Race-Ethnic Differences in Patent Foramen Ovale, Atrial Septal Aneurysm, and Right Atrial Anatomy Among Ischemic Stroke Patients

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Background and Purpose—Stroke remains a substantial cause of mortality and morbidity in the United States. Racial differences in stroke incidence and mortality persist with well-known excesses among blacks. Information on stroke among Hispanics is limited. In particular, little is known about whether patent foramen ovale (PFO), atrial septal aneurysm (ASA), and other atrial anomalies associated with cryptogenic stroke differ among minority populations.

Methods—As a part of the PFO in Cryptogenic Stroke Study, transesophageal echocardiography was performed in a cohort of 630 ischemic stroke patients (mean age, 59 ± 12 years; 44% women; 45% whites, 35% blacks, 17% Hispanics, 3% other). The prevalences of PFO, ASA, and right atrial (RA) anatomy favoring paradoxical embolization were compared among race-ethnic groups. Statistical analyses used analysis of variance for continuous variables and logistic regression for dichotomous variables with adjustments for age and sex.

Results—Age- and sex-adjusted prevalences of PFO and ASA were similar across race-ethnic subgroups. However, large PFO was significantly less prevalent among blacks than among whites (odds ratio, 0.47; 95% confidence interval, 0.24 to 0.91; P = 0.02). RA anatomy favoring paradoxical embolization was also significantly less prevalent among blacks compared with whites (odds ratio, 0.62; 95% confidence interval, 0.43 to 0.91; P = 0.01). There were no significant differences in prevalence between whites and Hispanics.

Conclusions—Although the frequency of PFO did not vary among race-ethnic groups, a large PFO and RA anatomy favoring paradoxical embolization were significantly more prevalent among whites and Hispanics compared with blacks. These may be relatively more important risk factors for stroke among whites and Hispanics than among blacks.

Key Words: echocardiography • epidemiology • ethnic groups • racial differences • stroke
Methods
PICSS methodology has been described elsewhere.14–16 Briefly, PICSS relied on the Warfarin-Aspirin Recurrent Stroke Study (WARSS) for patient recruitment. WARSS was a 48-center double-blind study that randomized 2206 stroke patients (30 to 85 years of age) to either warfarin or aspirin and followed them up for stroke recurrence or death over a 24-month period. At each center, cryptogenic stroke patients in WARSS were solicited to undergo TE. PICSS also included all WARSS patients who underwent TE for clinical purposes. All protocols for WARSS and PICSS were approved by the Institutional Review Board at each participating center. Informed consent was obtained from each participant. Patients with contraindication to TE, high-grade carotid stenosis, stroke related to a procedure, or stroke attributable to a known cardioembolic source such as atrial fibrillation were excluded from consideration for participation in PICSS.

Race-Ethnic Classification
Race-ethnic groups were defined by self-identification with the criteria developed by WARSS.14,15 Race was classified as American Indian, Asian or Pacific Islander, black, white, Hispanic, or other. Hispanics were defined as persons of Hispanic/Spanish/Latino origin or descent.

Stroke Subtyping
All baseline strokes were subtyped by a local neurology principal investigator based on predefined criteria modeled after the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank and the Trial of Org 10172 in Acute Stroke Therapy (TOAST).17 Subtypes were lacunar, large vessel, cryptogenic, other determined cause, and conflicting mechanisms.

Analysis of Tapes
The TE protocol emphasized delineation of TE-associated embolic sources, including extensive characterization of PFO. All TE tapes were analyzed by a single observer (S.H.) blinded to stroke subtype or outcome. PFO was determined to be present if, on saline contrast injection, there was appearance of at least 1 microbubble in the left atrium within 3 cardiac cycles after opacification of the RA.18,19 PFO size and shunt were determined by demonstrating the maximum separation of septum primum from secundum, and the maximum number of microbubbles visualized in the left atrium within 3 cardiac cycles from opacification of the RA. PFOs with ≥2 mm separation of the septum primum and secundum, or with ≥10 microbubbles appearing in the left atrium, were classified as large. All other PFOs were classified as small.

Atrial septal excision (ASE) was defined as a motion of interatrial septum from its midline position into the left atrium or RA. ASA was determined to be present when ASE was ≥10 mm.20 A prominent EV was defined as a protrusion of ≥10 mm of a linear membranelike structure from the junction of the RA with the IVC. RA filamentous strands were defined as freely mobile linear filamentous structures in the RA with attachment to any aspect of the RA wall visualized on any image plane.

Statistical Analysis
The distribution of stroke risk factors and stroke subtype was compared among the 3 race-ethnic groups (whites, blacks, Hispanics). The “other” racial categories did not include a sufficient number of subjects for statistical analysis. PFO and ASA prevalence and atrial morphological characteristics were then compared among the groups. Univariate analyses were performed with analysis of variance for continuous variables and the χ² test for categorical variables to test for any significant differences, defined as P<0.05. Multivariate analyses of categorical variables used a logistic regression model that included race-ethnic group, age, and sex. Odds ratios and 95% confidence intervals were calculated from the β coefficients and their standard errors. For assessment of racial differences in TE-defined cryptogenic stroke risk factors, whites were used as the reference group.

Results
TE was performed on a cohort of 630 ischemic stroke patients. TE studies were available and adequate for analysis in 602 subjects (96%) classified as white, black, or Hispanic. Characteristics of the study subjects are shown in Table 1. Although there was no significant difference in age or sex among the groups, there were significant differences in the prevalence of stroke risk factors. Stroke subtype also varied significantly (P<0.0001), with cryptogenic strokes seen predominantly among whites and lacunar strokes seen predominantly among blacks and Hispanics (Table 1).

PFO and ASA
Overall, the prevalence of PFO was similar across the race-ethnic groups (Table 2). Prevalence of ASA, a combination of ASA and PFO, and prominent EV or RA filamentous strands were also similar among the groups. However, whites and Hispanics were more likely to have a larger PFO and a greater degree of shunt across the PFO than blacks (Table 3). The degree of ASE correlated with PFO size in the
total cohort \((r=0.37, P<0.0001)\), among whites \((r=0.39, P=0.0002)\), and among Hispanics \((r=0.53, P=0.0008)\). However, among blacks, the degree of ASE did not correlate significantly with PFO size \((r=0.16, P=0.21)\). Thus, the degree of ASE was an indicator of PFO size among whites and Hispanics but not blacks.

When the 258 patients in the cryptogenic stroke subset were considered separately, there was no significant difference in the prevalence of PFO, but whites and Hispanics had a significantly higher prevalence of prominent EV or RA filamentous strands (Table 2). PFO size tended to be larger among whites and Hispanics than blacks (Table 3), but the difference did not attain statistical significance. The prevalence of ASA and degree of ASE among the cryptogenic stroke patients did not vary across race-ethnic groups (Tables 2 and 3).

In the total cohort, after adjustment for age and sex, with whites as the reference group, blacks were less likely to have a large PFO or RA anatomy likely to predispose to paradoxical embolization (Table 4). Hispanics were not significantly different from whites. When similar analyses were performed for the cryptogenic subset (Table 4), blacks again were less likely to have RA anatomical variation predisposing to paradoxical embolization. Although not achieving statistical significance, there was a trend toward a paucity of large PFOs among blacks.

**Discussion**

Although stroke mortality and risk factors differ greatly among the race-ethnic groups,1–3 little is known about TE-defined stroke risk factors and their relationship with race-ethnicity. Identifying a likely cause for stroke in different race-ethnic groups will enable us to test a variety of treatment and prevention strategies focused on the probable cause.

Since the initial description by Cohnheim21 in 1877, PFO has been recognized as a potential conduit for paradoxical embolization leading to cerebral ischemia. Because the prevalence of PFO in the general population is \(\approx 29\%\), there are specific morphological and functional characteristics of a PFO that are important in modifying the associated risk for stroke. Size of PFO and degree of right-to-left shunt have been associated with cryptogenic stroke.19,22

In the overall study cohort, although no difference in PFO frequency was observed among race-ethnic groups, a larger PFO size with a greater degree of shunt was seen among whites and Hispanics compared with blacks. When cryptogenic stroke patients were analyzed separately, a larger PFO and the presence of RA anatomy predisposing to paradoxical embolization were seen more frequently among whites and Hispanics. Thus, these may be relatively more important risk factors for stroke among whites and Hispanics than among blacks.

In this study, no significant difference was seen in the prevalence of ASA or degree of ASE among the race-ethnic groups. However, differences were seen regarding the correlation of ASE with PFO size. This relationship was seen in the overall population and persisted among whites and Hispanics. However, among blacks, the degree of ASE was not an indicator of PFO size, most likely because of a high prevalence of small PFOs in this group. As such, the importance of ASA as a risk factor for cryptogenic stroke may not be as significant among blacks as in the other race-ethnic groups. In the only other study that compared TE-defined stroke risk factors in a biracial cohort, Kizer et al23 found a lower prevalence of PFO among blacks compared with whites. This may be due to the high prevalence of small PFOs among blacks, which may have been difficult to detect.
TABLE 4. Adjusted Analyses

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<th></th>
<th>OR</th>
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<tr>
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*Adjusted for age and sex.
†Whites were used as the reference group.
‡Defined as ≥2 mm or ≥10 microbubbles.

In 1897, Chiari described a network of threads and fibers found in the RA. Filamentous strands in the RA can span the course of the EV along the atrial wall at the origin of the IVC. Along with a prominent EV, these structures are thought to be risk factors for paradoxical embolism by preferentially directing blood flow from the IVC toward the interatrial septum and through a PFO.11–13 Our study showed a greater prevalence of prominent EV or RA filamentous strands among whites and Hispanics compared with blacks. This was the case for both the overall stroke group and the cryptogenic subset. Because these anatomical features are thought to be associated with paradoxical embolization, this mechanism of stroke may not be as important for cryptogenic stroke in blacks.

PFO and ASA can be considered congenital anatomical variations. Studies of live-born infant databases have reported a significantly higher prevalence of small atrial septal defects among whites compared with blacks and Hispanics.25,26 Race-ethnic variations, including those of the present study, may reflect different genetic and environmental interactions.27

Ischemic stroke subtypes have been shown to differ by race-ethnicity.28 In this study, we confirm this observation in a triethnic population. Blacks and Hispanics are at a higher risk for lacunar infarcts, whereas whites are more prone to cryptogenic stroke. Much of this may derive from the different stroke risk profile among the 3 groups in our study. Hypertension and diabetes were more prevalent among blacks and Hispanics compared with whites. As such, the finding of a large PFO and RA anatomy that predisposes to paradoxical embolization is a reflection of a predominant stroke subtype among whites. Among cryptogenic stroke patients, the paucity of large PFOs and lack of RA anatomy favoring paradoxical embolization in blacks suggest that this may not be as important a mechanism for cryptogenic stroke among this race-ethnic group. Hispanics appear to reflect a heterogeneous cohort; although their stroke profile resembles that of blacks, their cardiac anatomy with regards to large PFO and RA anatomy is closer to that of whites.

Although not addressed in this study, genetic variation in the predisposition for prothrombotic state is likely to influence the importance of atrial anatomy associated with paradoxical embolization. That is, a combination of predisposition to form venous thrombus and atrial anatomy enhancing interatrial shunt may lead to a higher chance for paradoxical embolization.29,30 Indeed, the higher prevalence of such factors as factor V Leiden mutation31 and prothrombin G20210A in whites32 may have contributed to the greater prevalence of cryptogenic strokes among this race-ethnic group because the prothrombotic state is likely to enhance the role of large PFOs as a conduit for paradoxical embolization.

The strengths of this study are that it was multicenter, representative of a national cohort, and racially heterogeneous, including Hispanics, a group that has not been well studied. Its systematic assessment of TE-defined stroke risk factors represents one of the largest samples of TE-studied subjects to date. Our study is also the first to include data pertaining not just to the prevalence of PFO but also its morphological and functional characteristics, including RA anatomy, among different race-ethnic groups. Limitations include the fact that all subjects were stroke patients involved in a clinical trial, and some element of referral bias may have been present. Also the method of analyzing PFO size and shunt is semiquantitative at best and prone to variation. Nevertheless, this study remains the first to address the prevalence of ASA, PFO, and atrial anatomical variations in a well-characterized group of patients from different race-ethnic groups.

Appendix

National Institute of Neurological Disorders and Stroke (NINDS): J.R. Marler, program director.

Rodriguez et al Race-Ethnic Differences in Cryptogenic Stroke Risk Factors


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References


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