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Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defect or patent foramen ovale closure.

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#### Adverse Events Associated With Nickel Allergy in Patients Undergoing Percutaneous Atrial Septal Defect or Patent Foramen Ovale Closure

**To the Editor:** Percutaneous closure of patent foramen ovale (PFO) or atrial septal defect (ASD) interatrial communications is a relatively safe procedure with occasional side effects. Transcatheter closure of atrial septal communication has been reported to improve migraine headache with or without aura (MHA) in 60% of patients (1), but paradoxically, there are reports of patients who experience an increase in MHA for several weeks post-procedure (2,3). Nickel hypersensitivity occurs in up to 15% of the population (4) and has been associated with side effects in two patients who received nitinol implantable devices (5). This analysis addresses the association of nickel allergy and post-closure adverse events in 37 patients who had ASD or PFO closure with an Amplatzer (AGA Medical, Golden Valley, Minnesota) device composed of nitinol.

The patients received nickel allergy patch testing with the TRUE skin test (6) either before or after closure of the interatrial communication. Incidence of post-closure palpitations and chest discomfort was assessed by telephone interview and clinic visits. The MHA frequency and severity was evaluated using the Migraine Disability Assessment (MIDAS) questionnaire (7). All patients underwent transesophageal echocardiography at one month post-procedure. With the exception of one patient taking warfarin for a hypercoagulable state, all patients received antiplatelet therapy with aspirin indefinitely and clopidogrel for 30 to 90 days post-procedure.

Between 2001 and 2005, there were 108 patients who received a PFO closure device and 42 patients who received an ASD closure device. Of the 150 patients, 62 (41%) experienced chest pain, palpitations, or increased MHA. Nickel patch testing was available in 37 patients. There were seven patients (5%) who noted new-onset MHA or increased frequency and severity of MHA or aura post-procedure. The average MIDAS scores of these patients before and after the procedure were 0 and  $41 \pm 37$ , respectively. Of the seven patients, six were tested for nickel allergy, and four of these patients (67%) had a positive nickel skin test result (Table 1). This finding occurred more frequently with ASD devices compared with PFO devices (12% vs. 2%,  $p = 0.02$ ) (Table 2).

New-onset or worsening MHA was associated with nickel allergy ( $p = 0.035$ ) (Table 1). When adverse events (chest discomfort, palpitations, and MHA) were combined, there was a significant association with nickel allergy ( $p = 0.028$ ). The association was strongest ( $p = 0.005$ ) with chest discomfort and MHA.

Of the six patients in whom new or increased MHA developed, five patients had headaches that developed within one week of stopping clopidogrel. These patients were treated by re-initiating clopidogrel at 75 mg/day. Although the MHAs had been persistent for three to five days, all patients reported almost complete relief of their symptoms within a few hours of taking the first dose of clopidogrel. Clopidogrel was then stopped after one month in two patients, and both had recurrence of MHA within five days. The symptoms were abolished again within hours of restarting clopidogrel in both women. The sixth patient developed pericarditis with effusion and atrial fibrillation as well as MHA within one

week of the implantation. He was treated with a tapering dose of prednisone. Because he had a hypercoagulable condition, he was treated with warfarin and therefore had not been placed on clopidogrel before or after the procedure. After seven months and two courses of prednisone, the chest pain and palpitations have resolved and the headaches have improved.

The most important observation of this study was that 67% of the patients who had new onset or increased frequency and severity of MHA tested positive for nickel hypersensitivity. The two patients who also experienced symptoms but were not allergic to nickel had large ASD devices (38 mm). The sample size is small; nevertheless, these observations raise intriguing hypotheses.

One possible mechanism to explain the new onset or exacerbation of MHA is that a local inflammatory reaction to the implanted device results in the formation of platelet adhesions. These substances could then embolize to the brain, causing microinfarcts and MHA. An observation that lends support to this hypothesis is that five of the patients noted a marked increase in frequency of MHA shortly after discontinuing clopidogrel, suggesting that the pharmacologic suppression of platelet aggregation on the implanted device may be preventing embolization. One other report has documented the benefit of clopidogrel in reducing MHA after nitinol device implantation (8). All five patients noted an improvement in MHA after re-starting clopidogrel. However, there was no evidence of abnormal MRI lesions in the two cases with the most severe MHA. In addition, follow-up transesophageal echocardiography did not show any thrombus on any of these Amplatzer devices. Therefore, there is no evidence for thrombus formation as the etiology of these neurologic symptoms.

An alternative mechanism to explain new onset or exacerbation of MHA is that a localized reaction around the device releases inflammatory mediators into the left atrium, which then travel to the cerebral circulation and induce MHA. Presumably the inflammation is greater if the patient is sensitive to nickel, but an exaggerated response may occur without nickel allergy and produce the same symptom complex, especially if a large device is implanted. This may explain why MHAs are more likely to occur with ASD closure devices. This hypothesis opens research avenues to assess the effect of chemokines or other inflammatory proteins as primary triggers for MHAs in patients with or without implanted

**Table 1.** Incidence of Post-Procedural Complications as a Function of the Presence or Absence of Nickel Allergy

	Nickel Test + n = 10 (%)	Nickel Test - n = 27 (%)	p Value
Chest discomfort, palpitations, or MHA/aura	9 (90)	13 (48)	0.028
Chest discomfort or MHA/aura	6 (60)	3 (11)	0.005
New or worsening MHA/aura	4 (40)	2 (7)	0.035
Palpitations	5 (50)	11 (41)	0.7
Chest discomfort	3 (30)	2 (7)	0.1

MHA = migraine headache with or without aura.

**Table 2.** Presence of MHA, Palpitations, or Chest Discomfort as a Function of Device Type

	PFO Closure Device n = 108 (%)	ASD Closure Device n = 42 (%)	p Value
MHA	2 (2)	5 (12)	0.02
Palpitations	26 (24)	14 (33)	0.3
Chest discomfort	13 (12)	2 (5)	0.2

ASD = atrial septal defect; MHA = migraine headache with or without aura; PFO = patent foramen ovale.

devices. This concept is consistent with the observation that closure of PFO or ASD leads to a dramatic reduction or abolition of MHAs in 75% of patients (1). The observation that these patients responded dramatically and rapidly to administration of clopidogrel suggests that this drug may be acting as an anti-inflammatory agent, either to decrease the release of the trigger chemicals from the inflammatory site in the left atrium or by acting on nociceptive neural adenosine receptors to inhibit the migrainous response to inflammatory byproducts.

The initial recognition of nickel hypersensitivity as a potential problem occurred with our sentinel case. Subsequently, an attempt was made to contact previous patients that we had treated. All prospective patients thereafter were screened for nickel allergy. This selection bias captured all of the patients who complained of an adverse event, but the study population does not represent all of the patients without symptoms who might have a positive nickel allergy skin test result. This report of a 27% (10 of the 37) positive nickel allergy rate is therefore likely exaggerated.

In conclusion, new onset or increased frequency and severity of MHA after interatrial communication closure is associated with nickel hypersensitivity and large ASD devices. This phenomenon may be related to byproducts of an exaggerated inflammatory response. These events may persist for three to six months, but all eventually resolved. The MHAs and aura respond dramatically to

clopidogrel. A larger prospective trial evaluating the safety of ASD and PFO closure in patients with nickel allergy is warranted.

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## Prospective Aortic Screening in Men With Coronary Aneurysms

**To the Editor:** In older men, abdominal aortic aneurysm (AAA) is a frequent cause of morbidity and mortality. The prevalence of asymptomatic AAA is within the range of 5% to 7% in men >65 years old (1,2). Ultrasonography is the method of choice for the detection of AAA and may allow a significant reduction in aneurysm-related death (1). However, despite these positive results, systematic screening remains uncommon in usual practice (2). The yield of ultrasound detection of AAA would be increased by the introduction of more selective screening, but until now there has been no formal evaluation of using screening criteria other than gender or age.

Coronary angiography is widely used for the evaluation of suspected coronary artery disease (CAD). We recently reported that coronary aneurysms (CA), which are found in 2% to 5% of patients undergoing coronary angiography may share common genetic susceptibility factors with AAA (3). Retrospective studies also suggest that CA and AAA may be associated (3,4). However, a prospective evaluation of the risk of AAA in patients with CA is lacking. We thus designed the present study to test the hypothesis that these two aneurysmal diseases might be associated and that

patients who had CA identified at angiography may constitute a group at high risk of AAA in whom aortic screening would result in a high diagnostic yield.

Male patients undergoing coronary angiography in our institution, and with angiographic evidence of CAD, were eligible for inclusion immediately after the procedure. Our ethics committee approved the protocol, and all patients gave written informed consent. We excluded patients who underwent coronary angiography before AAA surgical repair. A single investigator, unaware of the clinical details of the patient, reviewed the angiograms. The CA group comprised patients with localized or diffuse coronary dilation that exceeded the diameter of the angiographically apparently normal adjacent segments by a factor of >1.5 (5). For every case, one control without CA was randomly selected from the same population.

An ultrasound scan of the abdominal aorta was performed within 24 h of coronary angiography by experienced ultrasonographers unaware of the group assignment of the patient. The maximal anterior-posterior diameters of the suprarenal aorta just upon the left renal artery ostium and the infrarenal aorta were