Cardiac Sources of Embolism in Patients With Pial Artery Infarcts and Lacunar Lesions

Henning Mast, MD; John L.P. Thompson, PhD; Heinz Völker, MD; J.P. Mohr, MD, MSc; Peter Marx, MD

**Background and Purpose** On the assumption that the majority of lacunes are caused by small-vessel diseases and that pial artery infarcts arise from cardioembolic or large-vessel diseases, 194 patients from the Berlin Cerebral Ischemia Data Bank with either lacunar or pial artery infarcts were analyzed for the frequency of cardiac sources of embolism. The primary hypothesis was that the frequency of cardiac sources of embolism is higher among pial artery infarct subjects.

**Methods** The presence of cardiac sources of embolism was estimated by electrocardiographic and transthoracic and transesophageal echocardiographic studies. Cranial computed tomography scans were evaluated by two masked observers.

**Results** The overall rate of cardiac sources of embolism did not differ significantly between the lacunar and the pial artery infarct group (66% versus 71%; odds ratio, 0.80; confidence interval, 0.43 to 1.50). Echocardiographic evidence of cardiac thrombi was positively associated with pial artery infarcts (odds ratio, 0.18; confidence interval, 0.04 to 0.80); atrial fibrillation and all other cardiac sources were not.

**Conclusions** Left cardiac thrombi are significantly associated with pial artery infarcts. Other presumed cardiac sources of embolism, including atrial fibrillation, may often represent coincidental findings or have a less strong tendency to result in pial artery infarcts. (Stroke. 1994;25:776-781.)

**Key Words** • cardioembolic stroke • tomography, x-ray computed

Most determinations of mechanisms underlying focal cerebral ischemia are based on clinical evaluation, cranial computed tomography (CT), and/or magnetic resonance (MR) scanning, Doppler sonography (DS), echocardiography (ECHO), and electrocardiography (ECG). Early angiography within the first hours from stroke onset or autopsy studies are rarely available.

Although clinical and CT/MR investigations often distinguish small, deep (presumed lacunar) lesions from infarcts affecting larger areas of brain parenchyma, ECHO, DS, and ECG tests are necessary to help determine the underlying mechanisms. As cardioembolic and transcardiac stroke mechanisms have been increasingly recognized, a large number of so-called cardioembolic sources of embolism (CSE) have been described, but so far no widely accepted classification of CSE and their associated risk for causing a cardioembolic stroke exists.1 Sandercock et al2 divided CSE into major and minor categories. Sherman3 distinguished high (>6% per year), intermediate (6% to 1% per year), and low (<1% per year) categories of stroke risk. Kittner et al4 proposed criteria for high and medium stroke risk without quantification. All three authors agree that atrial fibrillation (AF), with or without valvular heart disease, and mechanical prosthetic valve surgery constitute criteria for major/high or at least intermediate risk, but they disagree widely on other CSE definitions and their classification. For example, left ventricular wall motion abnormalities are listed by Kittner et al but do not appear in the other two classifications; mitral annulus calcification, mentioned by all authors, is considered a medium-risk criterion by Kittner et al but a low-risk criterion (<1% per year) by Sherman. (Because the incidence of stroke in the general population equals that in Sherman's category of low stroke risk, it is questionable whether CSE listed under this heading represent a special risk at all.)

Some CSE, such as atrial myxoma, infective endocarditis, mitral valve stenosis with AF, prostatic heart valves, and acute transmural anterior myocardial infarction, have clearly been shown to cause cardioembolic events.3-5-7 However, the extent to which other, more common CSE such as mitral valve prolapse or annular calcification, left ventricular wall motion abnormalities, atrial septal aneurysms, cardiomyopathies, congestive heart failure, mitral or aortic valve incompetence or stenosis, and transcardiac sources (patent foramen ovale, other septal defects) contribute to brain embolism remains unclear.

Atrial fibrillation is present in up to 24% of all ischemic strokes and is deemed to be the underlying stroke mechanism in almost half of those presumed cardioembolic.1 The combination of AF with hypertension, left atrial enlargement, mitral valve stenosis, left ventricular hypertrophy, or prior myocardial infarction has been seen as a strong risk marker for an ischemic stroke, but this does not necessarily imply a direct causal relation. Furthermore, van Merwijk et al,9 who

---

Received October 26, 1993; final revision received December 12, 1993; accepted January 10, 1994.

From the Neurovascular Unit, Neurological Institute, Columbia Presbyterian Hospital (H.M., J.P.M.), and Irving Center for Clinical Research, Presbyterian Hospital (J.L.P.T.), New York, NY, and the Departments of Cardiology (H.V.) and Neurology (P.M.), Universität'sklinikum Steglitz, Freie Universität Berlin, Berlin, Germany.

Reprint requests to Henning Mast, MD, Neurovascular Unit, Neurological Institute, Columbia Presbyterian Hospital, 710 W 168th St, New York, NY 10032.
compared the frequency of AF in patients with parenchymous brain hemorrhage and cerebral infarct, concluded that up to one third of AF findings in ischemic stroke cases are coincidental. In the same way, the mechanism(s) of strokes associated with thrombi in the left ventricle (remote from acute myocardial infarction) and left atrium remains uncertain.10

Assuming that the vast majority of lacunar lesions (LAC) are caused by small-vessel diseases (atheromatosis, lipohyalinosis) and that pial artery infarcts (PAI) arise from cardioembolic11 or large-artery diseases, the frequency of CSE in LAC and PAI patients was analyzed using prospective data from the Berlin Cerebral Ischemia Data Bank. The primary hypothesis was that the frequency of CSE is higher among PAI subjects.

Subjects and Methods

The Berlin Cerebral Ischemia Data Bank, which currently recruits 250 to 300 cases per year, is a prospective, hospital-based registry for consecutive transient ischemic attack and ischemic stroke patients. Its purpose is to explore stroke mechanisms and etiology and to evaluate the effectiveness of stroke treatment. From 1989 to 1992 two pilot projects were initiated, involving 500 patients. The objectives were to develop appropriate documentation forms, establish interrater variation and documentation logistics, and provide sufficient data to estimate sample sizes needed in the main project. A commercial database program (FOXPRO) and statistical software (SAS) on personal computers are used for data storage and analysis.

Four hundred sixty-six (93%) of the 500 pilot project patients were identified as having either transient ischemic attack or ischemic stroke. The remaining 34 were excluded because of discharge diagnoses of migraine, partial seizure, intracranial bleeding, tumor, or "unclassified." Baseline characteristics of the sample are provided in Table 1.

From the 466 patients two groups were selected: the PAI and LAC groups. The PAI group contained patients with supratentorial corticocortical territorial infarcts on CT and patients with ischemic CT lesions with a diameter >2 cm (presumed nonlacunar) in the nucleus lentiformis. All PAI represented acute or subacute infarcts matching the clinical syndrome. The criteria for fresh PAI were effacement and swelling with signs of compression of the surrounding tissue or ventricle. Sharply demarcated PAI with ventricular extension into the lesion were considered to be old and therefore excluded.

The LAC group included patients showing a small, deep (presumed lacunar) infarct (diameter <2 cm) in the lenticulostriate territories on CT and patients with pure motor syndromes and normal CT scans (other lacunar syndromes without corresponding LAC on CT were not included because of their less reliable association with morphological LAC). Because solid CT criteria for fresh LAC do not exist, we used additional clinical criteria: patients with signs of "higher cortical function" disturbance (aphasia, other neuropsychological deficits, neglect) or visual field deficits were excluded; patients with transient ischemic attacks were also excluded, so that events usually not long enough to result in a morphological lesion were rejected. Repeat CT scans (after 7 days) prevented the inclusion of late-appearing non-LAC infarcts. LAC group patients were not allowed to show old PAI or border-zone infarcts on CT. Lacunar CT lesions had to match the anatomic site of the clinical syndrome, but lacunar syndromes such as dysarthria/clumsy hand or ataxic hemiparesis, for which multiple anatomic sites including the brain stem have been shown, were nevertheless accepted when the syn-
assessed for chamber sizes, left ventricular wall thickness, and motion abnormalities according to the guidelines of the American Society of Echocardiography. A left atrial or ventricular thrombus was diagnosed when a protruding and/or mobile mass moving independently of the adjacent wall was observed. Color TEE was performed with a single-plane 3.75-MHz transesophageal transducer linked to a Toshiba SSH-160-A imaging system. Basal short-axis, four-chamber, and transgastric short-axis views were obtained. Left atrial and atrial appendage thrombi were defined as protruding and/or mobile masses moving independently of the chamber wall. Mitral valve prolapse was diagnosed when the four-chamber view showed protrusion into the left atrium of at least 3 mm beyond the valve plane by one or both myxomatous leaflets. A redundant interatrial septum with a base width of at least 1.5 cm and at least 1.1 cm excursion into the left or right atrium was interpreted as an atrial septal aneurysm. Interatrial shunting was evaluated by using the basal short-axis view. The appearance of contrast microbubbles in the left atrium after an intravenous injection of 2 to 10 mL of hand-agitated 5% solution of oxypolygelantine was taken as indication of patent foramen ovale or other atrial septal defect. All ECHO investigations were recorded on a Panasonic 7200 VHS-S video recorder and reviewed by two independent observers. A standard ECG was administered to all patients. Holter monitoring was performed in patients with a history of arrhythmia and normal standard ECG. It was not available for the remaining patients. Given the low additional yield of (intermittent) AF by Holter monitoring (2%), there should be no significant effect on the study results.

Following frequently used definitions, AF and left cardiac thrombi were considered to be major/high-risk CSE. Mitral valve prolapse and severe mitral annulus calcification, global or regional hypokinesia or dyskinesia of the left ventricle, atrial septal aneurysm, cardiomyopathy (dilated or hypertrophic), mitral and aortic valve insufficiency or stenosis, left atrial enlargement, and transcatheter sources (without deep vein thrombosis) were classified as CSE of undetermined risk. Major/high-risk CSE were analyzed separately for their association with other CSE. Data for single CSE of undetermined risk were only available from the second pilot project (51 LAC and 63 PAI patients).

The statistical analysis compared the frequency of CSE in LAC and PAI groups using the odds ratio (OR) and $\chi^2$ tests. Quantitative and qualitative differences in ECHO studies in the two groups and coexisting extracranial large-artery disease were taken into account.

### Results

Cardiac sources of embolism of all types were found in 66% of the LAC and 71% of the PAI patients, a difference not statistically significant (OR, 0.80; confidence interval [CI], 0.43 to 1.50; Table 2). Major CSE, however, were positively and significantly associated with PAI (OR, 0.33; CI, 0.15 to 0.74). The major CSE group consisted entirely of subjects with left cardiac thrombi or AF. Of these, left cardiac thrombi were significantly associated with PAI, whereas AF, found in 9.5% of the LAC cases, was not. The other, less common cardiac findings considered to be major sources—endocarditis, myxoma, patent foramen ovale with deep vein thrombosis, mechanical valve replacement, and acute anterior myocardial infarction—were not detected in either LAC or PAI patients.

The AF patients constituted a group at high risk for stroke because all were aged older than 60 years and displayed one or more of the following conditions: left atrial enlargement, mitral or aortic valve stenosis or insufficiency, left ventricular hypertrophy, previous myocardial infarction, hypertension, thrombus, mitral valve prolapse or severe mitral annulus calcification, left ventricular wall motion abnormalities, and patent foramen ovale. Patients with a left cardiac thrombus revealed the same coexisting CSE as AF subjects, but left ventricular wall motion abnormalities—a marker of severe ischemic heart disease/previous myocardial infarction—were significantly more frequent than in nonthrombus cases (OR, 0.08; CI, 0.01 to 0.45). Because the total number of thrombi is small (n=18), they could not be divided into atrial and ventricular subsets for further analysis. Nine (50%) thrombi, all in PAI patients and shown only by TEE, were located in the left atrium (5 in the auriculum). Only 3 of them were associated with AF. The other 7 thrombi in the PAI group and both thrombi in the LAC group were found in the left ventricle, most of them attached to the anterior wall or the apex.

The frequency of single CSE classified as undetermined risk did not differ significantly between the two groups (Table 3). However, left ventricular wall motion abnormalities and transcatheter sources (patent foramen ovale and other atrial septal defects) were more often

| TABLE 2. Cardiac Sources of Embolism in Patients With Lacunar and Pial Artery Infarcts |
|----------------|----------------|----------------|
|                | LAC (n=74) | PAI (n=120) |
|                | No. | %   | No. | %   | OR   | 95% CI |
| All CSE        | 49  | 66.2| 85  | 70.8| 0.80 | 0.43-1.50 |
| Subgroups of CSE |     |     |     |     |      |        |
| Major CSE      | 9   | 12.1| 35* | 29.1| 0.33†| 0.15-0.74 |
| CSE of undetermined risk | 40  | 54.0| 50  | 41.7| 1.64 | 0.91-2.95 |
| Subgroups of major CSE |     |     |     |     |      |        |
| Thrombi        | 2   | 2.7 | 16* | 13.3| 0.18†| 0.04-0.80 |
| Atrial fibrillation | 7   | 9.5 | 22* | 18.3| 0.46 | 0.18-1.15 |

LAC indicates lacunar infarcts; PAI, pial artery infarcts; OR, odds ratio; CI, confidence interval; and CSE, cardiac sources of embolism.

*Three PAI patients had both atrial fibrillation and a thrombus.
†Statistically significant difference (P<.05).
found in PAI subjects; the lack of statistical significance may be due to the small sample sizes. In contrast, mitral valve prolapse was (again insignificantly) more frequent among LAC patients.

A TTE was performed in 91% of LAC and 90% of PAI patients. The rate of TEE investigations differed significantly for the two groups (55% for LAC, 71% for PAI; OR, 0.51; CI, 0.27 to 0.93). Both TTE and TEE tests were administered in 54% of the LAC and 68% of the PAI patients (OR, 0.54; CI, 0.29 to 0.99). Because this favored the finding of left atrial thrombi in the PAI group, the frequency of thrombi was reexamined in those patients who underwent both TEE and TTE: 14 patients in the PAI group showed a thrombus, whereas only 1 in the LAC group did so (OR, 0.12; CI, 0.01 to 0.98).

The influence of coexisting extracranial large-artery disease was tested by excluding patients with additional carotid and/or vertebral artery stenosis (27% LAC, 19% PAI). As before, thrombi were significantly more frequent in PAI than in LAC patients (n=13 versus n=1; OR, 0.12; CI, 0.01 to 0.95). AF (OR, 0.45; CI, 0.17 to 1.20) and CSE of undetermined risk (OR, 0.57; CI, 0.22 to 1.49) including transcardiac sources (OR, 0.76; CI, 0.22 to 2.63) and left ventricular wall motion abnormalities (OR, 0.68; CI, 0.23 to 2.00) again showed no significant differences.

**Discussion**

The baseline characteristics, including the rate of AF, of our sample are similar to other study populations. Nevertheless, the rate of thrombi (9%) and other cardiac findings deemed to be possible sources of embolism (60%) exceeds those estimated by the Cerebral Embolism Task Force (30%) and other authors. The most likely reason is not ambiguity in the definition of CSE, but rather the recency of our study, making use of the technically advanced (TEE) ECHO evaluation of our patients. Only 28% of all cases in the Lausanne stroke registry, 40% in the Oxfordshire Community Stroke Project, 56% in the Stroke Data Bank had an ECHO. Because TEE was not available at the time these studies were done, they were less able to detect thrombi in the left atrium or appendage. The Oxfordshire Community Stroke Project did not identify any cardiac thrombus and found CSE, including AF, in 31% of the patients. The Lausanne registry did not report an overall frequency of CSE. Among the subjects investigated with ECHO, 3% had a thrombus. The rate of left ventricular wall motion abnormality (29%) was comparable to ours, but mitral valve prolapse, which may have been more broadly defined than in our study, was more frequent (34%). In the Stroke Data Bank, the oldest of the studies, thrombi were reported in 2% of patients tested. Thirtynine percent of all cases enrolled met high- or medium-risk criteria of CSE. Given that only 56% of the patients had an ECHO it can be estimated that a higher ECHO rate would have yielded a CSE frequency similar to ours. Finally, other more intensive ECHO investigations of stroke patients identified rates of left atrial thrombi that match our findings.

In general, our results are consistent with a recent report of a weak association between CT patterns and possible stroke mechanisms. However, the previous study was hampered by smaller subgroup sizes.

Of all CSE investigated, only left cardiac thrombi consistently showed a significant positive association with a PAI CT pattern. Because this association was also present in patients who did not display a competing extracranial large-artery stenosis, a causal relation between these thrombi and PAIs can be inferred. Whether the thrombi found in LAC patients represent coincidental findings or mirror the generally accepted small (<10%) proportion of (cardio-) embolic mechanisms in lacunes cannot be established here. Because of the small sample size, subsets of thrombus location (left appendage, atrium, ventricle), size, and morphology could not be statistically evaluated. However, atrial thrombi were all associated with PAI, indicating that this subgroup may be the main contributor to the significant association of left cardiac thrombi and PAI. Sacco et al have also shown a significantly higher rate of major CSE in patients with nonlacunar infarcts (28%) than in those with lacunar lesions (12%). However, their definitions of stroke subtypes (lacunes versus...
nonlacunes were mainly based on clinical criteria, and they had only limited data on the frequency of ECHO and ECG investigations. Furthermore, their large list of 21 major CSE included some findings (congestive heart failure, mitral valve disease) that were considered to be CSE of undetermined risk in our study. Other major CSE definitions were based on autopsy or related to surgical procedures and catheterization of the heart. Because no details regarding the frequency of any single CSE was provided, further comparisons are not possible.

Our results suggest that in PAI patients a TEE search for a thrombus is warranted to confirm a cardioembolic stroke mechanism, even when ECG has revealed AF and/or TTE has shown other CSE. The majority of atrial and ventricular thrombi were not associated with AF. Thus, the lack of AF does not indicate a lower yield of thrombus findings in either TTE or TEE, and the indication for ECHO investigations should not be influenced by normal ECG results. The presence of left ventricular wall motion abnormalities indicates a higher probability of a ventricular thrombus formation.

The lack of a statistically significant difference in the frequency of AF in the LAC and PAI groups could be due to the small sample size and does not, per se, preclude a potential role in stroke mechanism. However, our result supports the view\(^8\) that a large proportion of AF may be coincidental and that AF alone cannot be regarded as a strong marker for a cardioembolic stroke mechanism. A rate of AF similar to ours (9.4%) in patients with lacunar infarcts has been described by Horowitz et al (12%)\(^20\) and Boiten and Lodder (9.7%)\(^11\). The latter authors also tried to compare the frequency of CSE in lacunar and cortical infarct groups. Their rate of AF among cortical infarcts (29.9%) was higher than ours (18.3%), and it was also significantly greater than in their lacunar group. However, in 45% of their lacunar infarct patients the diagnosis was made on clinical grounds (no CT lesion), and the cortical infarct group did not exclude border-zone infarcts. No data on the rate of ECHO and ECG studies were provided, and AF constituted more than 80% of all CSE described. No comments were given on the possible presence of AF in the other group. Other CSE were discovered in only 5% of lacunar and cortical infarct patients, indicating that the ECHO investigation of the sample was insufficient.

Our results also have an implication for the interpretation of stroke prevention trials in AF patients. It is possible that these studies are not restricted to the prevention of cardioembolic strokes.\(^21\) If distinct stroke mechanisms vary in their responses to preventive medications, study designs that do not distinguish between them may fail to identify a positive preventive effect on one type of mechanism. This could explain the small margin of superiority of warfarin over aspirin in the Stroke Prevention in Atrial Fibrillation trial.\(^22\) A detailed analysis of the underlying mechanisms of stroke end points occurring in these trials could provide further information on this issue.

Although a significant association of patent foramen ovale with infarcts labeled "cryptogenic"—a group that supposedly harbors a large number of cardioembolic strokes—has been described,\(^23\) we could not show a corresponding association with a PAI CT pattern. Our rate of transcardiac CSE did not exceed the reported prevalence of patent foramen ovale in healthy individuals.\(^3\)

Left atrial enlargement, deemed to be a good marker of left atrial thrombus formation, was frequently found but evenly distributed between LAC and PAI patients. Therefore, it also does not seem to be a reliable sign of a cardioembolic stroke mechanism.

Our study design was based on the assumption of a uniform CT pattern of cardioembolic stroke, and this gained support from the results in thrombus/PAI association. Nevertheless, distinct CSE give rise to thrombi that differ in size and morphology.\(^1\) For example, mitral valve calcification and other valve alterations may lead to small embolic particles that could be more likely to result in an occlusion of a lenticulostriate artery. This effect would not be distinguished by our study design. Thus, the lack of an association of these CSE with PAI could also be due to a greater variety of CT patterns in cardioembolism than previously assumed.\(^1\)

In summary, left cardiac thrombi were significantly associated with PAI. Other CSE and up to 50% of all AF findings in PAI patients could be coincidental or have a less strong tendency to result in PAI CT patterns. Stroke prevention trials addressing the efficacy of warfarin and aspirin in AF patients probably observe a spectrum of stroke mechanisms broader than cardioembolic strokes only.

Acknowledgments

The authors thank the following individuals for assistance: Friedrich Nüssel, MD; Hans-Peter Vogel, MD; Hans-Christian Schumacher, MD; Christian Köencke, MD; Rüdiger Dissmann, MD; Susanne Blum, MD; Christiane Randel; Isabelle Möbs; Thomas Heinssius; and Lois Lynn.

References


Cardiac sources of embolism in patients with pial artery infarcts and lacunar lesions.
H Mast, J L Thompson, H Völler, J P Mohr and P Marx

Stroke. 1994;25:776-781
doi: 10.1161/01.STR.25.4.776

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/25/4/776

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/