Patients at High Risk with Atrial Fibrillation: A Prospective and Serial Follow-up During 12 Months with Transesophageal Echocardiography and Cerebral Magnetic Resonance Imaging

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Objective: **Patients with atrial fibrillation and echocardiographic risk factors have a relevant risk of cerebral embolism. However, there is little knowledge about the long-term fate and the rate of clinical silent cerebral embolism under continued oral anticoagulation. Our aims were to assess the prognosis of patients with atrial fibrillation and determine a high-risk group with an increased risk of cerebral embolism under oral anticoagulation.**

Methods: **A total of 173 consecutive patients with persistent or permanent atrial fibrillation and left atrial (LA) thrombi, dense spontaneous echocontrast, reduced LA appendage peak emptying velocities, or a combination of these were included in the study. In all, 169 patients with atrial fibrillation and without echocardiographic risk factors served as control patients. We performed serial and prospective transesophageal echocardiography, cranial magnetic resonance imaging, and clinical examinations during a period of 12 months.**

Results: **During the follow-up period 7 (4%) of the patients at high risk had cerebral embolism with neurologic deficits. A total of 4 (2%) patients died because of embolic events and 19 (11%) patients had silent embolism as documented on magnetic resonance imaging. In the control group, 10 (6%) patients had embolic events documented on magnetic resonance imaging; one was clinically apparent. Study patients with an event had more often previous thromboembolism ($P < .0001$).**

Conclusions: **Patients with persistent or permanent atrial fibrillation and LA thrombi, dense spontaneous echocontrast, or reduced LA appendage peak emptying velocities have an explicitly increased risk of cerebral embolism (17%) despite oral anticoagulation. Previous thromboembolic event is another important predictor for an event.** (J Am Soc Echocardiogr 2005;18:919-924.)

Patients with persistent or permanent atrial fibrillation and left atrial (LA) thrombi, dense spontaneous echocontrast, or reduced LA appendage (LAA) peak emptying velocities have a relevant risk of cerebral embolism.[1-8] Oral anticoagulation lowers the risk significantly. However, there is little knowledge about the long-term fate of patients with atrial fibrillation, above-mentioned echocardiographic risk factors, and the incidence of cerebral embolism in these patients. Transesophageal echocardiography (TEE) is suitable to detect echocardiographic risk factors for cerebral embolism.[1-8] Cranial magnetic resonance imaging (MRI) has a high accuracy for detecting cerebral embolism and allows even the detection of cerebral microembolism.[8-11] Therefore, our patients were monitored by means of TEE and cerebral MRI during the follow-up period.

The aims of our study were to: (1) assess the long-term fate of patients at high risk with persistent or permanent atrial fibrillation under continued oral anticoagulation; (2) evaluate the incidence of cerebral embolism during a follow-up period of 12 months; and (3) determine other predictors of cerebral embolism.

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METHODS

Study Patients

Consecutive patients with persistent or permanent nonvalvular atrial fibrillation (duration > 6 months) and LA

thrombi, dense spontaneous echocontrast, reduced LAA peak emptying velocities (≤ 0.2 m/s), or a combination of these were included in the study. Patients with persistent or permanent atrial fibrillation, but without previously mentioned echocardiographic risk factors, served as control patients. Exclusion criteria were contraindication to cerebral MRI, TEE, or oral anticoagulation; aortic plaques larger than 4 mm; carotid artery stenosis greater than 50%; severe or moderate valvular disease; valvular prothesis; and the inability to give written informed consent. Written informed consent was obtained from all patients and the study was approved by the institutional review board of the University of Bonn, Germany.

Study Protocol

All patients were examined clinically and embolic risk factors (age, sex, reduced left ventricular [LV] function, hypertension, diabetes mellitus, and history of embolism) were assessed. A 12-lead surface electrocardiogram and a Holter electrocardiogram were obtained at each visit. Follow-up time was presumed to be 12 months.

Echocardiographic Studies

Echocardiographic studies were performed with commercially available equipment (Vivid V or Vivid 7, GE, Milwaukee, Wis). A 1.7-/3.4-MHz electronic transducer was used for transthoracic echocardiography. The M-mode LA dimension and LV ejection fraction were measured according to the recommendations of the American Society of Echocardiography.[12]

A 6.7-MHz multiplane electronic transducer was used for TEE studies as previously reported by our study group.[8,12-14] Cineloops of the LA and the LAA were stored. To measure and record the profile of the LAA peak emptying velocities the sample volume of the pulsed Doppler was placed 1 cm into the orifice of the LAA.

All patients were screened for aortic plaques in the ascending aorta, the aortic arch, and the proximal descending aorta.

Echocardiographic Data Analysis

Evaluations of the studies were performed by two independent observers, blinded to clinical information about the patients, examining the digitized images after the original examination. Analyses were performed by means of the evaluation software provided by the manufacturer (Echopac, GE).

The cineloops of the LA and LAA were examined for thrombi and spontaneous echocontrast. The degree of spontaneous echocontrast was categorized as being absent (0), mild (1+), mild to moderate (2+), moderate (3+), or severe (4+) on the basis of the system described by Fatkin et al.[15] Spontaneous echocontrast of the degrees 3+ or 4+ was regarded to be dense. LAA area and peak emptying velocities were measured as previously reported.[16]

Anticoagulation

Patients without effective anticoagulation at admission received intravenous weight-adjusted unfractionated heparin (17 U/kg/h) during hospitalization; further dose adjustments were performed to achieve an activated partial thromboplastin time ratio of 1.5 to 2.5 times the control value that was presumed to be effective. Before discharge all patients were transferred to oral anticoagulation with phenprocoumon. The effectiveness of anticoagulation was assessed by the international normalized ratio (INR) level. An INR of 2.0 to 3.0 was defined as therapeutic range as recommended by the current guidelines.[17] The target INR was 2.5.

Cranial MRI

During the 12-month follow-up period MRI was performed at admission and after 1, 3, 6, and 12 months with a 1.5-T system (Gyroscan ACS-NT, Philips Medical Systems, Eindhoven, The Netherlands). The imaging protocol included a diffusion-weighted single shot spin echo echoplanar, turbo fluid attenuated inversion recovery and T2-weighted turbo spin echo sequence as previously reported.[8,10]

All MRI studies were evaluated by experienced consultant radiologists blinded to neurologic and clinic status and procedure. Images were evaluated for the presence of focal diffusion abnormalities in a pattern consistent with embolic lesions. Diffuse alterations in the diffusion-weighted sequence or pattern of watershed ischemia were not considered to be embolic types of lesions. Number, size (< 5 mm, 5-10 mm, > 10 mm), and vascular territory of all focal diffusion abnormalities were recorded.

For patients who showed a focal diffusion abnormality, a follow-up MRI investigation including T2-weighted turbo spin echo and fluid attenuated inversion recovery sequences was performed after 3 months to define the presence or absence of a subsequent infarct at the location of the diffusion abnormality.

Neurologic Examination

All patients underwent neurologic assessments during a 12-month follow-up period at admission and after 1, 3, 6, and 12 months. The assessments were performed by a board of certified neurologists. A neurologic complication was defined as any new cranial-nerve, motor, or sensory deficiency; reflex change; pyramidal sign; or occurrence of mental alteration.

Ultrasound of the Cerebral Arteries

Ultrasound examinations (HDI 3000, ATL, Bothell, Wash) were performed in all patients at admission and after 1, 3, 6, and 12 months for detection of atherosclerotic lesions of the carotids. Considering all information from B-mode, color Doppler, and Doppler ultrasound, stenoses of the common or the internal carotid artery were measured as a reduction of the luminal area according to established criteria.[18] All patients with stenoses greater than 50% were excluded from the study.

Statistical Analysis

Data are reported as mean (SD). Continuous variables between groups were compared by a *t* test for unpaired