Original Article

The prevalence of right to left shunt in chronic obstructive pulmonary disease patients with increased pulmonary hypertension

Maryam Nabavi Nouri[1]
Mohammad Rouhani (MD) [2]
Seyed Ali Javad Mousavi (MD)[3]
Shahab Shahabi Shahmiri [3]
Elyas Mostafapour[*3]
Houman Yahyazadeh (MD)[1]
Hamid Reza Baradaran (MD)[4]

1- Student's Research Committee, Iran University of Medical Sciences, Tehran, Iran.
2- Department of Neurology, Rasul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.
3- Pulmonary Science Research Center, Rasul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.
4- Department of Epidemiology, Iran University of Medical Sciences, Tehran, Iran.

*** Correspondence:**
Elyas Mostafapour, Medical & MPH student, Pulmonary Science Research Center, Rasul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.
Post Code: 46917-14141
E-mail:mostafapour_e@yahoo.com
Tel: +98-21-66558282
Fax: +98-21-66558282

Received: 25 Jan 2010
Revised: 5 May 2010
Accepted: 8 Jun 2010

Abstract

Background: *One of the important etiologies for cryptogenic stroke is paradoxical embolization secondary to Patent Foramen Ovale (PFO). Foramen ovale can secondarily reopen due to Pulmonary Arterial Hypertension (PAH) which is common among the older age. PAH is known as a frequent and life threatening complication of COPD. The aim of this study was to determine the prevalence of PFO between COPD patients with PAH and compare it with the ratio of PFO in non PAH COPD patients by Valsalva Maneuver (VM) following the TCD test.*

Methods: *This study was performed on 55 patients with COPD exacerbation who were admitted to Rasul-Akram Hospital in Tehran, Iran. The patients with high PAH were considered as the case group and the others without PAH were the control group. All patients underwent Trascranial Doppler (TCD) to detect intracardiac right-to-left shunt (RLS) related by PFO. The data were collected and analyzed.*

***Results*:** *In the case group, among 45 patients 25 (55.5%) males and 20 (44.5%) females] with the mean age of 64.68±10.73 years, 31 (68.8%) subjects had PFO. In 10 control patients whose PAP were normal during TTE, we detected PFO in 2 (20%) patients during VM ($p<0.001$). There was a significant correlation with the number of microembolic signals (MES) and the increase in PAP ($p=0.019$).*

Conclusion: *Right to left shunting was significantly more frequent in COPD patients with high PAP. High pulmonary pressure had a cardinal role in increasing the prevalence of RLS among these patients.*

Key words: *Patent Foramen Ovale, right-to-left shunt, COPD.*

Casp J Intern Med 2010; 1(2): 67-71.

Stroke is the second cause of death in the world and a major contributor to long-term functional impairment and disability (1,2). There are different subtypes of stroke and cryptogenic is one of the most common subtypes and consists of about 40 percent of all stroke cases (3). One of the important etiologies for cryptogenic stroke is paradoxical embolization secondary to Patent Foramen Ovale (PFO) and other atrial septal defects (4-7). Foramen ovale is a physiological defect in interatrial septum that closes in most people right after birth (8) but it can remain open in 10-30 percent of normal population that reduces with an increase in age (9-11). Also foramen ovale can secondarily reopen due to pathological conditions such as in Pulmonary Arterial Hypertension (PAH) which is more common among the older age (12). Pulmonary hypertension is known as a frequent and life threatening complication of COPD (13,14). One of the new and mini invasive methods for diagnosing PFO is using Trancranial Doppler (TCD) with valsalva maneuver (15,16).

In this method after the injection of contrast material in peripheral vessels and performance of valsalva maneuver by the patient, the number of high intensity transient signal (HITS) that are detected help make the diagnosis of PFO as well as its intensity (17). The emboli originate from systemic venous circulation and heart pass to systemic arterial circulation through atrial septal defect and block a part of cerebral circulation leading to ischemic stroke (18).

The aim of this study was to determine the prevalence of PFO in COPD patients with PAH and comparing it with the ratio of PFO in non PAH COPD patients by Valsalva maneuver following the TCD test.

Methods

Patients: This prospective, analytical cross-sectional study was performed on 55 patients with COPD exacerbation who were admitted to Rasoul-e-Akram Hospital in Tehran, Iran. At first pulmonary function test was requested .Also Pulmonary arterial pressure (PAP) was determined using transthoracic echocardiography (TTE) with (Probe: 3.5-5 *MHZ transducer*, Model: X-CD Megas, Italy) to rule out the cardiologic causes of possible right to left shunting (RLS). A four-chamber view was obtained to provide the best view of the fossa ovalis. During TTE, arterial oxygen saturation (SaO_2) by finger pulse oximetry was recorded for all patients continuously.

The patients with high PAP were considered as the case group and the others without PAH were the control group. It is noted that pulmonary artery hypertension (PAH) is defined as a mean pulmonary artery pressure greater than 25 *mmHg* at rest or 30 *mmHg* with exercise. Forty five (82%) patients with PAH (case) and ten subjects (18%) with normal PAP (control) were diagnosed. The Iran University Institutional Review Board approved the study, and all the subjects were provided with the written informed consent to participate.

Patent Foramen Ovale Detection: All patients underwent trascranial doppler (TCD) by injecting contrast agent during valsalva maneuver (VM) to detect intracardiac RLS. An emulsion of microbubbles as a sonographic contrast was prepared by agitating a mixture of 8 *ml* saline, 1 *ml* air and 0.5 *ml* of the patient's blood as an emulsificant. This emulsion was then immediately injected via an 18-gauge cannula in an antecubital vein. Our protocol involved two cycle injections followed immediately by a standardized VM (patients were asked to hold their breath and then release it for 5 seconds followed by the injection). Each cycle lasted 120 seconds to detect all the possible HITS passage, after a short rest, the patients had to undergo another set of injection followed by VM. Both middle cerebral arteries were insonated through the temporal windows using 2-*MHz* probes set at 50-60-*mm* depth.

A right-to-left shunt was considered present if at least two microembolic signals (MES) passed in the two 60 seconds time window after the injection while the first high intensity transient signals (HITS) occurred in the first 40 seconds- contributing to the diagnostic criteria of PFO, which confirmed the existence of RLS which in our cases is sustained by PFO. TCD recordings were analyzed offline by 2 independent trained observers.

Statistical analysis: The data were analyzed using SPSS version 16 software for Windows (SPSS Inc, Chicago, IL, USA). The parameters such as frequency, mean, mode and standard deviation (S.D.) were reported. The analyses were performed using statistical tests. Kolmogronov Smirnov (K.S) test was performed to evaluate the normal distribution of the quantitative variables. To compare the differences of the values of continuous variables between the case and the control groups Independent T-test was used. For finding any predicting factor associated with occurrence of PFO we used Logistic Regression test. A *p*-values<0.05 was considered statistically significant. All reported *p*-values are two-tailed.

Results

In the case group of 45 patients 25 (55.5%) males and 20 (44.5%) females with the mean age of 64.68 (SD=10.73) yr, 31(68.8%) patients have PFO. In our group of 10 control patients whose PAP was normal during TTE, we detected PFO in 2 (20%) patients during VM. This difference was statistically significant between the case and control groups (p=0.000). Other baseline and clinical characteristics of case and control groups are shown in Table 1.

As shown in Table 2, in COPD patients with or without PFO, the differences were statistically significant for parameters such as tricuspid regurgitation (TR) (p=0.00), mitral regurgitation (p=0.01) and right ventricular end diastolic volume (REDV) (p=0.001). And was not significant for Pao2 (p=0.64), smoking (p=0.74), PAP (p=0.20) and FEV1/FVC (p=0.65). Since we used TCD as our PFO detection method, the TCD characteristics were of importance: 31 (68.9%) patients passed shunts during VM,27 (60%) patients were accounted as PFO, 8(8.9%)

patients passed delayed shunts, shower of emboli (shunts during rest and VM) was detected in 7 (15.6%) patients. When we used Logistic Regression analysis to determine the important factors associated with the occurrence of a PFO, we found that a cigarette load, Pao2, Sao2, FEV1 and PAPs did not show any significant association with the occurrence of PFO.

Table1. Demographic Comparison between case (COPD with PAP more than 30 mmhg) and control group(COPD with PAP less than 30 mmhg)

Group Variable	Case (n=45)	Control (n=10)
Age (years)	64±1.07	72.77±1.05
Cigarette loading (pack/year)	17.88±7.78	11.77±2.17
Hg	14.04±2.27	13.15±2.50
PH	7.34±09	7.33±06
Pao2	71±2.27	90.1±4.4
FVC(%predicted)	61±20.7	63.13±25.21
FEV1(%predicted)	52.64±24	70.12±14
FEV1/FVC	68.17±16.9	82.4±18.1
PAP(mmhg)	50.37±14.42	22.77±2.6
RVED	3.5±0.9	2.8±54
PFO		
Yes	31(68.9%)	1(10%)
No	14(31.1%)	9(90%)

Hg: hemoglobin; PaO2: O2 gradient in the blood; FVC: forced vital capacity; FEV1: forced expiratory volume during the first minute; RVED: right ventricular end diastolic volume; PAP: pulmonary artery pressure;

Using the same method of analysis to determine the factors associated with occurrence of PFO showed that only the echocardiographic factors were in coordination with PFO occurrence. REDV (p=0.008) and TR (p=0.029) showed a meaningful association. And finally our regression in the field of neurosonology technique showed that there existed a significant correlation between the number of MES and the increase in PAP (p=0.019).

But denies any linear correlation between the amount of increase in PAP and the likeliness of MES passage, meaning that the high MES passage was associated with higher PAP, but higher PAP did not necessary mean the definite passage of MES.

Table 2.Comparison between the two groups in which PFO was/was not detected among our Case (raised-PAP) patients.

characteristics	with PFO (N=31)	without PFO (N=14)	pvalue
Age(years)	65.2±12	63±6	0.60
Gender			.067
Male	18(58.1%)	4(28.6%)	
Female	13(41.9%)	10(71.4%)	
Smocking			0.74
Yes	14 (45.2%)	5(35.7)	
No	17(54.8%)	9(64.3)	
Cigarette load (p/y)	20.48±31.12	12.14±18.05	0.01
hg	14.34±2.31	13.36±2.10	0.64
PH	7.31±09	7.41±06	0.09
PaO2	69.80±10	73.70±23	0.68
Paco2	53.10±13.09	47.35±8.1	0.12
O2sat	80.19±9.4	89.43±8.4	0.30
FVC	60.01±27.03	64.18±17.46	0.04
FEV1	50.71±26.11	53.52±19.18	0.08
FEV1/FVC	70.95±16.01	66.03±18.77	0.65
RVED	3.8±0.73	2.8±1.07	0.001
PAP(mmhg)	53.12±16	42.50±8.9	0.23
TR			
Yes	30(96.8%)	9(64.3%)	.0001
No	1(3.2%)	5(35.7%)	
PAP			0.20
<60mmhg	21(67.7%)	12(85.7%)	
>60mmhg	10(32.2%)	2(14.3%)	

PFO: Patent Foramen Ovale; PaO2: O2 gradient in the blood; O2sat: finger pulse oximetry arterial o2 saturation; FVC: forced vital capacity; FEV1: forced expiratory volume during the first minute; RVED: right ventricular end diastolic volume; PAP: pulmonary artery pressure.

Discussion

In this study, we used TCD to determine the prevalence of RLS in patients with COPD, who had pulmonary hypertension. We also evaluated the relationship between the amounts of increase in pulmonary hypertension and the presence of RLS. RLS was significantly more frequent in our 45 consecutively studied patients than in a group of control subjects. The main characteristic that differed between our case and control subjects was the pulmonary pressure,

leading us to think that it played a cardinal role in increasing the prevalence of RLS among our patients. Here, we showed that the prevalence of RLS in our study patients was statically greater than previous similar studies (19) though none of the previous work strictly focused on pulmonary hypertension secondary to COPD. Our study also supports the previous findings that the prevalence of RLS during VM is significantly greater in COPD patients than in normal population. Several considerations should be made in order to explain our observations. The first relates to the technique used in this study to visualize RLS. The presence of RLS can be confirmed both invasively and none invasively. We used TCD as it is the non-invasive, simple, rapid, sensitive and specific and can be used at the bedside in neurology unit and can detect right-to-left shunts of both intracardiac and intrapulmonary origin. Naturally the gold standard method for detecting PFO is TEE as the shunts can be visualized and the source can be identified.

Though in our study we worked with the PFO diagnostic criteria in TCD, we cannot be certain about the specific source of the shunts since TCD can confirm the existence of PFO only after it has been detected by TEE suggesting that TCD and TEE are complementary according to clinical situation and technological equipment. Our study did not focus on the shunt passage at rest, as we believe evaluations on that ground have been clear enough in pointing out that higher pulmonary pressure and longer duration of the disease are in definite correlation with RLS at rest as well as PFO re-occurrence. Since longer exposure to alveolar hypoventilation results in higher PAP which leads to permanent RLS through PFO.

We used VM to detect RLS in our patients as it is also known to increase the sensitivity of TCD. A significant correlation between the amount of increase in PAP and occurrence of RLS would have led to the conclusion that our patients were ultimately going to reach the permanent shunting phase as their disease progressed. Such information could help start dealing with the consequences of permanent shunt earlier on. However, in our 45 patients with pulmonary hypertension secondary to COPD, no such correlation was found, suggesting that though pulmonary hypertension as a risk factor plays a role in causing significant RLS in our patients, it does not have a linear correlation with RLS. Consequently with the rise in pulmonary pressure one cannot necessarily expect the patients to progress from passing shunts with Valsalva maneuver to passing shunts at rest. Though the comparison between our case and control patients confirm that pulmonary hypertension is more likely in patients with RLS, the incoherence between the amount of increase in pulmonary pressure and the tendency for RLS point to other possible factors related to RLS.

The only proven cause of stroke related to COPD is a transient rise of pressure inside the right sided cardiac chambers causing RLS of venous origin across either an incompletely sealed PFO or an intrapulmonary arterio-venous connection. Given the fact that hypoxia leads to higher pulmonary pressure and that these patients tend to mimic the Valsalva maneuver with heavy coughing, they have higher risk of RLS. The higher number of RLS in COPD patients is reported here and the possible relationship between RLS – via PFO – and cryptogenic stroke that has been reported recently (20) leads to the speculation that such patients may benefit from anti-coagulation therapy. However, there was no significant history of CVA in our patients' records and to our knowledge; there is no report in the literature of higher prevalence of CVA in COPD population. This leaves us with two possibilities: either our patients' shunts were strictly pulmonary which cannot be the case since TCD findings were restricted to FPO, or the course of supportive treatment protected the patients from paradoxical embolism. We, therefore conclude that though further evaluation and follow up is mandatory, our data do not provide any evidence for anti-coagulation therapy as a prophylactic measure in COPD patients with pulmonary hypertension.

Acknowledgment

We would like to express our sincere gratitude to Dr. Rohani, Dr. Mosavi, Dr. Zahmatkesh, and Dr. Naghshin for their utmost support and guidance. Likewise to Mrs Avanaki Mrs Taiee for ICD performance, the Pulmonary Science Research Center Staff and to all the participants of the study.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997 349: 1269-76.
2. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee Circulation 2008;117: e25-146

3. Lee BI, Nam HS, Heo JH, Kim DI, Yonesi Stroke team. Yonsei Stroke Registry. Analysis of 1,000 patients with acute cerebral infarctions. Cerebrovasc Dis 2001; 12: 145-51.
4. Corrin B. Paradoxical embolism. Br Heart J 1964; 26: 549-53.
5. 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: 706-11.
6. Khositseth A, Cabalka AK, Sweeney JP, et al. Transcatheter Amplatzer device closure of atrial septal defect and patent foramen ovale in patients with presumed paradoxical embolism. Mayo Clin Proc 2004; 79: 35-41.
7. Harvey JR, Teague SM, Anderson JL, Voyles WF, Thadani U. Clinically silent atrial septal defects with evidence for cerebral embolization. Ann Intern Med 1986; 105: 695-7.
8. Moore KL. The Developing Human: Clinically Oriented Embryology. 6th edition. Philadelphia, PA: Saunders, 1998.
9. Hagen PT, Scholz DG, Edwars 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: 17–20.
10. Lynch JJ, Schuchard GH, Gross CM, Wann LS. Prevalence of right to left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. Am J Cardiol 1984; 53: 1478-80.
11. Movsowitz C, Podolsky LA, Meyerowitz CB, Jacobs LE, Kotler MN. Patent foramen ovale: a nonfunctional embryological remnant or a potential cause of significant pathology? J Am Soc Echocardiogr 1992; 5: 259-70.
12. Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. Br Heart J 1986; 55: 449-58
13. Fishman AP. State of the art: chronic cor pulmonale. Am Rev Respir Dis 1976; 114: 775–94.
14. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–9.
15. Teague SM, Sharma MK: Detection of paradoxical cerebral echo contrast embolization by transcranial Doppler ultrasound. Stroke 1991; 22:740–5.
16. Bayuet JP, Besson G, Tremel F, et al. Should One Use Echocardiography or Contrast Transcranial Doppler Ultrasound for the Detection of a Patent Foramen Ovale after an Ischemic Cerebrovascular Accident? Cerebrovasc Dis 2001;12:318–24
17. Sliwka V, Job EP, Wissuwa D, et al. Occurrence of Transcranial Doppler High-Intensity Transient Signals in Patients With Potential Cardiac Sources of Embolism. Stroke 1995; 26: 2067-70.
18. Streifler JY, Furlan AJ, Barnett HJM. Cardiogenic brain embolism incidence, varieties, treatment. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, NY: Churchill Livingstone Inc; 1992: pp: 967-94.
19. Hacievliyagil SS, Gunen H, Kosar FM, Sahin I, Kilic T. Prevalence and clinical significance of a patent foramen ovale in patients with chronic obstructive pulmonary disease. Respir Med 2006; 100: 903-10.
20. Alsheikh-Ali AA, Thaler DE, Kent DM, Patent foramen ovale in cryptogenic stroke: Incidental or pathogenic Stroke. 2009;40:2349-55.