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Patent Foramen Ovale/Atrial Septal Defect Closure and Migraine: Searching the Rationale for the Procedure

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approximately 0.30 for LVM in the Framingham Heart Study. Analyzing data among hypertensive siblings, the HyperGEN study found that African American subjects had higher sibling correlation in LVM compared with white subjects (11) but that white subjects had a higher correlation in RWT than did African American subjects. However, no heritability was presented in their study.

Unlike most previous studies, we assessed the heritability of LVM after correction by the three most commonly used indices of body size. The estimates of heritability of LVM were not significantly affected by the type of indexing chosen, especially for model 3, with the greatest number of covariates (Table 1). This observation suggests that no single body size index appears preferable in studies on adult populations similar to ours. Adjustment for covariates other than body size, age, and gender had almost no influence on estimates of heritability in models 2 and 3.

More than 40% of our subjects were hypertensive, and 34.5% were taking antihypertensive medication. In our models, adjusting for SBP and antihypertensive medication did not appreciably influence the estimates of heritability after accounting for age, gender, weight, and height. Furthermore, excluding all participants taking antihypertensive medications had little effect on heritability estimations, although it yielded less significant p values (data not shown). Therefore, the effect of hypertension and antihypertensive medication may not be substantial in our study.

In summary, our study indicated that significant genetic factors influence the familial resemblance of LVM in the Caribbean Hispanic population. The considerable estimates of heritability provide the basis for our long-term goal of NOMAFS to map and detect genetic variants contributing to LVM and its related phenotypes.

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## Letters to the Editor

### Patent Foramen Ovale/Atrial Septal Defect Closure and Migraine: Searching the Rationale for the Procedure

Azarbal et al. (1) studied closing patent foramen ovale (PFO) or atrial septal defect (ASD) for prophylaxis of migraine. The accompanying editorial highlights areas of caution (2). Additional concerns are: 1) Both right-to-left shunt (PFO) and left-to-right shunt (ASD) appear associated with migraine (3). 2) Closure of ASD improves left ventricular stroke volume; this physiological variable (3) might be involved in precipitating daily migraines. 3)

Following ASD closure, plasma atrial natriuretic peptide levels would decrease (3). 4) Lateralization of headaches is a characteristic feature of migraine (4). With the concept of paradoxical embolization of gas, thrombi, or vasoactive neuromediators (2), these potential precipitants are presumed to be streamed regularly over decades to the same brain parenchymal site or circulatory segment in order to produce lateralizing headache (5). This is highly unlikely as paradoxical emboli are generally directed randomly. 5) Atenolol—a first-line migraine prophylactic—does not readily cross the blood-brain barrier (BBB) or significantly influence either brain neuronal function or circulation (4). 6) Drugs used to manage patients with migraine aura such as nifedipine, furosemide, and verapamil do not readily cross the intact BBB (6). These pharmacological absolutes challenge prevalent concepts of primary involvement of brain in migraine. 7) For a disease that can continue for decades, a follow-up period of 12 months (1) is rather short.

An explanation is required for the characteristic late appearance (in the teens or twenties) or disappearance (second and third trimesters of pregnancy and in later decades), in general, of migraine despite continued presence of PFO/ASD. Second, a high incidence of right-to-left shunt has been seen in cluster headache patients (42.5%, 17 of 40) (7). Cluster headache is a strictly lateralized primary headache; brain ischemia is not implicated in its pathogenesis. Third, migraine-with-aura patients seem to respond far better than migraine-without-aura patients (1). Headaches are less frequent, less severe, and shorter in migraine-with-aura patients. When the frequency of headache attacks is lessened, the possibility of the placebo effect in migraine trials is greater (5).

At this juncture, it is necessary to weigh carefully whether we need more reflection about the basic issues surrounding the apparent link between migraines and PFO/ASD or more clinical trials.

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## REPLY

The letter to the editor by Dr. Gupta raises some concerns, and it questions the validity of our hypothesis, which attempts to explain the observed connection between interatrial shunts and migraine headaches (1). It is appropriate to be skeptical of any new proposition, especially one that “rocks the boat” of currently accepted beliefs. We submit that there are enough independent observations of an association between patent foramen ovale (PFO) closure and significant reduction in migraine headache to allow this proposal a chance by performing a randomized clinical trial.

The clinical observation has been made that patients who have an interatrial communication 1) have an increased incidence of migraine headaches, and 2) closure of the interatrial communication results in significant improvement of the migraines. Although these studies are limited by their retrospective nature and a cohort that may not be reflective of the overall population of patients with migraine headache, the compelling findings of these studies have raised the possibility that closure of interatrial communications might provide a substantive treatment for migraine headaches.

Our hypothesis is that migraine headaches occur in people with a susceptible neuronal substrate. Several types of triggers might induce a migraine, but some of them may be chemically mediated, either through ingestion, or endogenously produced. Passing through the venous system, these chemicals are usually detoxified or perhaps just diluted in a first passage through the lungs. However, if a PFO or atrial septal defect (ASD) is present, then the intermittent right-to-left shunt that occurs with straining in either entity may permit these chemicals to enter the cerebral circulation in a high concentration and trigger the neurologic constellation that is recognized as a migraine headache. We agree with Dr. Gupta that emboli are unlikely to be the trigger of migraine headaches.

This hypothesis does not explain the mechanism of all migraine headaches. We do not understand why patients who have migraine with aura respond more frequently to PFO closure than do patients who have migraine without aura. These fascinating observations may open more avenues for research that might produce more successful therapeutic options for migraine sufferers than do current medical regimens.

With 12% of the population suffering from migraine headaches, we understand why the observations of reduction in migraine headaches following closure of interatrial shunts may generate interest and controversy. As with any new theory, the observations that support the theory come long before the randomized controlled trial that will test its validity. Our study supports the observations from other independent centers and provides a theoretical construct that “connects the dots” of rather disparate pieces of data. Let us turn the question around. How does one explain these independent observations of decreased headache following PFO closure? Placebo? This is unlikely when five independent centers all describe similar observations. Of the patients with migraine and aura, 75% had complete resolution of their headaches, with some patients followed up to three years. There is no drug or placebo that reports such a dramatic and long-lasting benefit to reduce migraine pain.

Finally, there are valid concerns with implanting a permanent device in someone's heart, especially when the indication is not life-threatening. We should use the observations of the studies as a starting point to generate a hypothesis and then perform a randomized clinical trial that will assess the potential benefits and