Lack of Evidence for Pulmonary Venous Thrombosis in Cryptogenic Stroke
A Magnetic Resonance Angiography Study

Armin J. Grau, MD; Stefan O. Schoenberg, MD; Christoph Lichy, MD; Florian Buggle, MD; Michael Bock, PhD; Werner Hacke, MD

Background—Even after extensive evaluation, the etiology of ischemic stroke remains undefined in a considerable proportion of cases, suggesting that causes of stroke may exist that have not yet been established. We tested the hypothesis that pulmonary venous thrombosis (PVT) is a potential source of brain embolism in patients with cryptogenic stroke.

Summary of Report—Within 7 days after mild to moderately severe ischemic stroke or transient ischemic attack, 18 patients (9 women, 9 men; mean age, 48 years) were studied in whom the etiology remained undefined despite complete workup. All patients received high-resolution pulmonary venography with the use of multiple-bolus, multiphase, 3-dimensional, gadolinium-enhanced MR angiography (MRA). Overall quality of the MRA was good in 14 and insufficient in 4 patients, mainly as a result of breathing artifacts. Visualization of the main and segmental veins and evaulability of their patency were good for most right pulmonary veins but often inadequate for left pulmonary veins, particularly for those in the left lower lobe. There was no evidence for PVT in any of the sufficiently visualized pulmonary veins.

Conclusions—The results do not support the hypothesis of PVT as a contributor to the etiology of ischemic stroke. However, the study was limited regarding scan volume, spatial discrimination, patient selection, and delay between ischemia and MRA. Therefore, further investigations, including postmortem studies, are needed to resolve the question of whether PVT may contribute to ischemic stroke. (Stroke. 2002;33:1416-1419.)

Key Words: cerebral infarction (etiology) • magnetic resonance angiography • stroke • venous thrombosis

Even after application of all modern diagnostic tools, the etiology of ischemic stroke remains undefined in >20% of all patients.1,2 Therefore, the search for alternative sources of ischemic stroke is warranted. Besides the heart and large extracranial arteries, pulmonary venous thrombosis (PVT) could be an additional origin of cerebral emboli. Pulmonary arteriovenous malformations and thrombosis at venous anastomoses after lung transplantation can cause ischemic stroke, indicating that emboli from pulmonary vessels can reach the brain.3–7 Several studies showed that recent respiratory tract infection is a risk factor for stroke, particularly among younger patients, in whom stroke often remains etiologically undefined.8,9 Lung infections may trigger pulmonary thrombophlebitis; however, only a few reports mentioned PVT as a cause of stroke.10–12

Gadolinium-enhanced MR angiography (MRA) was shown to possess high sensitivity and specificity for the diagnosis of pulmonary embolism.13 We applied recently developed high-resolution pulmonary venography using multiple-bolus, multiphase, 3-dimensional, gadolinium-enhanced MRA to investigate whether there is evidence for PVT in patients with otherwise undefined etiology of stroke.

Subjects and Methods
Patients were eligible for the study if the following conditions were fulfilled: (1) age <65 years; (2) no discernible cause of acute ischemic stroke or transient ischemic attack despite complete workup including brain imaging, Doppler ultrasound, and duplex studies of all brain-supplying arteries, transesophageal echocardiography including testing for open foramen ovale, and laboratory tests for vasculitis; (3) clinical and/or CT evidence of ischemia in the supply territory of 1 or more large intracerebral arteries; and (4) capability to give informed consent and to cooperate in pulmonary MRA examination within 7 days after ischemia.

We investigated 18 patients (9 women, 9 men; mean age, 48 years; range, 31 to 61 years). Cerebral ischemia (transient ischemic attack, n=4; ischemic stroke, n=14) occurred in territories of vertebrobasilar arteries (n=6), middle cerebral arteries (n=11), or both (n=1). Patients had hypertension (n=5), diabetes mellitus (n=1), hypercholesterolemia (n=5), hypertriglyceridemia (n=3), were current smokers (n=5), took oral contraceptives (n=2), had coagulation abnor-
MR Angiography

The MRA technique was specially developed for this study and successfully tested in healthy volunteers, as described in detail recently. Briefly, we used a 1.5-T MR system (Magnetom Vision, Siemens) with a resonant echo-planar imaging gradient overdrive. A standard 4-element phased-array body coil was centered on the chest. Aliasing from the patient’s arm was suppressed by copper mesh pillows. Pulmonary arteries were localized with T1-weighted, fast low-angle shot (FLASH) breath hold pulse sequences. For the multiphase, 3-dimensional, gadolinium-enhanced MRA, an ultrafast 3-dimensional FLASH sequence with asymmetrical k-space sampling was used (repetition time = 2.3 ms, echo time = 1.1 ms, bandwidth = 950 Hz per pixel), as described previously. A 26 × 35-cm field of view and a 12-cm 3-dimensional slab thickness were chosen. Within this volume, 90 phase-encoding and 30 partition-encoding steps were performed, resulting in a voxel size of 1.9 × 1.4 × 2 mm^3 after zero-filling and a scan time of 6.28 seconds. In a single breath hold of approximately 25 seconds, a total of 4 consecutive acquisitions were performed.

To improve separation of arteries and veins, we exploited the intrinsic enhancement kinetics of the pulmonary system using 2 contrast medium boluses (each 0.1 mmol/kg gadopentetate, Magnevist; injection rate 5 mLs) and a special postprocessing algorithm termed correlation analysis. The correlation analysis emphasizes all vessel structures with identical signal-time course (eg, veins) and suppresses so-called anticorrelating structures (eg, arteries).

The patient was asked to hold the breath as long as possible, preferably for the whole period of 25 seconds. Coronal and oblique maximum intensity projection images were calculated from the 3-dimensional arterial and venous correlation maps in multiple 15° viewing angles. The resulting pulmonary arteriograms and venograms were independently assessed by 2 physicians in regard to vessel visibility, venous/arterial overlay, and breathing/cardiac motion artifacts. Venous/arterial overlay and breathing and cardiac motion artifacts were graded on a scale from 1 to 3: 1, none; 2, minor, not affecting diagnostic evaluation; and 3, major, substantially affecting diagnostic evaluation. All veins summarized in the Table were systematically evaluated. Vessel visibility was defined by a semiquantitative score (Table). Criteria for abnormalities suggesting venous thrombosis included incomplete filling of the vessel diameter over a short distance (suggesting a wall-adhering thrombus) and sudden termination of contrast filling (suggesting complete vessel occlusion). Distal interruptions of vessels close to the margins of the 3-dimensional slab or inhomogeneities in veins with poor visibility were not taken into account. For comparison of the 2 independent readers, a weighted κ statistic was used (SAS, version 6.12; SAS Institute).

Results

The 3-dimensional, gadolinium-enhanced MRA could be performed in all patients who had given informed consent. Overall quality of the examinations was good or sufficient (grade 1 to 2) in 14 patients, including all 4 patients with recent infection (Figure 1). In 4 patients, breathing artifacts and insufficient arterious/venous subtraction substantially affected diagnostic evaluation (grade 3; Figure 2). The Table depicts the evaluability of all veins assessed. Visibility was substantially better for right than left pulmonary veins. Because of cardiac motion artifacts and superimposition of the left ventricle, which possesses the same enhancement kinetic as pulmonary veins, lower lobe veins mostly showed poorer visibility than upper lobe veins. Interrater agreement on vessel visibility was good (mean κ values of 0.95 and 0.87 for the 4 main pulmonary veins and the segmental veins, respectively).

None of the pulmonary veins that revealed sufficient diagnostic vessel visibility (mode score 5) showed signs of partial or complete vessel obstruction indicative of venous thrombosis.

Discussion

Pulmonary veins are the most distant of the various upstream sources of arterial emboli. However, this potential source of ischemic stroke has rarely been considered. One report described a patient who was hospitalized for bronchopneumonia and died from basilar artery occlusion. As the only potential source of embolism, autopsy revealed thrombophlebitis in the periphery of the left lung in an area of severe pneumonia, including a small abscess. The association between sudden cerebral deficit and pneumonia had already been reported earlier, and the term hémiplégie pneumonique had been coined.
We developed an MRA method to test the hypothesis that PVT may be an etiology of embolism in otherwise cryptogenic stroke. We failed to detect evidence of PVT among 18 younger patients. However, there are several limitations inherent to our study.

We could investigate only cooperative patients with mild to moderately severe stroke. If emboli from PVT should cause severe stroke, this would not be assessable with our method. Postmortem studies would then be helpful; however, a very low autopsy rate in our country made such approach impossible. Visibility of left pulmonary veins was often insufficient, the scan volume could not cover the whole pulmonary volume because of limited scan time, and spatial discrimination was limited to veins ≥3 mm. Furthermore, spontaneous thrombolysis could have occurred between ischemia and examination. Although 3-dimensional, gadolinium-enhanced MRA has improved and is a reliable technique to detect pulmonary embolism, conventional angiography is still the gold standard to investigate pulmonary vessels. However, periprocedural risk, radiation exposure, and nephrotoxic contrast media hindered our use of conventional angiography or CT angiography. Transesophageal echocardiography allows evaluation of only proximal parts of main pulmonary veins and was unremarkable in our patients.
Given the aforementioned methodical limitations, our negative results do not exclude that PVT contributes to the pathogenesis of stroke. In the future, further technical refinements and postmortem examinations will be required to study this issue.

References
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