	91 (18%)
Chronic obstructive pulmonary disease	25 (14%)	–
Hypertension	90 (50%)	206 (41%)
Hypercholesterolemia/ lipidemia	22 (12%)	181 (36%)
Peripheral vascular disease	19 (11%)	35 (7%)
Carotid stenosis	15 (8%)	141 (28%)
Recent history of smoking	10 (6%)	15 (10%)

[a]Latest surgery prior to stroke.

to the posterior circulation, whilst in 14 patients (10%) ischaemic areas were found in both the anterior and posterior cerebral circulation (Table 3). This means that in total 56 patients (41%) had a thromboembolic stroke that involved the posterior circulation (Fig. 1).

The cohort of ischaemic stroke patients not associated with cardiac surgery that was used as a 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. If our

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

Stroke subtype	N (%)
Thromboembolic stroke	135 (76%)
Intracranial hemorrhage	5 (3%)
Air embolism	3 (2%)
Hypoperfusion	38 (21%)

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

	N (%)
Localization	
Anterior circulation	79 (59%)
Posterior circulation	42 (31%)
Both anterior/posterior	14 (10%)
Number of infarcts	
1	108 (80%)
2	19 (14%)
3	6 (4%)
4	2 (2%)

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 infarctions that was already postulated to be associated with a cardiac etiology.

Approximately 40% of cerebral blood flow goes to each internal carotid 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 [15]. One-fifth was exactly the percentage of posterior strokes found in our control population, but an extended cardiological investigation was not performed 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 reported in 24% [16]. In contrast, the Hallym stroke registry reported that only 11% of 591 Korean patients with posterior circulation strokes had potential cardiac sources of embolism [17].

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 has an increased risk of being of cardioembolic origin. This may lower the threshold for additional cardiac diagnostic studies such as echocardiography or Holter electrocardiogram [4].

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 ischaemic lesion patterns in the posterior circulation were associated with the presence of a PFO [13]. Based on a 99mTc-MAA brain single-photon emission computerized tomography 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 [18]. However, PFO related stroke may not be a good model for cardioembolism in general, but to our knowledge there are no studies on
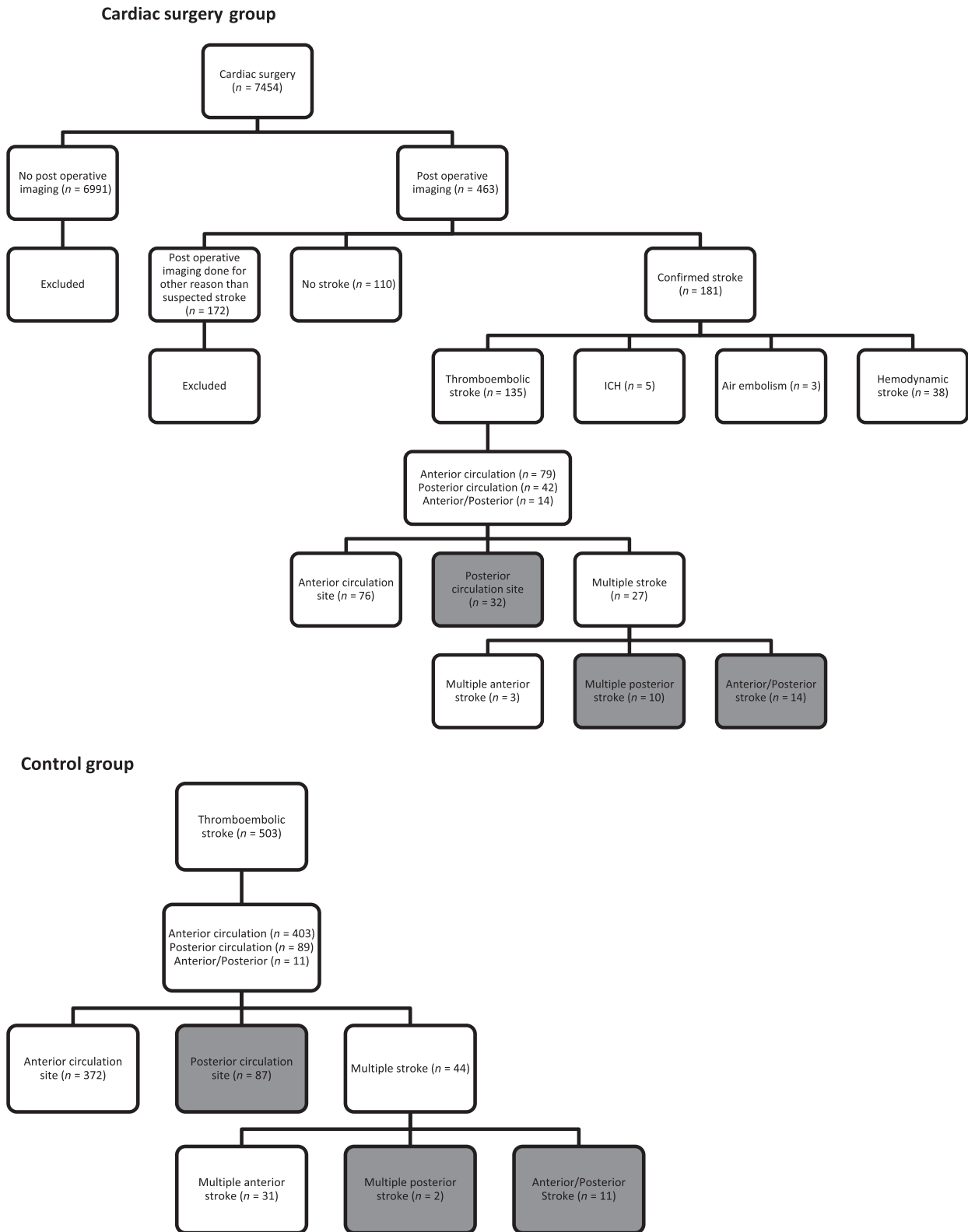
Cardiac surgery group

Control group

Figure 1 Flowchart of the study population (posterior stroke in gray).

Table 4 Posterior stroke and multiple strokes after cardiac surgery compared with the observational cohort (controls)

	Thromboembolic stroke after cardiac surgery (*n* = 135)	Ischaemic stroke controls (*n* = 503)	Relative risk (95% CI)
Posterior stroke	56 (41%)	100 (20%)	2.09 (1.60–2.27)
Multiple strokes	27 (20%)	44 (9%)	2.29 (1.47–3.55)
Localization multiple strokes			
Anterior	3 (11%)	31 (70%)	
Posterior	10 (37%)	2 (5%)	
Anterior/ posterior	14 (52%)	11 (25%)	
Posterior and multiple	24 (18%)	13 (3%)	6.88 (3.60–13.15)

well-established cardioembolic causes and stroke distribution.

Multiple stroke is associated with a cardioembolic source [10,19]. The possibility of a cardiac source in the case of multiple infarcts is strengthened on the basis of the results of our study in which one-fifth of patients with perioperative 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 seven times higher compared to the control population.

Several limitations of our study must be addressed. CT is known to have a limited sensitivity when it comes to detecting acute cerebral ischaemia, especially in the fossa posterior, and perioperative lesions may be quite small in some patients and may therefore be easily missed. As a result in some patients with clinically suspected stroke the CT images did not reveal stroke as a certain cause. However, all patients underwent brain CT 1 day or more after cardiac surgery, which might increase the sensitivity of finding ischaemic 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 were supplementarily examined with MRI. Furthermore, the search was restricted 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 it was assumed that all perioperative infarcts were attributed to cardiogenic embolism. Our post cardiac surgery stroke patients did not have 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 three (2%) patients an MR angiography was also performed revealing 11 patients with carotid stenosis (>70%) and four patients with vertebral artery stenosis. However, all four patients with vertebral artery stenosis had an anterior circulation stroke.

Lastly, angiographic imaging data were not available from all patients to confirm an occlusion of the affected vascular territory. On the other hand, a well-validated stroke subtype classification (Oxfordshire) was used 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 2 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 ischaemic area. All these patients were included in the analyses and were considered to have a stroke from a cardiac origin.

It is unclear if a post cardiac surgery stroke is a valid model for spontaneous cardioembolic stroke in the community, which is mainly caused by paroxysmal atrial fibrillation, as postoperative stroke may result from several causes including aortic cross-clamping or surgical manipulation, cerebral hypoperfusion, concomitant cardiac pathology (e.g. intracardiac thrombus, low ejection fraction, valve disease, atrial septal defect) as well as atrial fibrillation.

To address our hypothesis that ischaemic 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 ischaemic stroke located in the posterior cerebral circulation doubles the chance of a cardiac origin. This chance is further increased in the presence of multiple strokes. If our findings are confirmed in general stroke cohorts, ischaemic 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.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Hankey GJ. Stroke. *Lancet* 2017; **389**(10069): 641–654.
2. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; **337** (8756): 1521–1526.
3. Cillessen JP, Kappelle LJ, van Swieten JC, Algra A, van Gijn J. Does cerebral infarction after a previous warning occur in the same vascular territory? *Stroke* 1993; **24**(3): 351–354.
4. Nouh A, Remke J, Ruland S, *et al*. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. *Front Neurol* 2014; **5**: 30.
5. Tao WD, Liu MD, Fisher M, *et al*. Posterior versus anterior circulation infarction: how different are the neurological deficits? *Stroke* 2012; **43**(8): 2060–2065.
6. Sanna T, Diener HC, Passman RS, *et al*. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; **370**(26): 2478–2486.
7. Gladstone DJ, Spring M, Dorian P, *et al*. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; **370**(26): 2467–2477.
8. Arboix A. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010; **6**: 150–161.
9. Hart RG, Diener HC, Coutts SB, *et al*. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; **13**(4): 429–438.
10. Saver JF. Cryptogenic stroke. *N Engl J Med* 2016; **374**: 2065–2074.
11. Cray da Costa MA, Gauer MF, Gomes RZ, Schafranski MD. Risk factors for perioperative ischemic stroke in cardiac surgery. *Braz J Cardiovasc Surg* 2015; **30**(3): 365–372.
12. Selim M. Perioperative stroke. *N Engl J Med* 2007; **356** (7): 706–713.
13. Jauss M, Wessels T, Trittmacher S, Allendörfer J, Kaps M. Embolic lesion pattern in stroke patients with patent foramen ovale compared with patients lacking an embolic source. *Stroke* 2006; **37**(8): 2159–2161.
14. Rovira A, Grivé E, Alvarez-Sabin J. Distribution territories and causative mechanisms of ischemic stroke. *Eur Radiol* 2005; **15**(3): 416–426.
15. Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. Incidence and prognosis of > or = 50% symptomatic vertebral or basilar artery stenosis: prospective population-based study. *Brain* 2009; **132**: 982–988.
16. Caplan LR, Wityk RJ, Glass TA, *et al*. New England Medical Center posterior circulation registry. *Ann Neurol* 2004; **56**(3): 389–398.
17. Lee JH, Han SJ, Yun YH, *et al*. Posterior circulation ischemic stroke in Korean population. *Eur J Neurol* 2006; **13**(7): 742–748.
18. Hayashida K, Fukuchi K, Inubushi M, Fukushima K, Imakita S, Kimura K. Embolic distribution through patent foramen ovale demonstrated by 99mTc-MAA brain SPECT after Valsalva radionuclide venography. *J Nucl Med* 2001; **42**: 859–863.
19. Chalela JA, Kidwell CS, Nentwich LM, *et al*. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet* 2007; **369**(9558): 293–298.