Interatrial Shunting Through an Asymptomatic Patent Foramen Ovale in Thoracic Surgery

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Background. **Patent foramen ovale (PFO) is present in as many as 25% of the general population and is considered an irrelevant condition in healthy subjects. Here, we sought to determine an association between an asymptomatic PFO at baseline and postoperative short-term adverse events in patients undergoing major pulmonary resection for lung cancer. In addition, we evaluated for the rate of PFO after pulmonary resections.**

Methods. **This prospective, observational study assessed patients by transcranial Doppler with contrast at baseline and discharge. To confirm interatrial shunting, patients with positive transcranial Doppler at baseline also underwent contrast transthoracic echocardiography. Multivariate logistic regression models were adopted to investigate for independent factors that could have been associated with complications. Backward stepwise procedure was used for model selection.**

Results. **Median age was 67.7 ± 9.2 years (range, 36 to 86), and 67% were men. Overall, 18 patients underwent pneumonectomy, 11 bilobectomy, and 118 lobectomy; 54% underwent right-sided procedure and 46%, left-sided. One perioperative death was recorded, and 34 patients had one or more cardiopulmonary complications. At baseline, PFO was positive in 25% (37 of 147) and negative in 75% (110 of 147); of the latter, 11% were positive at discharge. Detection of PFO at baseline, on multivariate analysis, was significantly associated with a risk of postoperative complications (odds ratio 2.5; 95% confidence interval: 1.1 to 5.8). Specifically, we observed a significant association between atrial fibrillation and positive PFO at baseline (odds ratio 3.5; 95% confidence interval: 1.4 to 9.0).**

Conclusions. **Preoperative asymptomatic PFO was independently associated with postoperative adverse events. Moreover, 11% of patients who had negative transcranial Doppler studies at baseline had asymptomatic PFOs at discharge. Larger prospective studies are needed to further investigate for a prognostic impact of PFO in thoracic surgery.**

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Patent foramen ovale (PFO) is a remnant of the fetal circulation that is present in 20% to 25% of the general population [1–4]. Currently, it is considered to be an irrelevant condition in healthy subjects, and usually, it remains clinically silent for all life [5, 6]. However, transient right-to-left shunting, generally through PFO or a previously asymptomatic atrial defect, has been implicated in the pathophysiology of stroke, paradoxic embolism, migraine, and hypoxemia [1, 4, 7–9].

In thoracic surgery, we know that after right pneumonectomy, when the right-left pressure is challenged or the mediastinal anatomy is distorted, interatrial shunting through a PFO can provoke a rarely observed complication characterized by posture-dependent desaturation and dyspnea known as platypnea-orthodeoxia [10]. This event may have an early or late presentation, and its incidence is currently unknown [11]. Furthermore, the prognostic impact of PFO in thoracic surgery has not been thoroughly investigated. Given this high incidence of PFO in the general population, we sought to determine an association between an asymptomatic PFO at baseline and postoperative short-term adverse events in a series of patients who had undergone major pulmonary resection for non-small cell lung cancer (NSCLC). The secondary

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
cTCD = contrast transcranial Doppler sonography
cTTE = contrast transthoracic echocardiography
NSCLC = non-small cell lung cancer
OR = odds ratio
PFO = patent foramen ovale
TCD = transcranial Doppler sonography
TEE = transesophageal echocardiography
TTE = transthoracic echocardiographic
VATS = video-assisted thoracic surgery

endpoint was to estimate the rate of PFO after major pulmonary resections.

Material and Methods

Study Design

This was a prospective, single-center, short-term observational study carried out at a tertiary care hospital. We enrolled consecutive patients who had been scheduled to undergo elective major pulmonary resection for NSCLC between July 2014 and July 2016. All eligible patients gave their informed consent before inclusion. The study protocol was approved by the local Regional Ethics Committee (CEAS N.: 2316/14).

Study Population

Inclusion criteria were the following: aged 18 years or more, an American Society of Anesthesiologists score of 3 or less, and being scheduled for elective major pulmonary surgical resection (ie, lobectomy or pneumonectomy) for NSCLC. Exclusion criteria included unwillingness to participate, diagnosed or symptomatic PFO, a previous embolic transient ischemic attack, stroke or cerebral abscess, history of pulmonary hypertension, any arteriovenous malformation, cardiac rhythm other than sinus, paroxysmal, persistent or chronic atrial fibrillation (AF), antiarrhythmic drug use, recent diagnosed (less than 3 months) angina pectoris, myocardial infarction or pneumonia, symptomatic coronary artery disease or congestive heart failure, New York Heart Association classification greater than II, need for mechanical ventilation after the surgical procedure, and moderate or severe renal disease (serum creatinine >200 μmol/L).

The preoperative evaluation included a detailed history, physical examination, and cardiopulmonary assessment including blood gas analysis, 12-lead electrocardiogram, spirometry, diffusing capacity of the lung for carbon monoxide, and transthoracic echocardiographic (TTE) examinations to exclude right ventricle overload, left ventricle systolic and diastolic dysfunction and valvulopathies more than mild. The diagnostic evaluation consisted of a total body computed tomography, a video bronchoscopy, and an 18-fluorodeoxyglucose–positron emission tomography. Moreover, all the enrolled patients underwent contrast transcranial Doppler sonography (cTCD) at both admission and discharge. All patients who were cTCD positive at baseline preoperatively underwent a contrast transthoracic echocardiography (cTTE) to confirm the previous diagnosis of PFO and to exclude an intracardiac shunt due to atrial septal defect.

Contrast Transcranial Doppler Sonography and Contrast Transthoracic Echocardiography

Transesophageal echocardiography (TEE) is considered the gold standard for determining right-to-left shunting [12–14], with a reported sensitivity of 91% to 100% and accuracy of 88% to 97% [15, 16]; whereas transcranial Doppler sonography (TCD) can detect intracardiac right-to-left shunting with a sensitivity of 97% and a specificity of 93% when TEE is used as the reference [1]. Transesophageal echocardiography is much more time consuming, less tolerated by patients, and although rare, severe complications such as esophageal bleeding or perforation can sometimes occur [1]. Moreover, compared with TEE, the size and functional relevance of right-to-left shunting can be more easily assessed with TCD and patients better tolerate the Valsalva maneuver [12].

Regarding TCD, it has a higher sensitivity than specificity, as it does not show the operator the anatomic position of the right-to-left shunting and is not able to differentiate between pulmonary and intracardiac shunts [1]. Consequently, in our study, to exclude for an extracardiac shunt, all patients with positive TCD at baseline (n = 37) received preoperative cTTE to confirm the intracardiac localization of the shunt. The cTTE has comparable value to TEE in detecting right-to-left shunt due to PFO [17].

The cTCDs were performed by expert neurologists according to the recommendations by the international consensus meeting for the detection of right-to-left shunting by TCD [12]. Patients were prepared with an 18G needle inserted into the cubital vein (left arm, if possible) and examined in a supine position. Insonation of at least one middle cerebral artery using TCD was performed. The contrast agent was prepared using 9 mL isotonic saline solution and 1 mL air mixed with a three-way stopcock by exchange of saline/air mixture between the syringed and injected as bolus. Whenever there were few or no microbubbles in the middle cerebral artery under basal conditions, the examination was repeated using the Valsalva maneuver, the release of which allows right atrial pressure to exceed left atrial pressure [1]. The contrast agent was injected 5 seconds before initiating the Valsalva maneuver; the overall Valsalva maneuver duration was 10 seconds. The results were documented separately for basal condition and Valsalva maneuver testing, and we considered a level of 1 to 10 microbubbles as the TCD threshold for a positive shunt [12].

The cTTEs were performed by expert cardiologists according to the contrast echocardiography guidelines for the detection of right-to-left shunting [18]. Patients were prepared with a 20G needle inserted into the cubital vein

(right arm, if possible) and examined in left lateral decubitus position with an apical or a subcostal four-chamber view, or both. The contrast agent used was the same as for cTCD and injected as bolus both in basal conditions and at the release of the Valsalva maneuver. The presence of PFO was defined if at least one microbubble was visualized in the left atrium within three cardiac cycles of right atrium complete opacification [18]. The durations of the cTCD and the cTTE were a few minutes each.

Surgical Procedures

Two authors (F.P. and L.C.) carried out all of the surgical procedures. Moreover, all the patients undergoing resection received general anesthesia with selective one-lung ventilation. The surgical approaches included standard posterolateral thoracotomy or three-port video-assisted thoracic surgery (VATS). Patients starting with VATS and later converted to open thoracotomy were classified as open thoracotomy patients. Pulmonary resections were performed with curative intent and included systematic lymph node dissection. All patients were extubated in the surgical theater at the end of the operation, and thereafter no patient required reintubation. From postoperative day one, all patients received daily physiotherapy, which included deep breathing exercises, incentive spirometry, supported coughing, and mobilization.

Postoperative Complications

All patients during the postoperative period were screened for complications using clinical, biochemical, and instrumental methods. Likewise, all patients were monitored by continuous telemetry for at least 24 hours. The median duration of the postoperative period was 6 days (range, 3 to 32). Postoperative pulmonary complications were classified according to the Melbourne Group Scale version-2 score [19, 20]. The investigated postoperative cardiovascular complications included platypnea-orthodeoxia syndrome, arrhythmias (AF, paroxysmal supraventricular tachycardia, ventricular tachycardia), angina pectoris, myocardial infarction, congestive heart failure, thromboembolic events, deep vein thrombosis, acute renal failure, transient ischemic attack, and stroke. Stroke was defined as the sudden onset of a new focal neurologic deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. Transient ischemic attack was defined as a transient episode of neurologic dysfunction caused by focal brain ischemia without acute infarction. Postoperative surgical complications were not included in the analysis.

Statistical Analysis

The primary endpoint of the study was to investigate for an association between an asymptomatic PFO at baseline and postoperative short-term adverse events, and the secondary endpoint was to estimate the rate of PFO after major pulmonary resections. Our sample size was determined by the need to control any potential confounders. We did not assume any prespecified odds ratio (OR) for an association between X and Y. Based on our planned sample size of 150 patients and the result of a previous study [21], we expected a complications rate of 18% (27 outcome events). Moreover, according to the rule of thumb of 10 outcome events per predictors [22], we adopted a multivariate logistic regression model including three independent explanatory variables.

For statistical analyses, we used R software 3.3 [23]. Categoric data are presented as counts and percentages whereas age is summarized by use of median and interquartile ranges. Categoric data were compared using the χ^2 test using Yates correction for continuity. The 95% confidence intervals (CI) of proportions were calculated using the Agresti-Coull method [24]. Difference in age distribution was compared using Student's t test. Multivariate logistic regression was carried out to investigate for independent factors associated with complications, including preoperative PFO. We considered as potential independent factors demographic features such as sex and age, as well as surgical approach, type of pulmonary resection, side of the procedure, and chemotherapy. The final multivariate models for postoperative complications and AF were constructed using a backward stepwise procedure. A p value of less than 0.05 was considered statistically significant for all the analyses.

Results

Patients, Procedures, and Complications

The median age of the 147 patients was 69 years (interquartile range: 62 to 74), and 99 (67%) were male. As shown in Table 1, there were 118 (80%) lobectomies, 18 pneumonectomies (12%), and 11 bilobectomies (8%). Overall, 80 procedures (54%) were right sided and 67 (46%) were left sided. Most of the pneumonectomies were left sided (12 of 18); right upper lobectomy was the most frequently performed surgical resection with 33, and left upper lobectomy was the second most frequent with 30. The thoracotomy approach was performed in 92 of 147 patients (63%), whereas VATS was performed in 55 of 147 (37%). Finally, thoracotomy was performed in 16 of 18 pneumonectomies. Twenty-eight patients (19%) received induction chemotherapy, and 35 (24%) had one or more postoperative complications. There was one recorded postoperative death due to a pneumonia evolving into acute respiratory distress syndrome. The most frequent complication was AF in 27 patients, followed by pulmonary complications in 11. Three patients had acute renal failure, and there was a single case of deep vein thrombosis, pulmonary embolism, and transient ischemic attack. A flow chart of the study in shown in Figure 1. We did not observe any correlations between complications and either length of surgical procedure or type of surgery performed.

Primary Outcome Measures

The TCD assessment results were negative at baseline in 75% of patients (110 of 147, 95% CI: 67.2 to 81.2), whereas 25% of patients (37 of 147, 95% CI: 18.8 to 32.8) had

Table 1. Cohort Characteristics

Variable	Value
Age, years	67.7 ± 9.2
Sex	
Male	99 (67.3)
Female	48 (32.7)
Surgical approach	
VATS	55 (37.4)
Thoracotomy	92 (62.6)
Type of intervention	
Lobectomy	118 (80.3)
Bilobectomy	11 (7.5)
Pneumonectomy	18 (12.2)
Side	
Right	80 (54.4)
Left	67 (45.6)
Preoperative PFO	
Yes	37 (25.2)
No	110 (74.8)
Chemotherapy	
Yes	28 (19.4)
No	116 (80.6)
Complications	
All	35 (23.8)
Cardiovascular	27 (18.4)

Values are mean ± SD or n (%).

PFO = patent foramen ovale; VATS = video-assisted thoracic surgery.

positive results at both TCD and TTE. As shown in Table 2, positive PFO preoperatively (OR 2.5, 95% CI: 1.1 to 5.8) and the thoracotomy approach (OR 2.9, 95% CI: 1.2 to 7.9) were independently associated with higher risks of postoperative complications. Moreover, in the subset of patients who had AF, we observed significant associations between AF and positive PFO at baseline (OR 3.5, 95% CI: 1.4 to 9.0) as well as between AF and pneumonectomy (OR 5.3, 95% CI: 1.7 to 16.2).

A multicollinearity issue could explain the difference between the two models. That is, most of the pneumonectomies (16 of 18) were carried out using a thoracotomy approach. Indeed, a significant association between thoracotomy and the type of surgical resection was observed ($p = 0.028$).

In the 110 patients (75%) with negative TCD at baseline, 12 (10.9%) were positive after pulmonary resection (95% CI: 6.2% to 18.2%). None of the cohort characteristics investigated (age, sex, VATS/thoracotomy approach, side and type of surgical resection, length of surgical procedure, induction chemotherapy) was found to be associated with a postoperative PFO. Furthermore, no postoperative complications were recorded for these 12 patients. However, all the patients having positive TCD at baseline were also TCD positive after surgery. None of the 147 consecutively enrolled patients who had undergone major pulmonary resection for NSCLC went on to have platypnea-orthodeoxia syndrome.

Comment

We sought to determine an association between an asymptomatic PFO at baseline and postoperative short-term adverse events in a series of patients who had undergone major pulmonary resection for NSCLC. The secondary endpoint was to estimate the rate of PFO after major pulmonary resection. Our primary result suggests that an asymptomatic preoperative PFO might be associated with a higher rate of postoperative complications. Regarding our investigation into the possible risk factors for postoperative AF, our result is in line with past results from several recent studies [21, 25–27]. However, our result differs from those studies in that it indicates a potentially new risk factor for short-term postoperative AF. Specifically, in our study, AF resulted in being associated with an asymptomatic PFO at baseline.

We know that AF is the most frequently reported complication after noncardiac thoracic surgery. Overall, its incidence has been reported to range from 8% to 42% [28, 29], and its occurrence is associated with longer hospital stay, risk of stroke, and postoperative mortality [25–27]. The risk factors most frequently associated with the onset of AF subsequent to noncardiac thoracic surgery include advanced age, male sex, a history of congestive heart failure, B-type natriuretic peptide elevation, and extended pulmonary resection [21, 25–27, 30].

Preoperative asymptomatic PFO has never been suggested as a risk factor for postoperative AF. If our results are verified, knowing this risk in patients could allow for improved patient management in terms of better surgical risk stratification and the development of pharmacologic strategies. Moreover, the verification of this risk factor would most likely interest other fields of noncardiac surgery. We also observed that patients undergoing a thoracotomy approach or pneumonectomy had higher risks of postoperative complications compared with patients undergoing a VATS procedure or lobectomy. Moreover, the thoracotomy approach was utilized for all patients affected by advanced NSCLC, thereby requiring more invasive procedures or even extended resections.

Concerning the results of our secondary endpoint, 11% of patients (12 of 110) with negative cTCD at baseline had positive results of cTCD within a few days after surgery. Our investigation was the first to prospectively evaluate this topic. Therefore, we are unable to compare this result. However, this finding suggests that the rate of postoperative asymptomatic PFO, after pulmonary resection, might be more frequent than expected. In this regard, it has been previously reported that PFO after pneumonectomy can be attributed to the reduction of the pulmonary vascular bed, leading to an increase in pulmonary vascular resistance as well as a decrease in right ventricular compliance [31] that could be exacerbated by perioperative fluid loading [32]. Another factor involved in postoperative PFO is thought to be postoperative interatrial septum distortion by allowing the PFO to preferentially receive inferior vena cava flow [10]. In addition, PFO is more common after right-sided

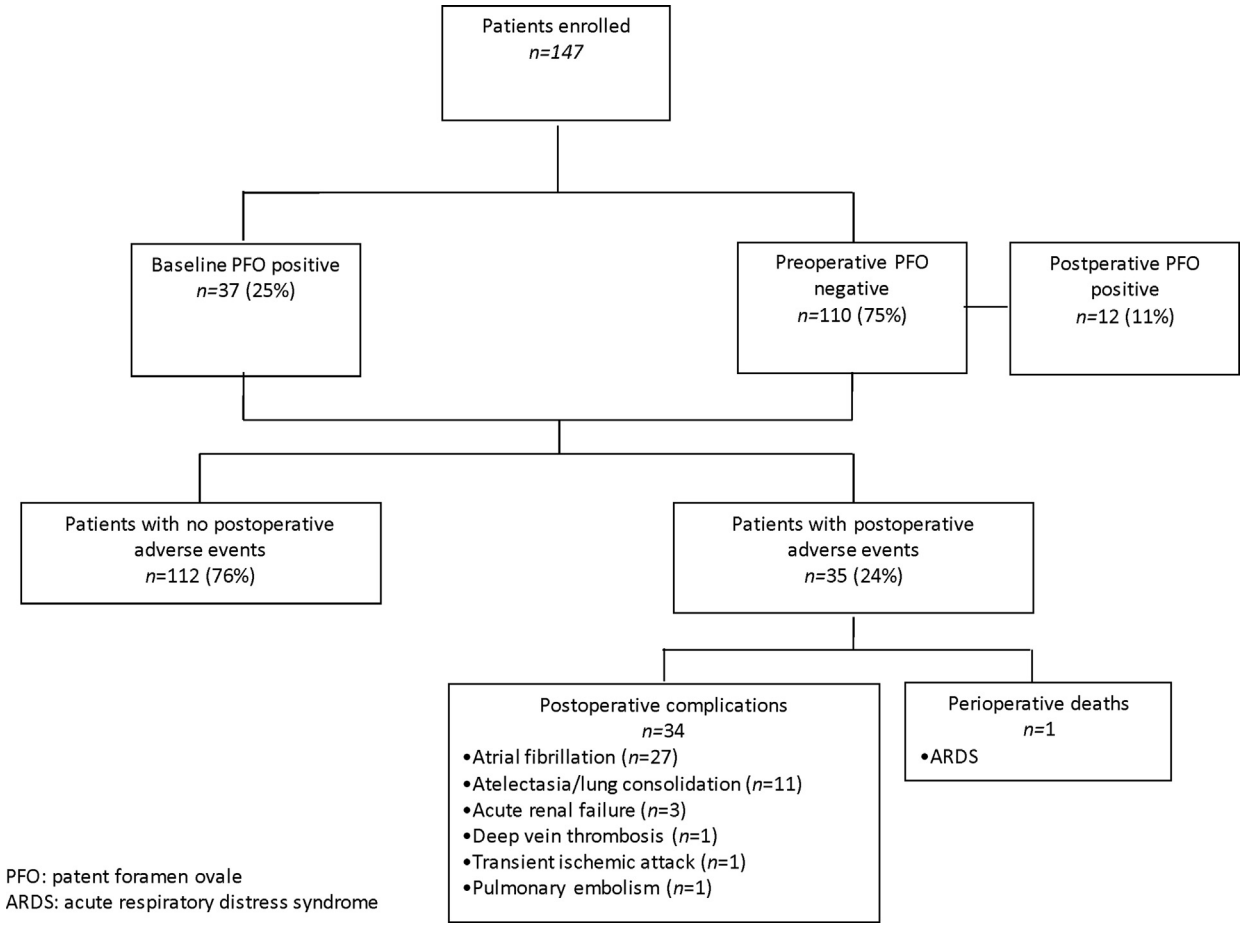

Fig 1. Flow chart of the study.

procedures owing to a relaxation and elevation of the right hemidiaphragm [1, 10, 11]. Nonetheless, in our series, none of the 13 patients who were TCD negative at baseline and underwent pneumonectomy went on to have an asymptomatic postoperative PFO. Likewise, none of the clinic factors investigated (side and type of resection, surgical approach, induction chemotherapy, sex, age, length of surgical procedure) resulted in being associated with postoperative PFO.

The major limits of this study were that it was a single-center study designed to assess only the impact of PFO before discharge, and a limited number of pneumonectomies were included. The major strength of this study was that it adopted a prospective multidisciplinary approach, including neurologists and cardiologists.

In conclusion, our results suggest that an asymptomatic PFO at baseline in patients who had undergone major pulmonary resection was associated with a threefold greater risk of having AF within a few days after surgery. Moreover, 11% of those patients (12 of 110) who had negative TCD at baseline had asymptomatic PFO at discharge. Considering that AF is the most frequently reported complication after noncardiac thoracic surgery, and transient right-to-left shunting through an asymptomatic PFO is implicated in the pathophysiology of stroke, migraine, and paradoxic embolism, larger prospective long-term studies are needed to further investigate a possible prognostic impact of PFO after lobectomies or pneumonectomies. Going forward, these findings, if confirmed, might indicate a subgroup of patients who have

Table 2. Odds Ratio (95% Confidence Interval) From Logistic Regression Models of Postoperative Complications

Variable	All Complications (n = 35)	*p* Value	Atrial Fibrillation (n = 27)	*p* Value
Thoracotomy	2.9 (1.2–7.9)	0.022	...	...
Pneumonectomy	...	...	5.3 (1.7–16.2)	0.003
Preoperative PFO	2.5 (1.1–5.8)	0.031	3.5 (1.4–9.0)	0.008

PFO = patent foramen ovale.

a higher risk of stroke, migraine, and paradoxic embolism compared with patients without PFO.

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