Transcatheter Closure of Patent Foramen Ovale
After Presumed Paradoxical Embolism

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Background. Many have proposed a relation between presence of a patent foramen ovale, with or without atrial septal aneurysm, and cryptogenic stroke. The effect of foramen ovale closure on the risk for subsequent strokes is unknown.

Methods and Results. Transcatheter closure of a patent foramen ovale was undertaken in 36 patients with known right-to-left atrial shunting and presumed paradoxical emboli (31 strokes, 25 transient neurological events, four systemic arterial emboli, and two brain abscesses). Individual patients had one and four such events. None had a left heart or carotid source of embolism; 31 of 35 had no known risk factors for stroke. Events occurred in 12 patients while they were taking warfarin. At cardiac catheterization, patent foramina ovale were significantly larger than predicted for age in 67% of the patients. Implantation of a double-umbrella device in the patent foramen ovale was achieved in all without serious procedural complications. Of 34 who have returned for follow-up, one has a residual atrial communication that may be clinically important, five had trivial leaks, and 28 have complete closure. There have been no strokes during a mean follow-up of 8.4 months.

Conclusions. Transcatheter closure of a patent foramen ovale can be accomplished with little morbidity and may reduce the risk of recurrence. Further investigations directed toward identifying the population at risk and assessing the effect of intervention are warranted. (Circulation 1992;86:1902-1908)

KEY WORDS • patent foramen ovale • stroke • embolism • closure

Interest in the prevalence of patent foramen ovale and its relation (if any) to embolic stroke has increased with the sophistication of methods for noninvasive cardiac assessment. In 1988, Lechat et al1,2 and Webster et al3 independently reported controlled studies using transthoracic echocardiography that demonstrated an increased prevalence of patent foramen ovale in patients with cryptogenic stroke compared with the general population. A recent study by de Belder et al4 also suggests an association between patent foramen ovale and stroke.

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Methods

Patient Population

The study included 36 patients, none previously reported, who had transcatheter closure of an interatrial communication after a probable paradoxical embolism. Each patient had one or more events (e.g., embolic stroke, transient focal neurological deficit, peripheral arterial embolism, or brain abscess) without a left heart or carotid source, and each had an interatrial communication with intermittent or continuous right-to-left shunting by echocardiography. In 35 patients, the atrial defect had the anatomic appearance of a patent foramen ovale; in one (patient 4), a secundum-type atrial septal defect was present. Atrial septal aneurysm was present in three patients, one with multiple fenestrations of septum primum.

"Embolic stroke" is defined here as an acute, permanent focal neurological deficit with a corresponding
destructive lesion in a recognized cerebrovascular distribution identified by computed tomography (CT) or magnetic resonance imaging (MRI) scan that did not fit clinical or imaging criteria for lacunar infarction. "Transient focal deficit" refers to an acute focal neurological deficit without a corresponding lesion on the CT or MRI scan. All 33 patients who had neurological events had a complete neurological evaluation, with migraine and seizure ruled out by clinical and/or laboratory means; all except two of the 33 had a carotid angiogram \( n=15 \), carotid Doppler studies \( n=17 \), or both, and all studies were negative. Of the remaining two patients, neither had a carotid bruit, and one was <1 year old at the time of her strokes. All patients were evaluated for a left heart source of embolism by transthoracic and/or transesophageal echocardiography; 29 of the 36 patients had at least one complete transesophageal echocardiogram, whereas the remaining seven had transthoracic studies only. A history of palpitations or atrial fibrillation was sought, and all patients had at least two ECGs. Holter studies were not routinely performed.

**Data Collection and Informed Consent**

Data pertaining to the transcatheter closure (e.g., indication for procedure, size of defect, size of device, procedural complications) were collected prospectively according to the requirements of the protocol for investigational use of the Bard Clamshell septal umbrella. Additional information regarding prior embolic events and neurological follow-up was collected from hospital records and by contacting patients and their referring physicians. Informed consent for transcatheter closure was obtained in each case. Both the investigational protocol and the informed consent were approved by the Food and Drug Administration and the clinical investigation committees at participating institutions.

The first phase of a multicenter clinical trial of the Clamshell septal umbrella was initiated in February 1989 and ended in June 1991. The device used in the patients in this report has been approved for continued trials for specific clinical indications (e.g., closure of postoperative residual defects, muscular ventricular septal defects, and fenestrated Fontan baffles). Among patients with secundum-type atrial septal defects and patent foramina ovale, follow-up has revealed an approximate 30% incidence of late fractures of one or more arms of the device. The clinical importance of these fractures remains uncertain. Nevertheless, the device has been redesigned for use in the atrial septum; initiation of trials of the newly designed device is anticipated in 1993.

**Technique of Transcatheter Closure of Atrial Defects**

The technique of transcatheter closure of atrial septal defects has been previously described in detail.\(^1\) \(^2\) \(^3\) \(^4\) \(^5\) \(^6\) \(^7\) \(^8\) \(^9\) \(^10\) \(^11\) \(^12\) Certain modifications of the technique were made for these patients with right-to-left shunting and presumed paradoxical embolism. First, noninvasive studies of the femoral vessels were performed to rule out the presence of thrombi that might embolize on introduction of catheters, a complication that has been reported.\(^15\) \(^16\) Second, the technique of balloon sizing of the defect was modified. In the case of a secundum-type atrial septal defect, the size of the hole is determined by pulling an inflated balloon from left to right across the septum, over a guidewire;\(^21\) the indentations in the balloon indicate the size of the hole (Figure 1). However, in a patent foramen ovale, the inferior portion of the balloon may get "caught" on septum primum (the anteroinferior edge of the defect), particularly when a standard end-hole balloon-tipped catheter rather than a specifically designed sizing balloon is used; it will then not pull through until it is almost completely deflated, giving the erroneous impression that the hole is quite small. A much larger balloon may in fact be advanced through the same hole from right to left. Thus, defects

**FIGURE 1.** Cineangiogram demonstrating balloon sizing of a patent foramen ovale. A wire and an end-hole catheter are advanced antegrade from the inferior vena cava to the right atrium, through the patent foramen ovale, into the left atrium, and out into a pulmonary vein. The balloon is inflated with contrast and pulled back over the wire through the patent foramen ovale. The indentations in the balloon indicate the diameter of the hole. The Clamshell umbrella device (in this case, 28 mm in length from arm tip to arm tip) is on the patient's chest to be used as a reference to correct for magnification.
were balloon sized from right to left as well as from left to right. Finally, our previous experience with closure of secundum-type atrial septal defects indicates that an umbrella that is at least 1.8 times the stretched size of the defect will be stable and occlusive. However, both the presence of a right-to-left shunt and the anatomic features of a patent foramen ovale tend to “destabilize” the umbrella; for this reason, the umbrella chosen for closure in these patients was at least twice the stretched size of the defect, whenever possible.

**Follow-up**

Of the 36 patients, 32 took warfarin until just before transcatheter closure. After closure, standard treatment was low-dose aspirin only, without anticoagulation; however, warfarin therapy was continued or later reinstated in three of the 36 patients by the referring physician. (Indications were morbid obesity and chronic immobility due to multiple sclerosis in patient 14; an episode of amaurosis fugax 1 month after transcatheter closure in patient 13, who had a residual right-to-left shunt; and vague symptoms of bilateral arm and leg weakness 2 months after closure in patient 20, who had complete closure.) All patients were advised to maintain prophylaxis against bacterial endocarditis in situations of increased risk for 6 months after the procedure.

Patients were evaluated by a physician at 1, 6, and 12 months after the procedure, at which times completeness of closure was assessed by transthoracic or transesophageal echocardiography.

**Statistical Analysis**

An actuarial analysis of time to event recurrence (Kaplan-Meier method) was carried out using STATA software (Computing Resource Center, Los Angeles, Calif.).

**Results**

Patients’ clinical characteristics are given in Table 1. There were 22 men, 13 women, and one girl. The average age was 39.4 years at the time of transcatheter closure (median, 39.1 years; range, 1.4–64 years). Of 36 patients, five had risk factors for stroke (hypertension in one, oral contraceptives in three, and cigarette smoking and hypertension in one). None had an identifiable cardiac or carotid source of embolism, and none had diabetes mellitus, recent (<6 months) myocardial infarction, atrial fibrillation, or lacunar cerebral infarction. Femoral venous thrombus was not identified in any patient.

Events attributed to paradoxical embolism before transcatheter closure also are listed in Table 1. There were 31 strokes, 25 episodes of transient focal neurological deficit, four systemic arterial emboli (including one coronary infarction), and two brain abscesses. Individual patients had between one and four events, with an average of 1.7 events per patient.

The mean stretched diameter of the interatrial communication was 12.3 mm (range, 3.2–22 mm; see Table 1). The pulmonary-to-systemic flow ratio by oximetry (Fick method) ranged from 0.8 to 1.5. Stable transcather implantation of the Clamshell umbrella in the atrial defect was achieved in each case (Figure 2). Atrial septal aneurysms, when present, were obliterated by the device, and multiple fenestrations, when present, all were closed with one device. No serious complications occurred. Specifically, there were no strokes, no episodes of hemodynamic instability, and no infectious complications. A brachial plexus injury, probably related to positioning during the catheterization, occurred in one patient, with subsequent full recovery. The average fluoroscopy time was 38 minutes, and a blood transfusion was given to one patient.

As of December 31, 1991, there were 287 patient-months of follow-up on 34 of the 36 patients (mean, 8.4 months per patient; range, 1–24 months). Two patients refused follow-up; they are known to be alive and report feeling well, without further strokes. However, they have not been seen by a physician. By echocardiographic color flow mapping, closure of the patent foramen ovale was complete in 28 patients (82%), five had tiny (<1 mm) leaks (four predominantly right to left and one left to right), and one patient had a 2–3-mm right-to-left leak. The latter patient had a transient focal neurological deficit (amaurosis fugax) 1 month after the procedure. Three patients who have complete closure of the atrial defect have had transient events—one continues to have episodes of focal paresthesia and weakness identical to those that occurred before patent foramen ovale closure, now thought to be due to cerebral vasculitis; one had a transient focal deficit 4 days after transcatheter closure, with complete resolution; and one had a vague episode of transient bilateral leg and arm weakness. No patient has had a stroke, brain abscess, systemic arterial embolism, or bacterial endocarditis after closure of the atrial defect.

Figure 3 shows an actuarial analysis of event recurrence before and after defect closure in the subset of 28 patients who had at least one documented arterial embolic event and who complied with follow-up. Inclusion in the analysis required at least one documented arterial embolic event (i.e., stroke, systemic arterial embolism, or brain abscess) to focus on patients who were most likely to have had a paradoxical embolism rather than another mechanism for the neurological event that led to referral for transcatheter closure of their atrial defect. (If the analysis had included all 34 patients with follow-up, rather than only those patients with at least one documented embolic event, there would have been two additional patients with recurrent events before transcatheter closure and two additional patients with recurrent events after transcatheter closure; analysis of the data in that fashion would not change the inferences drawn from the study.) A “recurrent event” within this subset of patients was defined as a stroke, transient focal deficit, or systemic arterial embolism. For the preclosure period (Figure 3A), the time of entry for an individual patient is the time of the first documented arterial embolic event (stroke, peripheral arterial embolism, or brain abscess) within the 24-month period preceding transcatheter closure. For the postclosure period (Figure 3B), the time of entry is the date of transcatheter closure. The total surveillance period was 242 patient-months in the preclosure period and 221 months in the postclosure period. The average time between the initial and first recurrent events was 7.1 ± 6.7 months (median, 4 months); between initial event and transcatheter closure of the patent foramen ovale, 7.9 ± 6.8 months (median, 5.5 months); and between the last event and transcatheter closure, 5.1 ± 4.0
months (median, 3.5 months). Before transcatheter closure, the average observation period among patients having recurrent events (n=12) was 5.8±4.4 months; among those without recurrent events (n=16), the average observation period was 9.8±7.8 months. After transcatheter closure, the average observation period among those with recurrent events (n=2) was 5.5 months; among those without recurrent events (n=26), the average observation period was 8.0±4.7 months.

Discussion
In this report, we present our experience with transcatheter closure of patent foramina ovalia in a group of patients referred after presumed paradoxical embolism. Successful implantation of the occlusion device was accomplished in all patients; 82% of those complying with follow-up had complete closure, and one of 34 had a residual leak that was considered clinically important.

The patients in this report are a heterogeneous group who were selected because they were referred for closure of an interatrial defect after a presumed paradoxical embolic event. Among the 36 patients, five had transient focal deficits as the only indication for the procedure; in retrospect, it appears likely that at least one of these five patients (patient 26) never truly had a paradoxical embolism. Thus, the group cannot be considered represe-
tative of the population of patients with either patent foramen ovale or with cryptogenic stroke. Nevertheless, given the potential usefulness of this closure technique as a means of further study of the mechanism and recurrence risk of paradoxical embolism, consideration of this experience, in the context of other available information from the literature, is warranted.

Review of the Literature

Similar patients have been previously reported.\textsuperscript{11,22–24} Gautier et al\textsuperscript{25} reported 29 patients with patent foramen ovale who had a total of 47 neurological events attributed to paradoxical embolism (36 strokes and 11 transient ischemic events). Harvey et al\textsuperscript{26} reported four patients with presumed paradoxical emboli who subsequently underwent surgical closure of their patent foramina ovalia and had no subsequent embolic events with follow-up of 7–21 months. Unfortunately, reports such as these (and ours) do not offer insight into the significance of patent foramen ovale as a risk factor for stroke in the population-at-large.

Other currently available information may be considered in an attempt to assess the importance of a patent foramen ovale as a risk factor for embolic stroke. First, right-to-left shunting, an obligate condition in the pathophysiology of paradoxical embolism, is common in the presence of an atrial septal defect or a patent foramen ovale, even when the intracardiac pressures are normal.\textsuperscript{20,27–29} Second, both cryptogenic stroke and stroke attributed to paradoxical embolism tend to occur in young people,\textsuperscript{30–32} that is, those less likely to have other important risk factors for stroke. Third, patent foramen ovale is common, occurring in 27% of patients at autopsy.\textsuperscript{33}

The yearly incidence of cryptogenic stroke and the prevalence of patent foramen ovale in both the general population and the population with cryptogenic stroke can be used to estimate the number of strokes attribu-
able to patent foramen ovale. The yearly incidence of stroke in the United States may be estimated at 400,000, and roughly 40% of these strokes are without identifiable cause. If one accepts the echocardiographic findings of de Belder et al and assumes a prevalence of patent foramen ovale of 3% in the general population and 26% in patients with cryptogenic stroke, then the number of strokes attributable each year in the United States to a patent foramen ovale is 19,723. If one uses Lechat et al’s findings and assumes that the prevalence of patent foramen ovale in the general population is 10% versus 40% in patients with cryptogenic stroke, then as many as 47,422 strokes each year may be attributable to the presence of a patent foramen ovale. There are no data to help predict which patients with a patent foramen ovale are likely to have a stroke due to paradoxical embolism.

**Findings in This Report**

Certain features of the patients in this report are notable. First, the average stretched patent foramen ovale diameter was more than twice that reported by Hagen et al in a series of 965 autopsy specimens; 22 of 36, the stretched dimension was larger by more than 2 SDs than the mean in Hagen et al’s series. Even considering that there may have been mild shrinkage in Hagen et al’s autopsy specimens as a result of formalin fixation, this suggests that patients with larger patent foramina ovalia may be more likely to have paradoxical emboli. The patent foramen ovale is a flap, rather than a discrete hole; unlike a secundum-type atrial septal defect, its stretched size is not easily predicted from its echocardiographic appearance. Thus, merely identifying the presence of a patent foramen ovale by transesophageal echocardiography (or comparison of prevalence of a patent foramen ovale in different subgroups) may not, in itself, be an accurate way of identifying patients (or groups) at risk because estimation of the potential size of the hole by noninvasive means is difficult, if not impossible. Second, atrial septal aneurysm, which appears to be associated with arterial embolism and is commonly found to coexist with a right-to-left shunt, was present in three of 36 (8%) versus a prevalence in the general population of 0.6% and 1.2%. Finally, among 32 patients treated with warfarin before closure of their patent foramen ovale, 12 claimed compliance with oral warfarin treatment at the time of a recurrent embolic event. The reported risk of major bleeding events in patients treated with warfarin ranges from 1.5% to 11% per year. An intervention that reduces the risk of stroke recurrence without chronic anticoagulation and without the need for patient compliance would be particularly advantageous in the relatively young population in whom cryptogenic stroke occurs.

Interpretation of the data in Figure 3 requires consideration of the fact that the time of greatest risk for recurrence in patients who have had a paradoxical embolism is unknown. For other types of cardioembolic stroke, there is evidence to suggest that the risk of recurrence is greatest within the first month. Thus, the probability of stroke recurrence during the two periods shown in Figure 3, independent of treatment, cannot be assumed to be equal and may have been greater during the preclosure period. On the other hand, the average time to recurrence within the arbitrarily defined 2-year surveillance period before transcatheter closure was 7.1 months; six patients had, in addition, between one and three documented events that occurred 2–20 years earlier.

Three patients with complete occlusion of their atrial defects had recurrent transient focal deficits. This is not unexpected for at least two reasons. First, the diagnosis of an embolic event in these patients is presumptive, based on clinical findings, absence (in most cases) of other risk factors, and presence of an atrial defect with right-to-left shunting. In at least one patient, the diagnosis of paradoxical embolism appears in retrospect to have been incorrect. Second, as discussed above, both patent foramen ovale and stroke are common, and in a substantial number of patients, the two conditions will coexist without a causal relation. Closure of a patent foramen ovale in those patients would not, therefore, lessen their risk of recurrence.

**Conclusions**

The patients in this report are a subset of a larger group who participated in the initial clinical trials of the Clamshell septal umbrella. The manner of their selection does not allow conclusions about the relation between patent foramen ovale and stroke or about the effectiveness of closure of a patent foramen ovale in preventing recurrent stroke. However, we believe that several observations are valid. First, there appears to be a group of patients in whom paradoxical embolic events occur and recur — without a readily identifiable etiology other than the presence of a patent foramen ovale, or without atrial septal aneurysm. Second, in most of these patients, the patent foramen ovale can be closed and the aneurysm obliterated without open-heart surgery and with very little short- or intermediate-term risk. Third, based on the absence of stroke recurrence after transcatheter closure, we speculate that this may be an effective means of preventing stroke recurrence in some patients without chronic anticoagulation. Finally, further investigations designed to identify the population at risk and assess the effect of intervention are warranted.

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