Prevalence and Repair of Intraoperatively Diagnosed Patent Foramen Ovale and Association With Perioperative Outcomes and Long-term Survival

Richard A. Krasuski, MD
Stephen A. Hart, BS
Drew Allen, DO
Athar Qureshi, MD
Gosta Pettersson, MD
Penny L. Houghtaling, MS
Lillian H. Batizy, MS
Eugene Blackstone, MD

Context A recent survey suggested that cardiothoracic surgeons may alter planned procedures to repair incidentally discovered patent foramen ovale (PFO). How frequently this occurs and the impact on outcomes remain unknown.

Objective To measure the frequency of incidentally discovered PFO closure during cardiothoracic surgery and determine its perioperative and long-term impact.

Design, Setting, and Patients We reviewed the intraoperative transesophageal echocardiograms of 13 092 patients without prior diagnosis of PFO or atrial septal defect undergoing surgery at the Cleveland Clinic, Cleveland, Ohio, from 1995 through 2006. Postoperative outcomes were prospectively collected until discharge.

Main Outcome Measures All-cause hospital mortality and stroke were predetermined primary outcomes; length of hospital stay, length of intensive care unit stay, and time on cardiopulmonary bypass were secondary outcomes.

Results Intraoperative PFO was diagnosed in 2277 patients in the study population (17%), and risk factors for stroke were similar in patients with and without PFO. After propensity matching was performed with the comparator groups, patients with PFO demonstrated similar rates of in-hospital death (3.4% vs 2.6%, $P=.11$) and postoperative stroke (2.3% vs 2.3%, $P=.84$). Surgical closure was performed in 639 PFO patients (28%), and surgeons were more likely to close defects in patients who were younger (mean [SD] age, 61.1 [14] vs 64.4 [13] years; $P<.001$), were undergoing mitral or tricuspid valve surgery (51% vs 32%, $P<.001$), or had history of transient ischemic attack or stroke (16% vs 10%, $P<.001$). Patients with repaired PFO demonstrated a 2.47-times greater odds (95% confidence interval, 1.02-6.00) of having a postoperative stroke compared with those with unrepaired PFO (2.8% vs 1.2%, $P=.04$). Long-term analysis demonstrated that PFO repair was associated with no survival difference ($P=.12$).

Conclusions Incidental PFO is common in patients undergoing cardiothoracic surgery but is not associated with increased perioperative morbidity or mortality. Surgical closure appears unrelated to long-term survival and may increase postoperative stroke risk.

JAMA. 2009;302(3):290-297 www.jama.com

The role that patent foramen ovale (PFO) plays in cryptogenic stroke remains controversial. The debate over an association has existed for more than a century, but causal data linking PFO and cryptogenic stroke remain anecdotal.[1-7] Epidemiological evidence is consistent with an increased risk of stroke associated with PFO but data are not conclusive.[8-17] The paucity of evidence supporting PFO as the mechanism for cryptogenic stroke has left many questions in the field unanswered, including when PFO repair is appropriate. A number of ongoing randomized trials comparing medical management and percutaneous closure are attempting to answer this question in the cryptogenic stroke population, despite the fact that optimal medical therapy also remains unknown. Incidentally diagnosed PFO in asymptomatic patients presents yet another management challenge that clinicians regularly face.[18]

Widespread use of intraoperative transesophageal echocardiography (TEE) during cardiothoracic surgery has made incidental discovery of PFO common.[19] Sukernik and Bennett-Guerrero[18] recommend routine PFO closure when almost no alteration of the surgical plan is required, such as during mitral or tricuspid valve surgeries. It has also been suggested that PFO be repaired when the probability of post-

Author Affiliations: Section of Clinical Cardiology, Department of Cardiovascular Medicine (Dr Krasuski and Mr Hart); Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (Mr Hart); and Departments of Internal Medicine (Dr Allen), Pediatric Cardiology (Dr Qureshi), Quantitative Health Sciences (Mss Houghtaling and Batizy and Dr Blackstone), and Cardiothoracic Surgery (Drs Pettersson and Blackstone), Cleveland Clinic, Cleveland, Ohio.
Corresponding Author: Richard A. Krasuski, MD, Department of Cardiovascular Medicine, J2-4, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (krasusr@ccf.org).

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

operative right-to-left shunting is significant.[20,21] Clearly the increased morbidity and mortality associated with intraoperative repair must be weighed against the risks of cyanosis or postoperative stroke.

A recent survey of cardiothoracic surgeons in the United States with a 64% response rate demonstrated a high degree of variability in management of intraoperatively discovered PFO.[22] For example, during planned on-pump bypass surgery, 27.9% of responders stated they always closed intraoperatively discovered PFO while 10.3% never did. Interestingly, 11% always converted a planned off-pump procedure to on-pump to close the defect, and this rate rose to 96% if the patient had a history of possible paradoxical embolism. In light of these data, we sought to examine the prevalence of intraoperatively diagnosed PFO in cardiothoracic surgery patients and investigate the relationship of repair on perioperative outcomes and long-term survival.

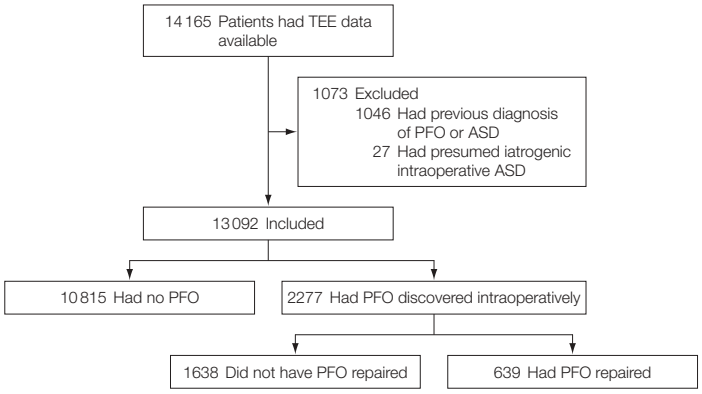
METHODS

Study Population

We reviewed the intraoperative transesophageal echocardiograms of patients undergoing cardiothoracic surgery between 1995 and 2006 at the Cleveland Clinic, Cleveland, Ohio. Data were matched with operative records from the Cleveland Clinic Cardiovascular Information Registry to obtain standardly collected demographic features, surgical management characteristics, and perioperative outcomes. Race/ethnicity was self-identified as either Asian, black, Hispanic, Native American, other, unknown, or white at the time of surgery. Long-term survival was assessed using the Social Security Death Index. The study was conducted with institutional review board approval.

During the study period, 41 578 cardiothoracic surgeries were performed and 14 165 entries (34%) had available intraoperative TEE data both preoperatively and postoperatively. A total of 1046 patients were excluded because of previous diagnosis of PFO or atrial septal defect (ASD). Patients with ASD noted postoperatively but not preoperatively (n=27) were also excluded from analysis, because it was assumed these defects resulted from septal manipulation during surgery. A single reviewer (R.A.K.) reviewed a random sampling of 100 study echocardiograms for quality control and agreed with the reported PFO interpretation in each study. Medical records and operative notes were reviewed for entries missing PFO status or intraoperative repair status to recover missing data. The final data set comprised 13 092 surgeries (FIGURE 1). The frequency of the different types of surgeries performed are listed in TABLE 1.

Figure 1. Study Population Selection



ASD indicates atrial septal defect; PFO, patent foramen ovale; TEE, transesophageal echocardiography.

Table 1. Surgical Procedure Frequency

Procedure	No. (%)
CABG only	3236 (25)
Valve only	3679 (28)
Isolated AV	1241 (9)
Isolated MV	1730 (13)
Isolated TV	47 (0.4)
CABG plus valve	2312 (18)
CABG plus AV only	1047 (8)
CABG plus MV only	805 (6)
CABG plus TV only	22 (0.2)
CABG plus other[a]	553 (4)
Valve plus other[a]	1594 (12)
CABG plus valve plus other[a]	893 (7)
Other only[a]	825 (6)

Abbreviations: AV, aortic valve; CABG, coronary artery bypass graft; MV, mitral valve; TV, tricuspid valve.
[a] Includes coronary and carotid artery endarterectomy, ventricular aneurysm repair, and other unclassified procedures.

Outcome Measures and Risk Factors

Postoperative stroke and all-cause hospital death were the primary outcome measures of the study. Length of stay from surgery to discharge, length of stay in intensive care units (ICUs), and total time spent on cardiopulmonary bypass were included as secondary outcome measures. Surgical complications that could result from prolonged operations, such as postoperative myocardial infarction, bleeding, renal failure, septicemia, and circulatory arrest, were also included. Established risk factors for stroke, such as previous stroke or transient ischemic attack (TIA), atrial septal aneurysm, aortic arch atheroma, atrial fibrillation, and left atrial dilation, were included along with other comorbidities as potential confounders in propensity analyses.[14,23-33]

Statistical Analysis

Two perioperative analyses were performed. The first analysis stratified the cohort by presence of intraoperatively diagnosed PFO, and the second analysis stratified patients with intraoperatively diagnosed PFO by whether patients underwent PFO repair. Group comparisons were made using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Multivariable logistic regression was used to evaluate comparator groups. Bootstrap bagging methods were used to determine reliable pre-

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

dictors of PFO in the first analysis and PFO repair in the second analysis with random resampling and automated stepwise selection (with entry criteria of $P \leq .07$ and retention criteria of $P \leq .05$).[34,35] Variables or clusters of variables that entered more than 50% of 1000 models were chosen for the final model.

Once a set of reliable predictors was found, the models were augmented with the most reliable predictors from clinically relevant groups including established risk factors to form a saturated model. Variables used in propensity models included demographic characteristics, risk factors for stroke, preoperative health status, valve pathology, comorbidities, and surgery details. A propensity score was calculated for each patient by solving the saturated model for the probability of PFO detection in the first comparison and the probability of repair in the second comparison.[36] The propensity scores from the saturated models were used to perform greedy matching.[37] Long-term follow-up analyses were performed in a similar manner and represented in Kaplan-Meier survival curves compared using log-rank tests.[38] By using propensity analyses and matching methods, we were able to eliminate bias while still maintaining adequate power to detect differences in complication rates. Data management and statistical analysis were performed in SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Table 2. Incidence of Intraoperative PFO and Repair Rate by Year

Year of Surgery	Procedures, No.	No. (%) PFO	No. (%) Repair
1995[a]	39	7 (18)	1 (14)
1996	748	97 (13)	20 (21)
1997	862	117 (14)	18 (15)
1998	961	94 (10)	24 (26)
1999	1137	202 (18)	48 (24)
2000	1819	223 (12)	56 (25)
2001	1773	326 (18)	107 (33)
2002	1739	372 (21)	110 (30)
2003	1477	327 (22)	126 (39)
2004	1190	239 (20)	59 (25)
2005	712	155 (22)	43 (28)
2006[a]	635	118 (19)	27 (23)
Total	**13 092**	**2277 (17)**	**639 (28)**

Abbreviation: PFO, patent foramen ovale.
[a]Data came from part of the year.

Table 3. Demographics and Clinical Characteristics of Study Population

	Intraoperative PFO (n = 2277)	No PFO (n = 10 815)	*P* Value
Female sex, No. (%)	802 (35)	3638 (34)	.15
Age, mean (SD), y	63.5 (13)	62.9 (13)	.03
Body mass index, mean (SD)[a]	28.2 (6)	27.9 (6)	.17
Mitral or tricuspid valve surgery, No. (%)	843 (37)	4127 (38)	.31
Established stroke risks, No. (%)			
Prior transient ischemic attack or stroke	260 (11)	1220 (11)	.85
Atrial septal aneurysm	116 (5)	105 (1)	<.001
Aortic arch atheroma	1627 (71)	7712 (71)	.89
Left atrial dilation	1224 (54)	6154 (57)	.006
Atrial fibrillation	237 (10)	1223 (11)	.22
Comorbidities, No. (%)			
Hypertension	1465 (65)	7068 (67)	.32
Diabetes mellitus	522 (23)	2572 (24)	.32
Smoking	1309 (58)	6147 (58)	.60
Myocardial infarction	892 (39)	4183 (39)	.67
Peripheral vascular disease	933 (41)	4319 (40)	.36
Carotid artery disease	851 (37)	3931 (36)	.36
Chronic obstructive pulmonary disease	505 (23)	2304 (23)	.55
Renal disease	114 (5)	579 (5)	.50

Abbreviation: PFO, patent foramen ovale.
[a]Calculated as weight in kilograms divided by height in meters squared.

RESULTS

Baseline Characteristics

Patent foramen ovale was intraoperatively discovered in 2277 patients (17%). TABLE 2 demonstrates a nearly constant rate of intraoperative PFO diagnosis during the study period with a 95% confidence interval of 17% to 18%. However, the rate of repair demonstrates an increasing trend, reaching a peak of almost 40% in 2003 (Table 2).

Risk factors for stroke, including history of stroke or TIA (11% vs 11%, $P = .85$), aortic arch atheroma (71% vs 71%, $P = .89$), hypertension (65% vs 67%, $P = .32$), atrial fibrillation (10% vs 11%, $P = .22$), and smoking status (58% vs 58%, $P = .60$), were similar between those with and without PFO (TABLE 3). Intraoperative PFO was more likely to occur in patients who were older (mean [SD] age, 63.5 [13] vs 62.9 [13] years; $P = .03$), were white (91% vs 88%, $P < .001$), and had atrial septal aneurysm (5% vs 1%, $P < .001$). Patent foramen ovale was also more likely to be discovered in more recent surgeries (mean [SD] time from beginning of study to surgery, 6.9 [3] vs 6.4 [3] years; $P < .001$), in tricuspid valve repairs (9% vs 7%, $P = .002$), and with 2 of the 13 surgeons included in the study.

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

Of patients with incidentally discovered PFO, 639 (28%) underwent surgical repair, nearly all of which were suture closures (97%). Patients undergoing repair were more likely to be women (42% vs 33%, $P<.001$), be younger (mean [SD] age, 61.1 [14] vs 64.4 [13] years; $P<.001$), be undergoing mitral or tricuspid valve surgery (51% vs 32%, $P<.001$), have a history of stroke or TIA (16% vs 10%, $P<.001$), have a dilated left atrium (61% vs 51%, $P<.001$), and have atrial fibrillation (13% vs 10%, $P=.03$) (TABLE 4). Three surgeons demonstrated increased rates of PFO closure compared with the other 10. Patients who had PFO repaired also had fewer comorbidities, including hypertension, previous myocardial infarction, smoking, peripheral vascular disease, and carotid artery disease.

Table 4. Demographics and Clinical Characteristics of Population With Intraoperatively Diagnosed PFO

	Repair (n = 639)	No Repair (n = 1638)	*P* Value
Female sex, No. (%)	267 (42)	535 (33)	<.001
Age, mean (SD), y	61.1 (14)	64.4 (13)	<.001
Body mass index, mean (SD)[a]	28.1 (6)	28.2 (6)	.91
Mitral or tricuspid valve surgery, No. (%)	324 (51)	519 (32)	<.001
Established stroke risks, No. (%)			
Prior transient ischemic attack or stroke	100 (16)	160 (10)	<.001
Atrial septal aneurysm	40 (6)	76 (5)	.11
Aortic arch atheroma	438 (69)	1189 (73)	.06
Left atrial dilation	388 (61)	836 (51)	<.001
Atrial fibrillation	81 (13)	156 (10)	.03
Comorbidities, No. (%)			
Hypertension	384 (62)	1081 (67)	.02
Diabetes mellitus	133 (21)	389 (24)	.11
Smoking	334 (53)	975 (60)	<.001
Myocardial infarction	210 (33)	682 (42)	<.001
Peripheral vascular disease	232 (36)	701 (43)	.005
Carotid artery disease	209 (33)	642 (39)	.004
Chronic obstructive pulmonary disease	138 (22)	367 (24)	.50
Renal disease	30 (5)	84 (5)	.67

Abbreviation: PFO, patent foramen ovale.
[a]Calculated as weight in kilograms divided by height in meters squared.

Perioperative Outcomes

The perioperative outcomes between those with incidentally discovered PFO and those with no PFO are shown in TABLE 5. After we performed propen-

Table 5. Patient Intraoperative and Postoperative Outcomes for PFO and No PFO

	Unadjusted			Propensity Matched		
Outcome Measure	No PFO (n = 10 815)	PFO (n = 2277)	*P* Value	No PFO (n = 2265)	PFO (n = 2265)	*P* Value
Stroke, No.	227	53	.49	51	53	.84
% (95% CI)	2.1 (1.8 to 2.4)	2.3 (1.7 to 2.9)		2.3 (1.6 to 2.9)	2.3 (1.7 to 3.0)	
Hospital death, No.	258	76	.009	58	76	.11
% (95% CI)	2.4 (2.1 to 2.7)	3.3 (2.6 to 4.1)		2.6 (1.9 to 3.2)	3.4 (2.6 to 4.1)	
Length of stay, mean (SD), d	12 (12.2)	12.7 (14)	.006	12.1 (11.7)	12.7 (14.0)	.21
15/50/85 percentiles	5/8/18	5/9/18		5/8/18	5/9/18	
ICU stay, mean (SD), d	3.1 (6.3)	3.5 (7.7)	.16	3.1 (6.2)	3.5 (7.7)	.70
15/50/85 percentiles	1/1/4	1/1/5		1/1/4	1/1/5	
Cardiopulmonary bypass, mean (SD), min	105 (42.7)	110 (46.4)	<.001	104 (41)	110 (46.4)	.001
15/50/85 percentiles	63/99/146	65/104/156		64/98/144	65/104/155	
Myocardial infarction, No.	55	11	.88	10	11	.83
% (95% CI)	0.5 (0.4 to 0.6)	0.5 (0.2 to 0.8)		0.4 (0.2 to 0.7)	0.5 (0.2 to 0.8)	
Bleeding, No.	466	116	.10	100	116	.26
% (95% CI)	4.3 (3.9 to 4.7)	5.1 (4.2 to 6.0)		4.4 (3.6 to 5.3)	5.1 (4.2 to 6.0)	
Renal failure, No.	253	51	.77	49	51	.84
% (95% CI)	2.3 (2.1 to 2.6)	2.2 (1.6 to 2.8)		2.2 (1.6 to 2.8)	2.3 (1.6 to 2.9)	
Septicemia, No.	355	91	.09	87	91	.76
% (95% CI)	3.3 (2.9 to 3.6)	4.0 (3.2 to 4.8)		3.8 (3.0 to 4.6)	4.0 (3.2 to 4.8)	
Circulatory arrest, No.	625	189	<.001	162	188	.15
% (95% CI)	5.8 (5.3 to 6.2)	8.3 (7.2 to 9.4)		7.2 (6.1 to 8.2)	8.3 (7.2 to 9.4)	

Abbreviations: CI, confidence interval; ICU, intensive care unit; PFO, patent foramen ovale.

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

sity matching to control for differences between comparator groups, patients with intraoperatively diagnosed PFO had similar rates of in-hospital stroke (2.3% vs 2.3%, $P=.84$) and hospital death (3.4% vs 2.6%, $P=.11$). Length of hospital stay (mean [SD] time, 12.7 [14.0] vs 12.1 [11.7] days; $P=.21$) and days spent in the ICU (mean [SD] time, 3.5 [7.7] vs 3.1 [6.2] days; $P=.70$) were also similar between those with intraoperatively diagnosed PFO and those without. Secondary outcomes, including myocardial infarction, bleeding, renal failure, septicemia, and cardiac arrest, also demonstrated no differences between groups. However, patients with PFO were exposed to cardiopulmonary bypass longer than those without intraoperatively diagnosed PFO (mean [SD] time, 110 [46.4] vs 104 [41] min; $P=.001$).

Perioperative outcomes for patients undergoing intraoperative repair compared with those who did not undergo repair are shown in TABLE 6. The only difference noted between the 2 groups was the rate of in-hospital stroke, which was 2.8% in the repaired group vs 1.2% in the unrepaired group ($P=.04$), representing 2.47-times greater odds of having in-hospital stroke (95% confidence interval, 1.02 to 6.00). The rate of hospital deaths (2.5% vs 3.2%, $P=.50$), hospital length of stay (mean [SD] time, 12.2 [11.8] vs 12.3 [15.5] days; $P=.88$), ICU length of stay (mean [SD] time, 3.4 [7.4] vs 2.8 [7.6] days; $P=.26$), and time on cardiopulmonary bypass (mean [SD] time, 107 [45] vs 104 [45.6] days; $P=.08$) were all similar.

Long-term All-Cause Mortality

There were 66 228 patient years available for long-term survival analysis. Mean [SD] time for follow-up among survivors was 5.6 [3.1] years (median, 5.7 years). Nine hundred fifty-six patients (7.3%) were followed up for more than 10 years (FIGURE 2). Before matching, survival rates in patients without PFO at 2, 4, 6, 8, and 10 years were 90%, 85%, 78%, 70%, and 63%, respectively, and in patients in the PFO group, 89%, 83%, 76%, 68%, and 60%, respectively. There was no significant difference in the 2 groups (log-rank $P=.06$). After matching, survival at 2, 4, 6, 8, and 10 years was 89%, 84%, 77%, 70%, and 65%, respectively, in patients without PFO and 89%, 83%, 76%, 68%, and 60%, respectively, in the PFO group, still with no significant difference in the 2 groups (log-rank $P=.40$).

Before matching, survival in patients with PFO and no operative repair at 2, 4, 6, 8, and 10 years was 89%, 82%, 75%, 66%, and 59%, respectively, and in patients undergoing repair of PFO, 87%, 85%, 80%, 74%, and 66%, respectively. These differences were statistically significant (log-rank $P=.03$). However, after matching, survival at 2, 4, 6, 8, and 10 years was 91%, 83%, 74%, 65%, and 63%, respectively, in patients with PFO and no operative repair and 89%, 85%, 80%, 73%, and 67%, respectively, in the repair group, with the differences being nonsignificant (log-rank $P=.12$).

Table 6. Patient Intraoperative and Postoperative Outcomes for Repaired PFO and Unrepaired PFO

	Unadjusted			Propensity Matched		
Outcome Measure	Unrepaired PFO (n = 1638)	Repaired PFO (n = 639)	*P* Value	Unrepaired PFO (n = 603)	Repaired PFO (n = 603)	*P* Value
Stroke, No.	34	19	.20	7	17	.04
% (95% CI)	2.1 (1.4 to 2.8)	3 (1.7 to 4.3)		1.2 (0.3 to 2.0)	2.8 (1.5 to 4.1)	
Hospital death, No.	57	19	.55	19	15	.49
% (95% CI)	3.5 (2.6 to 4.4)	3 (1.7 to 4.3)		3.2 (1.8 to 4.5)	2.5 (1.2 to 3.7)	
Length of stay, mean (SD), d	12.7 (14.2)	12.7 (13.5)	.33	12.3 (15.5)	12.2 (11.8)	.88
15/50/85 percentiles	5/9/18	5/8/18		5/8/18	5/8/18	
ICU stay, mean (SD), d	3.4 (7.6)	3.5 (7.7)	.24	2.8 (7.6)	3.4 (7.4)	.26
15/50/85 percentiles	1/1/5	1/1/4		1/1/4	1/1/4	
Cardiopulmonary bypass, mean (SD), min	111 (46.7)	107 (45.4)	.17	104 (45.6)	107 (45)	.08
15/50/85 percentiles	65/105/157	62/101/154		61/98/146	63/102/154	
Myocardial infarction, No.	8	3	.95	4	3	.70
% (95% CI)	0.5 (0.2 to 0.8)	0.5 (–0.1 to 1.0)		0.7 (0.0 to 1.3)	0.5 (–0.1 to 1.1)	
Bleeding, No.	82	34	.76	27	29	.78
% (95% CI)	5.0 (4.0 to 6.1)	5.3 (3.6 to 7.1)		4.5 (2.8 to 6.1)	4.8 (3.1 to 6.5)	
Renal failure, No.	37	14	.92	12	12	>.99
% (95% CI)	2.3 (1.5 to 3.0)	2.2 (1.1 to 3.3)		2.0 (0.9 to 3.1)	2.0 (0.9 to 3.1)	
Septicemia, No.	66	25	.90	22	20	.75
% (95% CI)	4.0 (3.1 to 5.0)	3.9 (2.4 to 5.4)		3.6 (2.1 to 5.1)	3.3 (1.9 to 4.8)	
Circulatory arrest, No.	138	51	.73	46	49	.75
% (95% CI)	8.4 (7.1 to 9.8)	8.0 (5.9 to 10.1)		7.6 (5.5 to 9.8)	8.1 (5.9 to 10.3)	

Abbreviations: CI, confidence interval; ICU, intensive care unit; PFO, patent foramen ovale.

 ©2009 American Medical Association. All rights reserved.

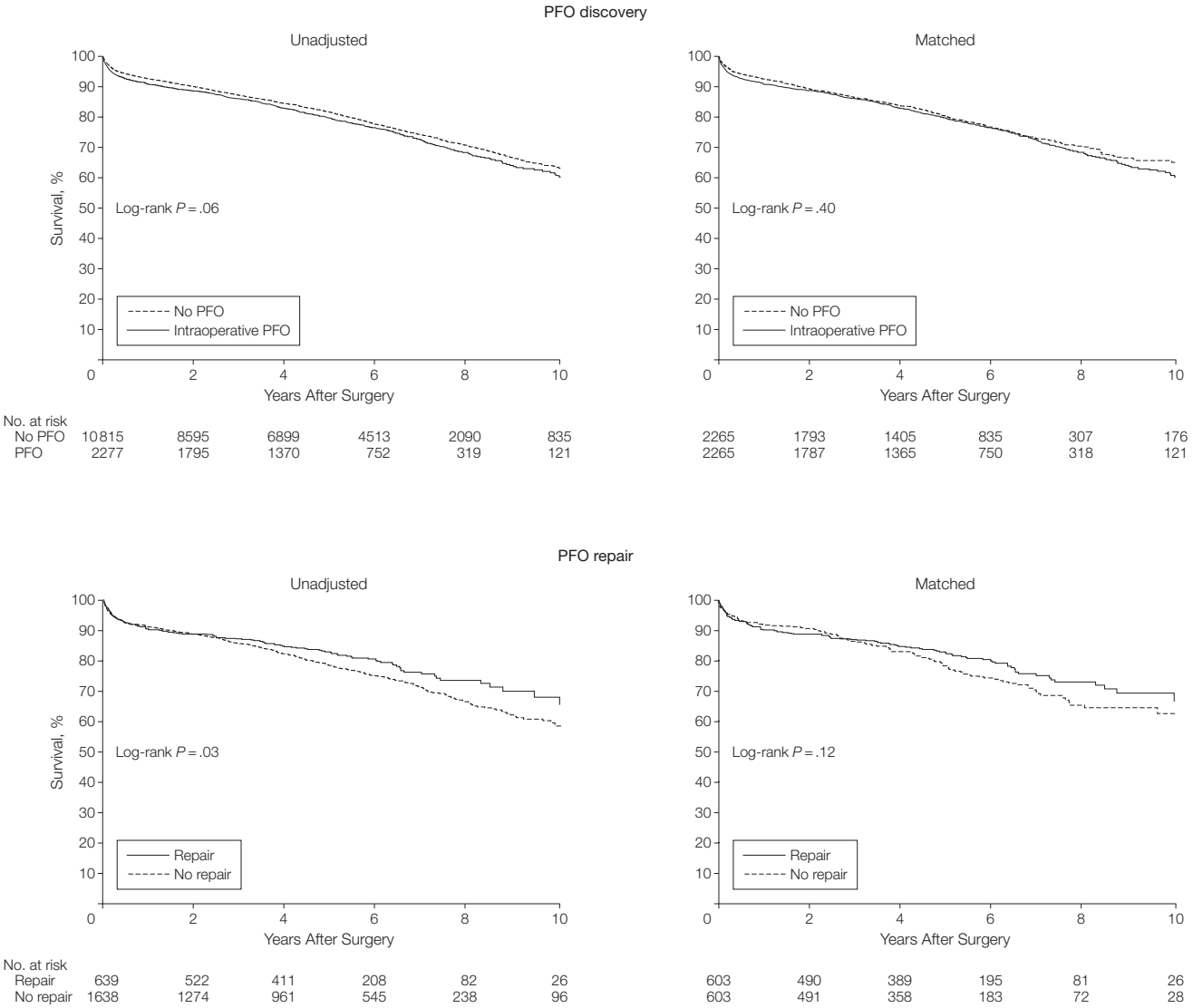
Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

COMMENT

Our population of patients undergoing cardiothoracic surgery was markedly different from those of prior studies investigating the relationship between PFO and stroke. Many patients in our study had comorbid conditions and risk factors for stroke, while past studies have chosen randomly selected healthy subjects or subjects with a history of ischemic stroke.[14-16] Our population, however, was uniquely suited to examine the perioperative impact of intraoperatively diagnosed PFO and its repair.

We observed the incidence of intraoperative PFO to be 17%. Since our analysis specifically excluded patients with known septal defects, our reported rate of intraoperative PFO underestimates the true prevalence in our initially selected population. If we include the 1046 patients excluded for a previously established diagnosis of either PFO or ASD (with the former expected to outnumber the latter by more than 500:1), the prevalence of PFO in this population becomes 23.5%, which is in line with prior autopsy analysis that estimated the prevalence of PFO in the general population to be as high as 27%.[39] Of note, the prospective study conducted by Meissner and colleagues[15] found the prevalence to be 24% while the study by Di Tullio and colleagues[16] found the prevalence to be

Figure 2. Unadjusted and Matched Long-term Survival Rates



Between patients with no patent foramen ovale (PFO) and those diagnosed with PFO intraoperatively, there were no statistically significant differences in survival rates, before or after propensity-based matching. Between patients whose PFO was repaired and those with no operative repair, differences in survival rates were statistically significant before matching. However, after matching, differences between the 2 groups were statistically nonsignificant.

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

15%. Our analysis cannot be directly compared with the latter study, however, because of our use of TEE, which is now considered to be the gold standard in PFO diagnosis.

A consistent prevalence of intraoperatively diagnosed PFO throughout the study suggests that we did not capture a highly selected cohort for identifying PFO. Atrial septal aneurysm was present in approximately 5% of patients with PFO and 1% of patients without PFO. This is consistent with the study from Meissner and colleagues,[15] who reported septal aneurysm in 4% of patients with PFO and 1% of patients without. Aortic arch atheroma was present in more than 70% of the study population, and severe aortic arch atheroma was present in 5%, appropriate frequencies given our aged patient population.

Our data indicate that the rate of intraoperative PFO diagnosis remained fairly constant during the study period, but the rate of PFO repair increased, peaking in the early 2000s. We attribute this trend to increased attention and awareness of PFO as a potential mechanism for stroke, similar to the recent proliferation of percutaneous PFO closure procedures.[40]

Our data show that surgeons were more likely to repair PFO in patients who were younger, were undergoing mitral or tricuspid surgery, had left atrial dilation, or had a history of prior stroke or TIA. However, we also found that patients with incidental PFO were no more likely to have previously experienced a stroke or TIA than patients without PFO. Repair tended to occur in patients with fewer comorbidities, including hypertension, smoking, myocardial infarction, peripheral vascular disease, and carotid disease. These observations are consistent with current opinions regarding the most appropriate patients in whom to repair PFO.[18] The decision of whether to close an incidental PFO is difficult since the optimal management is largely unknown.[41] The surgeon must balance the additional risks from changes in the surgical plan necessary to close a defect with the potential long-term complications, such as paradoxical embolic stroke, if left intact.

Mean length of stay from surgery to discharge was approximately 12 days across the study population. Presence of incidental PFO was only linked to increased time on cardiopulmonary bypass but was not associated with poorer outcomes. The risks of hospital death, days spent in the ICU, and time spent on cardiopulmonary bypass were similar for patients with PFO and those without PFO. Repair of PFO did not appear to change the risk of in-hospital death but was associated with an increased risk of stroke after controlling for differences between comparator groups. Long-term survival analysis also demonstrated no difference between those with intraoperatively diagnosed PFO and those without. Furthermore, long-term mortality appeared similar between those undergoing repair and those whose PFO was left unrepaired.

One might argue that no long-term difference was detected because surgeons were able to properly select patients undergoing repair, but this seems improbable given our extensive propensity-matched analysis. In contrast, we feel these data suggest that asymptomatic PFO in our population was likely a benign entity and repair might have increased the risk of postoperative stroke.

It was standard protocol to obtain intraoperative TEE for the cardiothoracic surgical procedures reviewed. We cannot ensure, however, that full studies were performed in every case (although our sampling suggests that they were), nor can we be assured that PFO detection was rigorously pursued in every case (ie, by using bubble contrast studies or provocative Valsalva maneuvers). Furthermore, we are unaware of what medications our patients were taking before or after surgery. The effect of stopping or starting anticoagulation or antiplatelet therapy could therefore not be assessed and might also serve as a confounder.

In summary, PFO is commonly detected during intraoperative imaging at the time of cardiothoracic surgery. When incidentally discovered, it appears to have a benign short-term and long-term clinical course. While the number of events is small, there was no clear benefit of closure on short-term perioperative outcomes or longer-term mortality. The finding that repair may increase postoperative stroke risk should discourage routine surgical closure and foster further investigation to delineate whether there is any benefit in terms of long-term stroke prevention and which patients might benefit from this intervention.

Author Contributions: Dr Krasuski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Krasuski, Hart, Qureshi, Blackstone.
Acquisition of data: Krasuski, Hart, Allen, Blackstone.
Analysis and interpretation of data: Krasuski, Hart, Pettersson, Houghtaling, Batizy, Blackstone.
Drafting of the manuscript: Krasuski, Hart, Blackstone.
Critical revision of the manuscript for important intellectual content: Krasuski, Hart, Allen, Qureshi, Pettersson, Houghtaling, Batizy, Blackstone.
Statistical analysis: Krasuski, Hart, Houghtaling, Batizy, Blackstone.
Administrative, technical, or material support: Krasuski, Blackstone.
Study supervision: Krasuski, Qureshi, Blackstone.
Financial Disclosures: Dr Krasuski reported having served as a consultant to Gore Medical and on the speakers' bureau of AGA Medical. No other disclosures were reported.

REFERENCES

1. Cohnheim J. *Thrombose Und Embolie: Vorlesung Uber Allgemeine Pathologie.* Berlin, Germany: Hirschwald; 1877.
2. Aggarwal K, Jayam VK, Meyer MA, Nayak AK, Nathan S. Thrombus-in-transit and paradoxical embolism. *J Am Soc Echocardiogr*. 2002;15(9):1021-1022.
3. Koullias GJ, Elefteriades JA, Wu I, Jovin I, Jadbabaie F, McNamara R. Images in cardiovascular medicine: massive paradoxical embolism: caught in the act. *Circulation*. 2004;109(24):3056-3057.
4. Srivastava TN, Payment MF. Images in clinical medicine: paradoxical embolism: thrombus in transit through a patent foramen ovale. *N Engl J Med*. 1997;337(10):681.
5. Thanigaraj S, Zajarias A, Valika A, Lasala J, Perez JE. Caught in the act: serial, real time images of a thrombus traversing from the right to left atrium across a patent foramen ovale. *Eur J Echocardiogr*. 2006;7(2):179-181.
6. Krasuski RA. When and how to fix a "hole in the heart": approach to ASD and PFO. *Cleve Clin J Med*. 2007;74(2):137-147.
7. Hansen A, Kuecherer H. Caught in the act: entrapped embolus through a patent foramen ovale. *Eur J Echocardiogr*. 2008;9(5):692-693.
8. Fedullo AJ, Swinburne AJ, Mathew TM, Ryan GF, Dvoretsky PM, Davidson KH. Hypoxemia from right to left shunting through patent foramen ovale. *Am J Med Sci*. 1985;289(4):164-166.
9. Lechat P, Mas JL, Lascault G, et al. Prevalence of

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016

patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318(18):1148-1152.
10. Van Camp G, Schulze D, Cosyns B, Vandenbossche JL. Relation between patent foramen ovale and unexplained stroke. *Am J Cardiol*. 1993;71(7):596-598.
11. Weiss SJ, Cheung AT, Stecker MM, Garino JP, Hughes JE, Murphy FL. Fatal paradoxical cerebral embolization during bilateral knee arthroplasty. *Anesthesiology*. 1996;84(3):721-723.
12. Banks TA, Manetta F, Glick M, Graver LM. Carbon dioxide embolism during minimally invasive vein harvesting. *Ann Thorac Surg*. 2002;73(1):296-297.
13. Kizer JR, Devereux RB. Clinical practice: patent foramen ovale in young adults with unexplained stroke. *N Engl J Med*. 2005;353(22):2361-2372.
14. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology*. 2000;55(8):1172-1179.
15. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? evidence from a prospective population-based study. *J Am Coll Cardiol*. 2006;47(2):440-445.
16. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol*. 2007; 49(7):797-802.
17. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002; 105(22):2625-2631.
18. Sukernik MR, Bennett-Guerrero E. The incidental finding of a patent foramen ovale during cardiac surgery: should it always be repaired? a core review. *Anesth Analg*. 2007;105(3):602-610.
19. Morewood GH, Gallagher ME, Gaughan JP, Conlay LA. Current practice patterns for adult perioperative transesophageal echocardiography in the United States. *Anesthesiology*. 2001;95(6):1507-1512.
20. Baldwin RT, Duncan JM, Frazier OH, Wilansky S. Patent foramen ovale: a cause of hypoxemia in patients on left ventricular support. *Ann Thorac Surg*. 1991;52(4):865-867.
21. Ouseph R, Stoddard MF, Lederer ED. Patent foramen ovale presenting as refractory hypoxemia after heart transplantation. *J Am Soc Echocardiogr*. 1997; 10(9):973-976.
22. Sukernik MR, Goswami S, Frumento RJ, Oz MC, Bennett-Guerrero E. National survey regarding the management of an intraoperatively diagnosed patent foramen ovale during coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth*. 2005;19 (2):150-154.
23. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age: a study using transesophageal echocardiography. *Stroke*. 1993;24(12):1865-1873.
24. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med*. 1994;331(22):1474-1479.
25. Ferrari E, Vidal R, Chevallier T, Baudouy M. Atherosclerosis of the thoracic aorta and aortic debris as a marker of poor prognosis: benefit of oral anticoagulants. *J Am Coll Cardiol*. 1999;33(5): 1317-1322.
26. Jones EF, Kalman JM, Calafiore P, Tonkin AM, Donnan GA. Proximal aortic atheroma: an independent risk factor for cerebral ischemia. *Stroke*. 1995; 26(2):218-224.
27. Matsumura Y, Osaki Y, Fukui T, et al. Protruding atherosclerotic aortic plaques and dyslipidaemia: correlation to subtypes of ischaemic stroke. *Eur J Echocardiogr*. 2002;3(1):8-12.
28. Molina CA, Santamarina E, Alvarez-Sabin J. Cryptogenic stroke, aortic arch atheroma and patent foramen ovale. *Cerebrovasc Dis*. 2007;24(suppl 1): 84-88.
29. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke*. 2008;39(6):1901-1910.
30. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology*. 2007; 69(6):546-554.
31. Lakshminarayan K, Anderson DC, Herzog CA, Qureshi AI. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. *Neurologist*. 2008;14(3):143-150.
32. Mas JL, Zuber M; French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. *Am Heart J*. 1995;130(5):1083-1088.
33. Lamy C, Giannesini C, Zuber M, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA study: atrial septal aneurysm. *Stroke*. 2002;33(3):706-711.
34. Breiman L. Bagging predictors. *Mach Learn*. 1996; 24(2):123-140.
35. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall/CRC; 1998.
36. Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg*. 2002;123(1):8-15.
37. Bergstralh EJ, Kosanke JL. Computerized matching of cases to controls [technical report No. 56]. Mayo Foundation. http://mayoresearch.mayo.edu/biostat/techreports.cfm. Accessed June 17, 2009.
38. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53:457-481.
39. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59(1):17-20.
40. Opotowsky AR, Landzberg MJ, Kimmel SE, Webb GD. Trends in the use of percutaneous closure of patent foramen ovale and atrial septal defect in adults, 1998-2004. *JAMA*. 2008;299(5):521-522.
41. Rigatelli G, Cardaioli P, Chinaglia M. Asymptomatic significant patent foramen ovale: giving patent foramen ovale management back to the cardiologist. *Catheter Cardiovasc Interv*. 2008;71(4):573-577.

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/14/2016