Atrial Septal Defect and the Risk of Ischemic Stroke in the Perioperative Period of Noncardiac Surgery

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Stroke is a serious complication of noncardiac surgery. Congenital defects of the interatrial septum may be a potent risk factor for perioperative stroke. The aim of the present study was to determine the association between atrial septal defect (ASD) or patent foramen ovale (PFO) and in-hospital perioperative ischemic stroke after non-cardiac surgery in a large nationwide cohort of patients hospitalized in the United States. Patients undergoing noncardiac surgery between 2004 and 2014 were identified using the Healthcare Cost and Utilization Project's National Inpatient Sample. Patients without an in-hospital echocardiogram were excluded. The presence of an ostium secundum-type ASD or PFO was identified by ICD-9 diagnosis code 745.5. The primary study outcome was perioperative acute ischemic stroke. Between 2004 and 2014, there were 639,985 admissions for noncardiac surgery with an in-hospital echocardiogram. An ASD or PFO was documented in 9,041 (1.4%) hospitalizations. Perioperative ischemic stroke occurred more frequently in patients with an ASD or PFO compared with those without an ASD or PFO (35.1% vs 6.0%, p <0.001). The association between ASD or PFO and ischemic stroke persisted after adjustment for demographics and clinical covariates (adjusted odds ratio 6.30, 95% confidence interval, 5.59 to 7.10) and in all non-cardiac surgery subtypes. In conclusion, in a large, nationwide analysis of patients undergoing noncardiac surgery, a diagnosis of ASD or PFO was associated with an increased risk of acute ischemic stroke overall and in all surgical subtypes. Additional measures are necessary to mitigate stroke risk in patients with septal defects who are planned for non-cardiac surgery. Published by Elsevier Inc. (Am J Cardiol 2019;124:1120−1124)

Background

Worldwide, more than 300 million surgeries are performed annually.[1] Stroke is a serious complication of surgery that is associated with long-term morbidity and mortality.[2] The risk of perioperative stroke varies based on patient characteristics and surgical factors, with the highest risks in patients undergoing cardiac and vascular procedures.[2] Congenital defects of the interatrial septum may be a potent risk factor for perioperative stroke. Atrial septal defects (ASD) are present in 1.6 per 1000 live births and patent foramen ovale (PFO) is identified in nearly 25% of adults.[3,4] Both ASD and PFO are associated with ischemic stroke in a variety of clinical settings.[5−8] In single-center studies and surgery-specific analyses, PFO appears to be associated with increased odds of stroke in the perioperative period,[9,10] and over long-term postoperative follow-up.[11] The aim of the present study was to determine the association between ASD or PFOs and in-hospital perioperative cardiovascular and cerebrovascular outcomes after noncardiac surgery in a large nationwide cohort of patients hospitalized in the United States.

Methods

Patients undergoing noncardiac surgery between 2004 and 2014 were identified using the Healthcare Cost and Utilization Project's National Inpatient Sample.[12] The NIS is a large administrative database that contains data from more than 7 million hospitalizations in the United States each year. The NIS approximates a 20% stratified sample of all discharges from nonfederal hospitals in the United States.[12] Patients were eligible for inclusion if they had a principal *International Classification of Diseases, Ninth Revision* (ICD-9) procedure code for a major therapeutic operating room procedure (HCUP Procedure Class 4) during the hospital admission. Principal Clinical Classifications Software procedure codes, aggregates of related ICD-9 procedure codes, were used to stratify operating room procedures by surgical subtype. Hospitalizations with primary cardiac procedures and surgery, cardiac transplantation, bone marrow transplantation, ophthalmologic surgery, radiation therapy, dental surgery and nonoperating room procedures were excluded. The remaining patients were clustered by major surgical subtype into the following groups: endocrine, general, genitourinary, gynecologic, gynecologic and obstetric, neurosurgery, orthopedic, otolaryngology, skin and breast, thoracic, noncardiac solid organ transplant, and vascular surgery.

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The presence of an ostium secundum-type ASD or PFO was identified by the ICD-9 diagnosis code 745.5. Since ASD and PFO may go undetected in patients without dedicated cardiac imaging, only patients who underwent an echocardiogram during the surgical admission were included in the analysis. Echocardiography was identified by the ICD-9 procedure code 88.72.

The primary study outcome was acute ischemic stroke defined by ICD-9 diagnosis codes 433.x, 434.x, 436.x, 437.0, and 437.1.[13] Transient ischemic attack (TIA) was defined by ICD-9 diagnosis code 435.x.[14] Myocardial infarction (MI) was defined using ICD-9 diagnosis code for acute ST-segment elevation MI (STEMI) (ICD-9 diagnosis codes 410.01 to 410.61, 410.81, and 410.91) and non-ST-segment elevation MI (NSTEMI) (ICD-9 diagnosis code 410.71), as previously described.[15]

Continuous variables were reported as means with the standard error of measurement and were compared using linear regression. Categorical variables were reported as percentages and were compared by Chi-square tests. Multivariable logistic regression models were generated to estimate odds ratios adjusted for patient demographics, cardiovascular risk factors, and comorbidities, including age, sex, race, hypertension, hyperlipidemia, diabetes mellitus, end stage renal disease, valvular heart disease, atrial fibrillation or atrial flutter, malignancy, year of operation, urgent/emergent surgery, and noncardiac surgical subtype. Sensitivity analyses were preformed excluding patients who underwent noncardiac vascular surgery, a surgical subtype strongly associated with cardiovascular complications, including stroke.[16] Sampling weights were applied to determine national incidence estimates, including prespecified clustering and strata, unless otherwise noted. Statistical analyses were performed using SPSS 25 (IBM SPSS Statistics, Armonk, NY). Two-sided p-values <0.05 were considered to be statistically significant. The NIS is a publicly available, deidentified dataset, and the study was exempt from institutional board review.

Results

Between 2004 and 2014, we identified 639,985 admissions for noncardiac surgery in which in-hospital diagnostic echocardiography was performed. An ASD or PFO was documented in 9,041 (1.4%) of noncardiac surgical hospitalizations with an in-hospital echocardiogram. Patients with a diagnosis of ASD or PFO were younger, more likely to be white, and more likely to have peripheral vascular disorders, a history of venous thromboembolism, and prior stroke compared with patients without ASD or PFO. Surgical patients with ASD or PFO were less likely to have hypertension, diabetes mellitus, coronary artery disease, heart failure, atrial fibrillation or flutter, and renal disease. Full baseline characteristics of patients undergoing noncardiac surgery with and without ASD or PFO are shown in Table 1.

Table 1
Baseline characteristics of patients hospitalized for noncardiac surgery who underwent echocardiography, with and without an atrial septal defect (ASD) or patent foramen ovale (PFO)

Variable	All patients (n = 639,985)	Atrial septal defect (ASD) or patent foramen ovale (PFO)		p Value
		Yes (n = 9,041)	No (n = 630,944)	
Age (years), mean (S.E.)	65.87 (0.22)	59.45 (0.43)	65.96 (0.22)	<0.001
Female sex	315,744 (49.3%)	4,302 (47.6%)	311,442 (49.4%)	0.117
White non-Hispanic	378,672 (59.2%)	5,814 (64.3%)	372,858 (59.1%)	<0.001
Black non-Hispanic	87,266 (13.6%)	834 (9.2%)	86,432 (13.7%)	
Hispanic	46,385 (7.2%)	550 (6.1%)	45,834 (7.3%)	
Other race	36,363 (5.7%)	378 (4.2%)	35,986 (5.7%)	
Unknown race	91,299 (14.3%)	1,465 (16.2%)	89,834 (14.2%)	
Current or former smoker	137,204 (21.4%)	2,349 (26.0%)	134,855 (21.4%)	<0.001
Hypertension	404,342 (63.2%)	5,177 (57.3%)	399,165 (63.3%)	<0.001
Hyperlipidemia	185,108 (28.9%)	2,974 (32.9%)	182,134 (28.9%)	<0.001
Diabetes mellitus	194,826 (30.4%)	2,079 (23.0%)	192,747 (30.5%)	<0.001
Coronary artery disease	171,622 (26.8%)	1,785 (19.7%)	169,837 (26.9%)	<0.001
Prior percutaneous coronary intervention	26,801 (4.2%)	205 (2.3%)	26,596 (4.2%)	<0.001
Prior coronary bypass grafting	37,031 (5.8%)	326 (3.6%)	36,705 (5.8%)	<0.001
Congestive heart failure	132,157 (20.7%)	1,137 (12.6%)	131,020 (20.8%)	<0.001
Peripheral vascular disorders	93,927 (14.7%)	1,654 (18.3%)	92,273 (14.6%)	<0.001
Atrial fibrillation or flutter	167,028 (26.1%)	1,833 (20.3%)	165,195 (26.2%)	<0.001
Valvular disease	93,589 (14.6%)	1,460 (16.1%)	92,130 (14.6%)	0.102
Prior venous thromboembolism	17,648 (2.8%)	406 (4.5%)	17,242 (2.7%)	<0.001
Prior stroke	23,916 (3.7%)	582 (6.4%)	23,334 (3.7%)	<0.001
Pulmonary disease	134,503 (21.0%)	1,707 (18.9%)	132,796 (21.0%)	0.027
Chronic kidney disease	121,102 (18.9%)	1,166 (12.9%)	119,936 (19.0%)	<0.001
End stage renal disease	48,446 (7.6%)	478 (5.3%)	47,969 (7.6%)	<0.001
Malignancy	47,692 (7.5%)	532 (5.9%)	47,160 (7.5%)	0.019
Anemia	184,758 (28.9%)	2,259 (25.0%)	182,499 (28.9%)	0.001
Hypercoagulable state	66,227 (10.3%)	1,048 (11.6%)	65,179 (10.3%)	0.088
Collagen vascular disease	20,222 (3.2%)	254 (2.8%)	19,968 (3.2%)	0.390

A total of 41,167 ischemic strokes (6.4%) were identified during hospitalizations for noncardiac surgery. Perioperative ischemic stroke occurred more frequently in patients with an ASD or PFO diagnosed by echocardiography compared with those without an ASD or PFO (35.1% vs 6.0%, p <0.001, unadjusted odds ratio [OR], 8.46, 95% confidence interval [CI], 7.61 to 9.41). The association between ASD or PFO and perioperative stroke persisted after adjustment for demographics and clinical covariates (adjusted OR [aOR] 6.30, 95% CI, 5.59 to 7.10). The frequencies of perioperative stroke in patients with and without ASD or PFO are shown by surgical subtype in Figure 1. TIA was also more frequent in patients with ASD or PFO (2.3% vs 0.7%, p <0.001; aOR, 2.28, 95% CI, 1.64 to 3.18).

Overall, patients undergoing noncardiac surgery with an ASD or PFO did not have an increased risk of death or perioperative MI. In analyses adjusted for demographics and comorbidities, patients with ASD or PFO had a decreased risk of in-hospital death and no difference in the risk of MI compared to patients without a septal defect (Table 3).

Due to the excess risk of stroke associated with vascular procedures, we performed a sensitivity analysis that excluded hospital admissions for vascular surgery (Supplementary Tables 1 and 2). In the cohort of patients undergoing nonvascular, noncardiac surgery, ischemic stroke occurred more frequently in patients with an ASD or PFO compared with those without a septal defect (29.3% vs 3.7%, p <0.001; aOR, 10.69, 95% CI, 9.03 to 12.65). TIA was also associated with ASD or PFO in this cohort. Complete perioperative cardiovascular and cerebrovascular outcomes for noncardiac, nonvascular surgery are shown in Supplementary Table 3. The adjusted odds of ischemic stroke associated with ASD or PFO for each surgical subtype are shown in Figure 1.

Discussion

In this analysis of 639,985 hospitalizations for major noncardiac surgery in the United States, a diagnosis of an ASD or PFO by echocardiography was associated with perioperative acute ischemic stroke, even after adjustment for baseline demographics, cardiovascular risk factors, and comorbidities. Similar associations were identified in a sensitivity analysis excluding patients undergoing vascular surgery. In contrast, ASD or PFO was not associated with an increased risk of MI or in-hospital death. This is among the largest analyses of the associations between ASD or PFO and perioperative cardiovascular events in multiple subtypes of noncardiac surgery.

Venous thromboembolism during the perioperative period is common and is attributed to increased hypercoagulability, venous stasis, and perioperative withdrawal of antithrombotic agents.[2] In normal circumstances, small venous thromboemboli are filtered by the pulmonary circulation. However, ASDs and PFOs, congenitally acquired communications between the right and left atria, provide a mechanism for paradoxical embolism. The greater frequency of perioperative cerebrovascular events in patients with ASD or PFO observed in this analysis is consistent with previous literature and strongly suggests that paradoxical embolization may be an important mechanism of perioperative cerebrovascular risk. Furthermore, the greater incidence of perioperative stroke in patients with PFO or ASD was observed despite younger ages, a lower prevalence of hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, and atrial arrhythmias. There was no association between ASDs and MI in the present study, despite the theoretical risk of paradoxical embolism to the coronary arteries. In aggregate, these data suggest that the increase in ischemic stroke risk in patients with ASD or PFO is not attributable to a greater burden of atherosclerotic cardiovascular disease in this cohort.

The magnitude of the association in the present study is somewhat greater than that reported in smaller studies evaluating the risk of perioperative stroke in patients with PFO. In a retrospective cohort study of 150,198 patients undergoing noncardiac surgery, PFOs were associated with a twofold increased odds of perioperative ischemic stroke.[10] This

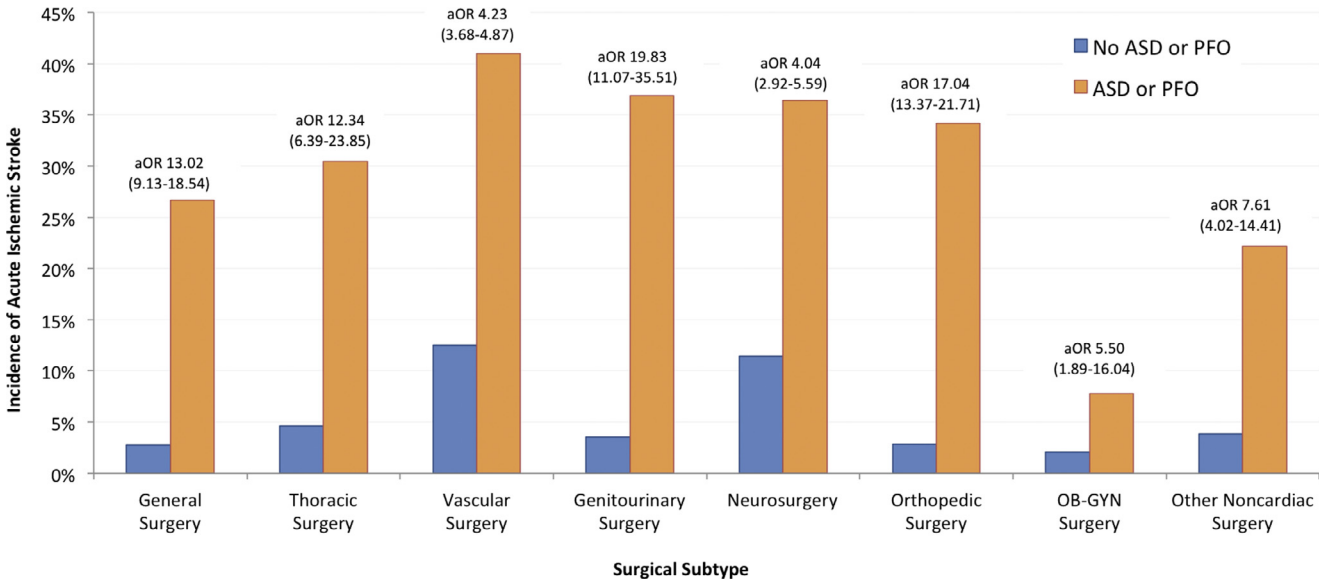

Figure 1. Perioperative ischemic stroke by surgical subtype in patients undergoing echocardiography, with and without atrial septal defect (ASD) or patent foramen ovale (PFO).

Table 2
Characteristics of the surgical hospitalization for patients who underwent echocardiography, with and without an atrial septal defect (ASD) or patent foramen ovale (PFO)

	All patients (n = 639,985)	Atrial septal defect (ASD) or patent foramen ovale (PFO)		p Value
		Yes (n = 9,041)	No (n = 630,944)	
Urgent/emergent surgery	502,238 (78.7%)	7,029 (78.0%)	495,209 (78.7%)	0.538
Endocrine surgery	3,188 (0.5%)	20 (0.2%)	3,168 (0.5%)	<0.001
General surgery	127,984 (20.0%)	957 (10.6%)	127,027 (20.1%)	
Genitourinary surgery	27,324 (4.3%)	234 (2.6%)	27,090 (4.3%)	
Gynecologic surgery	7,333 (1.1%)	69 (0.8%)	7,264 (1.2%)	
Gynecologic and obstetric surgery	16,027 (2.5%)	258 (2.9%)	15,770 (2.5%)	
Neurosurgery	37,796 (5.9%)	715 (7.9%)	37,081 (5.9%)	
Orthopedic surgery	189,315 (29.6%)	1,597 (17.7%)	187,718 (29.8%)	
Otolaryngology surgery	4,374 (0.7%)	49 (0.5%)	4,325 (0.7%)	
Skin and breast surgery	29,599 (4.6%)	260 (2.9%)	29,339 (4.7%)	
Thoracic surgery	28,904 (4.5%)	243 (2.7%)	28,661 (4.5%)	
Noncardiac solid organ transplant surgery	4,968 (0.8%)	175 (1.9%)	4,793 (0.8%)	
Vascular surgery	170,507 (26.6%)	4,534 (50.2%)	165,973 (26.3%)	

finding was also consistent in 20% of patients who had echocardiographic data available for analysis. In a separate study, Friedrich et al also reported similar increases in long-term risk of perioperative stroke in surgical patients with a PFO.[11] The greater odds of perioperative stroke observed in the present analysis compared with previous reports may be related to more selective coding for large PFOs or frank ASD, which would provide a larger defect through which a paradoxical embolism could travel. Differences in demographics, comorbidities, surgical subtypes, and perioperative medical management may also account for differences in the results. In contrast, the strength of the association between ASD and perioperative stroke identified in the present analysis was less robust than that reported by Perfetti et al, in which an ASD was associated with a nearly 30-fold increased risk of stroke among patients undergoing total hip arthroplasty.[9]

There are several important limitations to this study. First, these analyses are based on administrative data, which are subject to selection bias in reporting or errors in coding. Second, to avoid confounding based on the presence of undiagnosed ASD or PFO in patients without known cardiac imaging, we limited our analysis to patients who underwent in-hospital echocardiography. Unfortunately, we cannot exclude bias in the referral for evaluation by echocardiogram during the surgical admission, which may enrich the cohort for both perioperative stroke and/or a diagnosis of ASD or PFO. In addition, the frequency of all perioperative complications was significantly higher among patients undergoing echocardiography in this large administrative database than has been previously reported in the surgical population at large. Thus, the requirement for echocardiography introduces a selection bias and may not reflect the perioperative risks in the overall surgical population nationwide. Third, detailed echocardiographic data were not available in the present analysis, and the identification of ASD or PFO was performed using ICD-9 diagnosis codes. Similarly, the size of the septal defect, which may be associated with the risk of paradoxical embolism, was not available for analysis. Left ventricular systolic function was not reported. The presence of an interatrial septal aneurysm, a structural abnormality also associated with stroke, was not reported. Other high-risk echocardiographic features, such as the presence of left atrial appendage thrombus, were not available. Fourth, medical therapy was not captured in the NIS and the use of perioperative antithrombotic therapy could not be determined. We cannot exclude additional unmeasured confounders that may have impacted the study findings. Fifth, the timing of ischemic stroke during the hospital admission is not known, although patients were unlikely to have undergone a major noncardiac surgery in the days following an acute ischemic stroke.

Table 3
Perioperative outcomes of patients who underwent echocardiography, with and without an atrial septal defect (ASD) or patent foramen ovale (PFO)

	Atrial septal defect (ASD) or Patent foramen ovale (PFO)		p Value	Unadjusted OR (95% CI)	Partially adjusted OR (95% CI)*	Fully adjusted OR (95% CI)†
	Yes (n = 9041)	No (n = 630,044)				
Ischemic stroke	3,178 (35.1%)	37,989 (6.0%)	<0.001	8.46 (7.61-9.41)	6.51 (5.79-7.33)	6.30 (5.59-7.10)
Transient ischemic attack	208 (2.3%)	4,638 (0.7%)	<0.001	3.17 (2.31-4.37)	2.38 (1.71-3.30)	2.28 (1.64-3.18)
Myocardial infarction	346 (3.8%)	35,300 (5.6%)	0.001	0.67 (0.52-0.86)	0.78 (0.61-1.00)	0.79 (0.62-1.01)
Death	359 (4.0%)	42,082 (6.7%)	<0.001	0.58 (0.45-0.74)	0.64 (0.50-0.82)	0.66 (0.51-0.84)
Death and AMI	660 (7.3%)	71,567 (11.3%)	<0.001	0.62 (0.52-0.73)	0.70 (0.59-0.83)	0.71 (0.60-0.85)

* Adjusted for age, sex, race, year of operation, urgent/emergent surgery, and noncardiac surgical subtype.

† Adjusted for: age, sex, race, hypertension, hyperlipidemia, diabetes mellitus, end stage renal disease, valvular heart disease, atrial fibrillation/flutter, malignancy, year of operation, urgent/emergent surgery, and noncardiac surgical subtype.

In this large, nationwide analysis of patients undergoing noncardiac surgery in the United States, we found that a diagnosis of ASD or PFO was associated with an increased risk of perioperative acute ischemic stroke across all major surgical subtypes. These data confirm the findings of smaller studies and support efforts to identify additional measures to mitigate stroke risk in patients with septal defects who are planned for noncardiac surgery.

Disclosures

The authors report no relationships that could be construed as a conflict of interest

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.030.

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