Patent foramen ovale and the risk of **cerebral infarcts** in patients with acute **pulmonary embolism**: *a prospective observational study*

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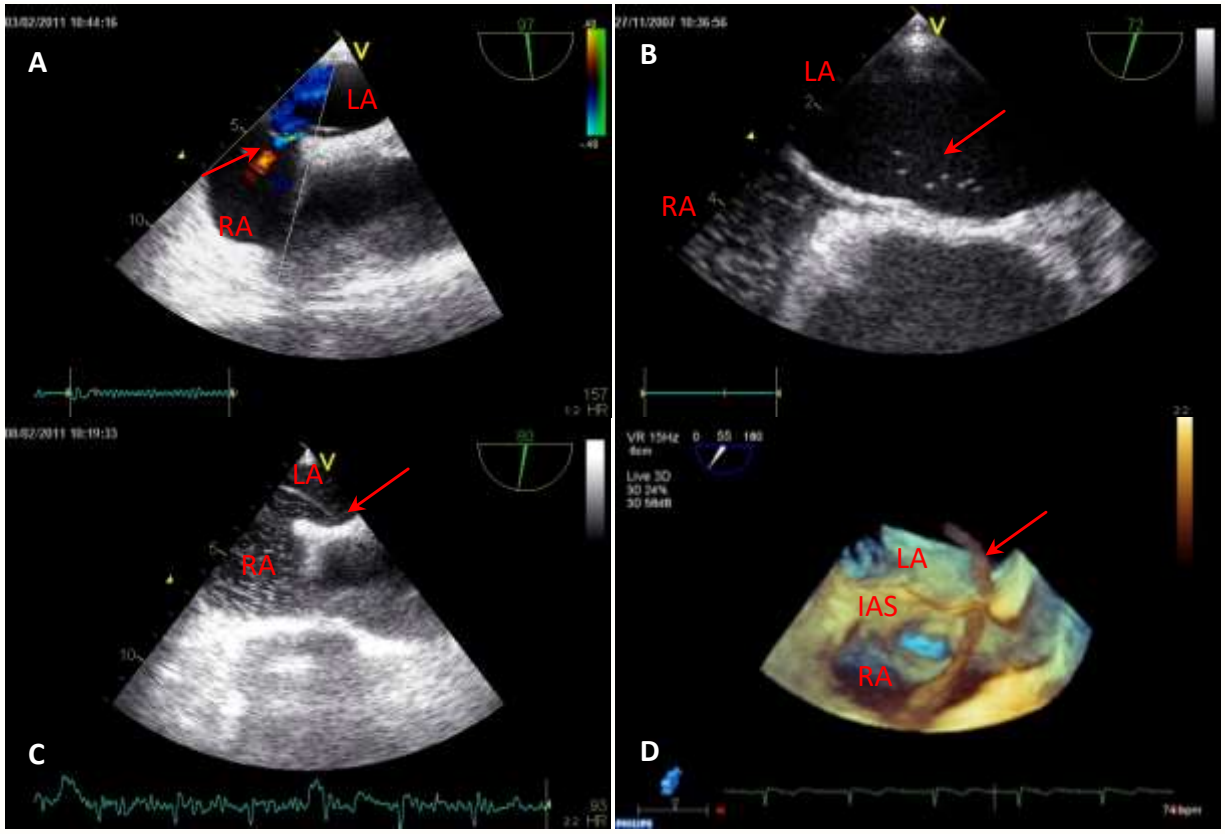
Background and aims

- A **patent foramen ovale (PFO)** is a known risk factor for paradoxical embolism, including ischemic stroke (IS). **(1, 2)** The closure of a PFO has been discussed controversially. The results of recent meta-analyses showed a trend to a favorable effect of the closure as a secondary prevention of IS. **(3, 4, 5)**
- **Paradoxical embolism** has been observed in patients with acute pulmonary embolism (PE) with coexisting PFO, and PFO was reported to be a significant predictor of poor outcome in this group. **(6)**
- Clinically **silent ischemic brain lesions** were detected in patients with PE and PFO, especially in patients with significant right ventricular dysfunction leading to right-left interatrial shunt via PFO in the acute phase of PE. **(7)** Magnetic resonance imaging (MRI) enables the reliable detection of ischemic brain lesions (IBL); moreover, the use of diffusion-weighted MRI allows the sensitive detection of acute cerebral ischemia.

The **aims** of our prospective study were **1) to assess** *the rates of new clinically silent brain ischemic embolism* detected on MRI and *clinical IS events* in patients with present acute PE during a 12-month follow-up period on effective anticoagulation therapy and **2) to evaluate** a potential *relationship with the presence of PFO and right-left shunt (RLS)* on transesophageal echocardiography (TEE).

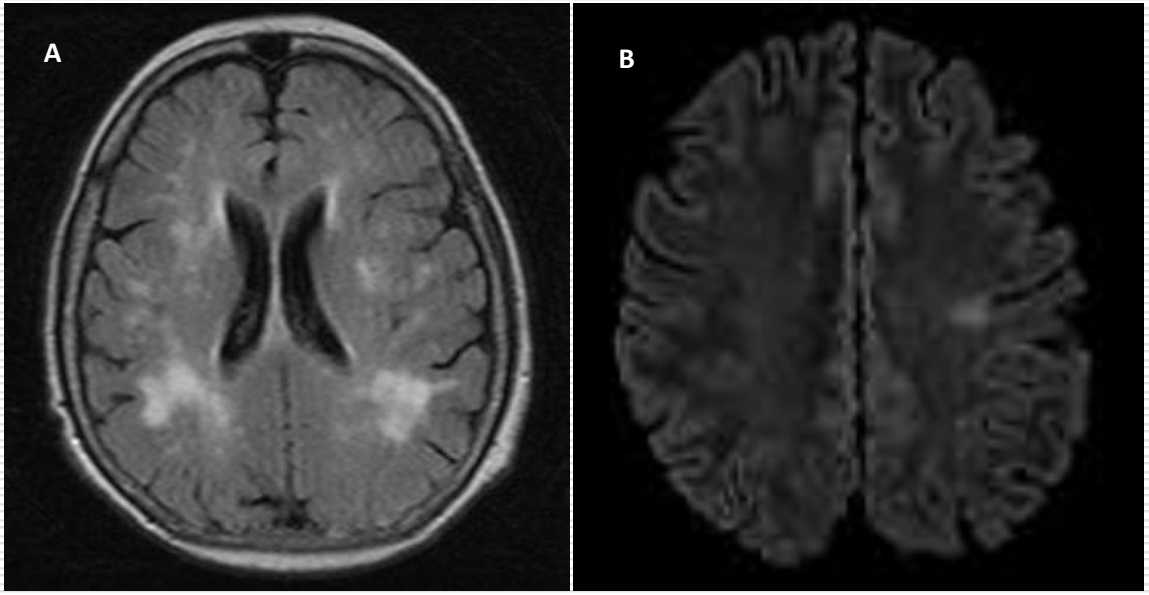
1. Di Tullio MR. J Am Coll Cardiol. 2007;49(7):797-802.
2. Handke M. N Engl J Med. 2007;357(22):2262-8.
3. Meier B. Engl J Med. 2013;368(12):1083-91.
4. Carroll JD. Engl J Med. 2013;368(12):1092-100.
5. Stortecky S. Eur Heart J 2015;36:120-128.
6. Konstantinides S. Circulation. 1998;97(19):1946-51.

Patent foramen ovale



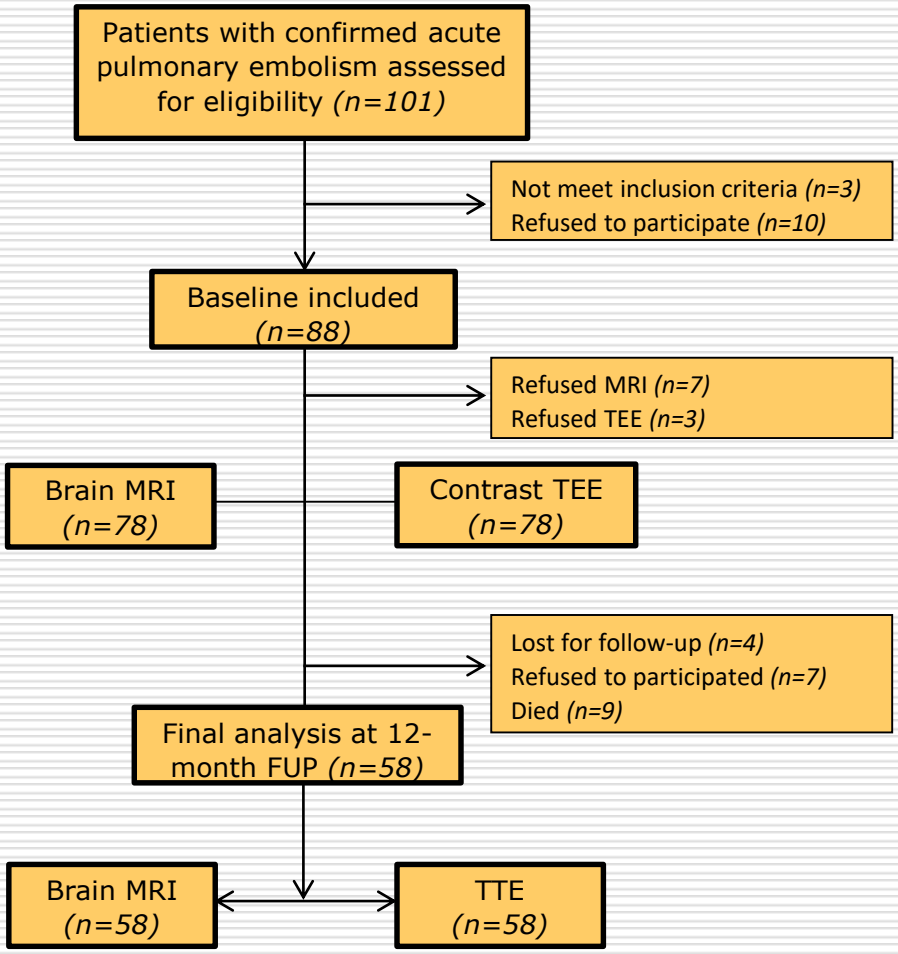
A. Transesophageal echocardiography in the midesophageal view revealing a small, simple patent foramen ovale. Color Doppler shows a small jet shunting from left atrium (LA) to right atrium (RA), confirming patent foramen ovale.
B. Medium sized (7 microbubbles) patent foramen ovale with right-to-left shunting demonstrated using echocontrast agent.
C. Large patent foramen ovale with right-to-left shunting demonstrated using echocontrast agent.
D. 3-dimensional transesophageal echocardiography revealing a large transient thromus in patent foramen ovale.

Brain magnetic resonance imaging – stroke protocol



A. fluid attenuated inversion recovery **(FLAIR) sequence**
B. diffusion-weighted imaging **(DWI) sequence** with ischemic brain lesions finding consistent with embolic lesions.

Flow chart detailing patient enrollment in the study



88 consecutive acute PE patients were **enrolled**.

78 underwent **baseline** contrast TEE with brain MRI.

After a **12-month follow-up period**, 58 underwent brain MRI. The rates of MRI documenting new IBL and clinical IS events were measured based on the presence of PFO and RLS.

Baseline patient group characteristics

	*Baseline total *(n=78)*	*[1]PFO present *(n=31)*	*[1]PFO absent *(n=47)*	*P*
BASELINE CHARACTERISTIC				
Men, n (%)	39 (50.0%)	16 (51%)	23 (48%)	*0.731*
Age (years)	62.7/66.0 (33.0; 81.0)	64.5/70.5 (54.8; 75.0)	61.4/64.0 (48.0; 74.1)	*0.390*
Height (cm)	169.7 / 168.0 (158.0; 184.0)	169.1/167.5 (164.0; 176.0)	169.4/169.0 (164.0; 175.8)	*0.872*
Weight (kg)	84.7/84.0 (55.0; 110.0)	86.6/84.5 (74.7; 95.3)	85.16/86.0 (78.0; 91.8)	*0.699*
Body-mass index (BMI)	29.3/29.4 (19.7; 37.1)	30.1/29.6 (25.4; 35.7)	28.3 /29.1 (27.5; 32.3)	*0.674*
COMORBIDITIES IN MEDICAL HISTORY				
Arterial hypertension, n (%)	48 (61.5%)	20 (64.5%)	28 (59.6%)	*0.661*
Atrial fibrillation, n (%)	9 (11.5%)	3 (9.7%)	6 (12.7%)	*0.676*
Peripheral arterial disease, n (%)	3 (3.8%)	1 (3.2%)	2 (4.2%)	*0.817*
Stroke/TIA[2], n (%)	6 (7.7%)	4 (12.9%)	2 (4.3%)	*0.161*
Coronary heart disease, n (%)	11 (14.1%)	5 (16.1%)	6 (12.8%)	*0.676*
Diabetes mellitus type 2, n (%)	13 (19.2%)	6 (19.4%)	7 (14.9%)	*0.721*
Thromboembolic disease, n (%)	7 (9.0%)	4 (12.9%)	3 (6.4%)	*0.072*
Malignancy, n (%)	11 (14.1%)	6 (19.4%)	5 (10.6%)	*0.279*
Advanced lung disease[3], n (%)	4 (5.1%)	1 (3.2%)	3 (6.4%)	*0.536*
Chronic renal insufficiency, n (%)	2 (2.6%)	1 (3.2%)	1 (2.1%)	*0.157*
PULMONARY EMBOLISM TREATMENT				
[4]UFH/LMWH only, n (%)	7 (8.9%)	2 (6.4%)	5 (10.6%)	*0.315*
[4]LMWH/warfarin, n (%)	68 (87.2%)	27 (87.1%)	41 (87.2%)	*1.000*
[4]LMWH/edoxaban or warfarin, n (%)	3 (3.8%)	2 (3.2%)	1 (4.2%)	*0.901*
Thrombolysis ([5]rt-PA), n (%)	9 (11.5%)	3 (9.7%)	6 (12.7%)	*0.651*
BASELINE ECHOCARDIOGRAPHY				
Tricuspid valve regurgitation, n (%)	70 (89.7%)	30 (96.7%)	40 (85.1%)	*0.489*
Tricuspid valve regurgitation peak pressure gradient (mmHg)	36.3/30.0 (30.0; 48.1)	36.1/30.0 (25.3; 47.0)	35.9/29.0 (20.9; 50.0)	*0.964*
[6]Right ventricle diameter (mm)	41.3/41.0 (36.0; 46.6)	42.0/41.0 (36.7; 48.0)	40.4/41.0 (34.7; 46.0)	*0.304*
Atrial septal aneurysm, n (%)	18 (23.1%)	14 (45.1%)	4 (8.5%)	***0.0002***
[7]TA peak systolic velocity (cm/s)	15.4/15.0 (12.0; 18.0)	15.3/15.5 (13.0; 17.0)	15.4/15.0 (12.0; 18.0)	*0.865*
[8]TAPSE (mm)	24.1/24.0 (21.0; 28.0)	24.4/24.0 (21.0; 28.0)	23.8/23.0 (21.4; 28.6)	*0.626*
CARDIAC MARKERS				
[9]NT-proBNP (ng/L)	2744.3/1276.0 (63.9; 10144.0)	3086.2/1949.5 (288.4; 4453.1)	2516.8/894.2 (166.6; 2783.3)	*0.649*
Troponin T (ng/L)	0.11/0.02 (0.00; 0.33)	0.08/0.06 (0.00; 0.33)	0.07/0.01 (0.00; 0.04)	*0.751*
CLINICAL ENDPOINTS				
Mortality follow-up, n (%)	4 (5.1%)	3 (9.7%)	1 (2.3%)	*0.097*
Stroke clinically apparent, n (%)	7 (9.0%)	4 (12.9%)	3 (6.4%)	*0.324*
[2]TIA clinically apparent, n (%)	4 (5.1%)	2 (6.4%)	2 (4.2%)	*0.715*
[10]Pulmonary hypertension, n (%)	12 (15.4%)	3 (9.7%)	9 (19.1%)	*0.506*

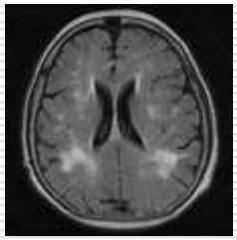
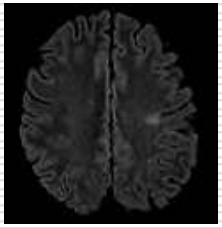
PFO was detected in 31 patients (39.7%)

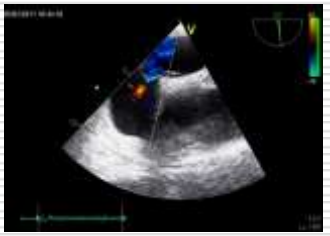
At baseline MRI, IBL was present in 39 (50%) pts.

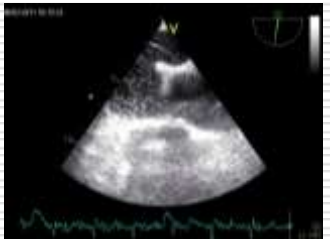
*Number and percentage of total for categorical parameters; mean/median (5-95[th] percentile range) for continuous parameters

[1] PFO – patent foramen ovale
[2] TIA – transient ischemic attack
[3] chronic obstructive pulmonary disease (n = 3, FEV1 <60%), interstitial lung disease (n=1, TLC <70%)
[4] UFH/LMWH – unfractionated heparin/low molecular weight heparin
[5] rt-PA - recombinant tissue Plasminogen activator (Alteplase)
[6] Apical four chamber view endiastolic right ventricle basal diameter
[7] TA - tricuspid anulus
[8] TAPSE - tricuspid annular plane systolic excursion
[9] NT-proBNP - amino-terminal fragment of brain natriuretic peptide
[10] high and intermediate echocardiographic probability after a 12-month follow up

Relationship between presence of PFO/RLS and detection of ischemic brain lesions on MRI

		Patent foramen ovale*			Right to left shunt*		
		absent	**present**	*P* †	**absent**	**present**	*P* †
Baseline [3]MRI ischemic brain lesions							
	**absent**	n=28 (59.6%)	n=11 (35.5%)	*0.063*	n=29 (58.0%)	n=10 (35.7%)	*0.098*
	present	**n=19 (40.4%)**	**n=20 (64.5%)**		n=21 (42.0%)	n=18 (64.3%)	
New ‡MRI ischemic brain lesions at follow-up							
	**absent**	n=35 (94.6%)	n=14 (66.7%)	***0.008***	n=38 (95.0%)	n=11 (61.1%)	***0.002***
	present	**n=2 (5.4%)**	**n=7 (33.3%)**		n=2 (5.0%)	n=7 (38.9%)	





* Categories of parameters as n and % of total
† Statistical comparisons was made with Fischer exact test for categorical parameters
‡ MRI – magnetic resonance imaging

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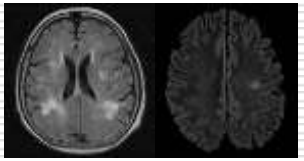
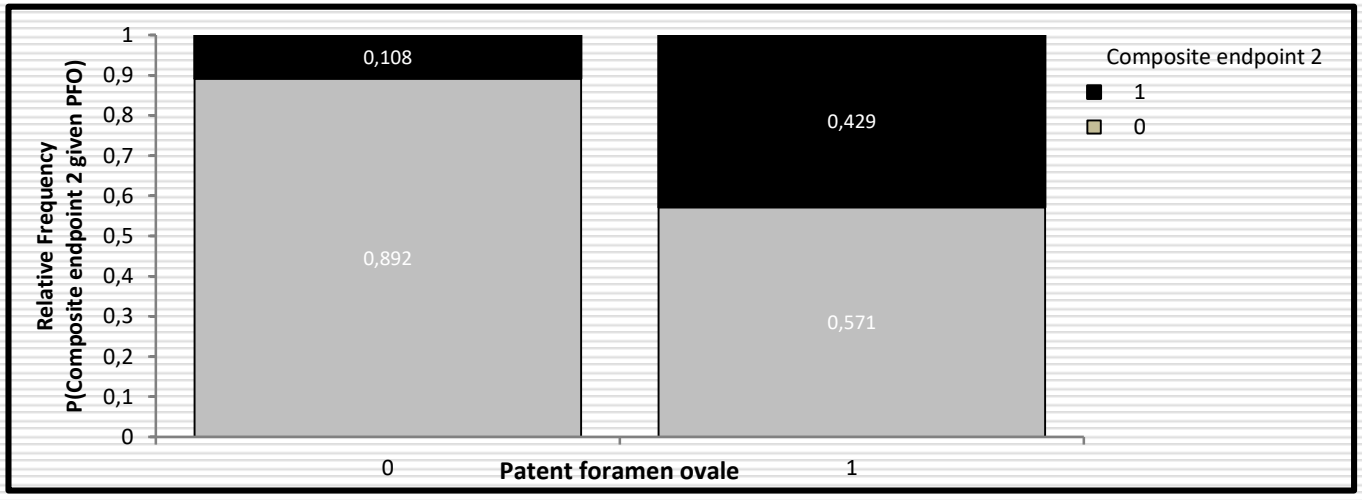
Composite endpoint of new IBL on MRI and clinically presented IS events without MRI finding

	* Total (n=58)	†PFO present (n=21)	†PFO absent (n=37)	*P*
New ‡ MRI ischemic brain lesions (n)	9 (15.5%)	7 (33.3%)	2 (5.4%)	***0.008***
Stroke/§ TIA with no ‡ MRI finding (n)	4 (6.9%)	2 (9.5%)	2 (5.4%)	*0.615*
COMPOSITE ENDPOINT	13 (22.4%)	9 (42.8%)	4 (10.8%)	***0.0082***

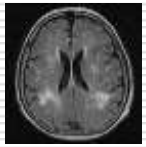
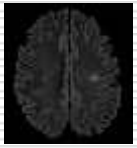


* Categories of parameters as number and percentage of total

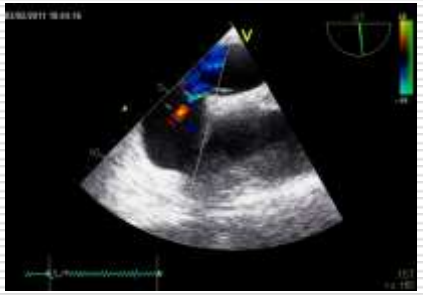
† PFO – patent foramen ovale, ‡ MRI – magnetic resonance imaging, § TIA – transient ischemic attack

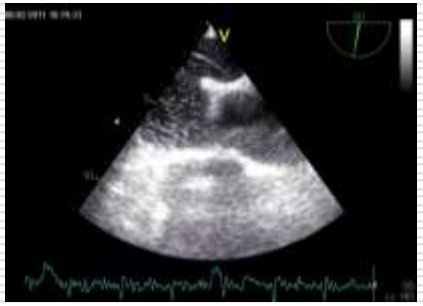


Predictive value of PFO and right-to-left shunt for ischemic brain lesion presence on MRI

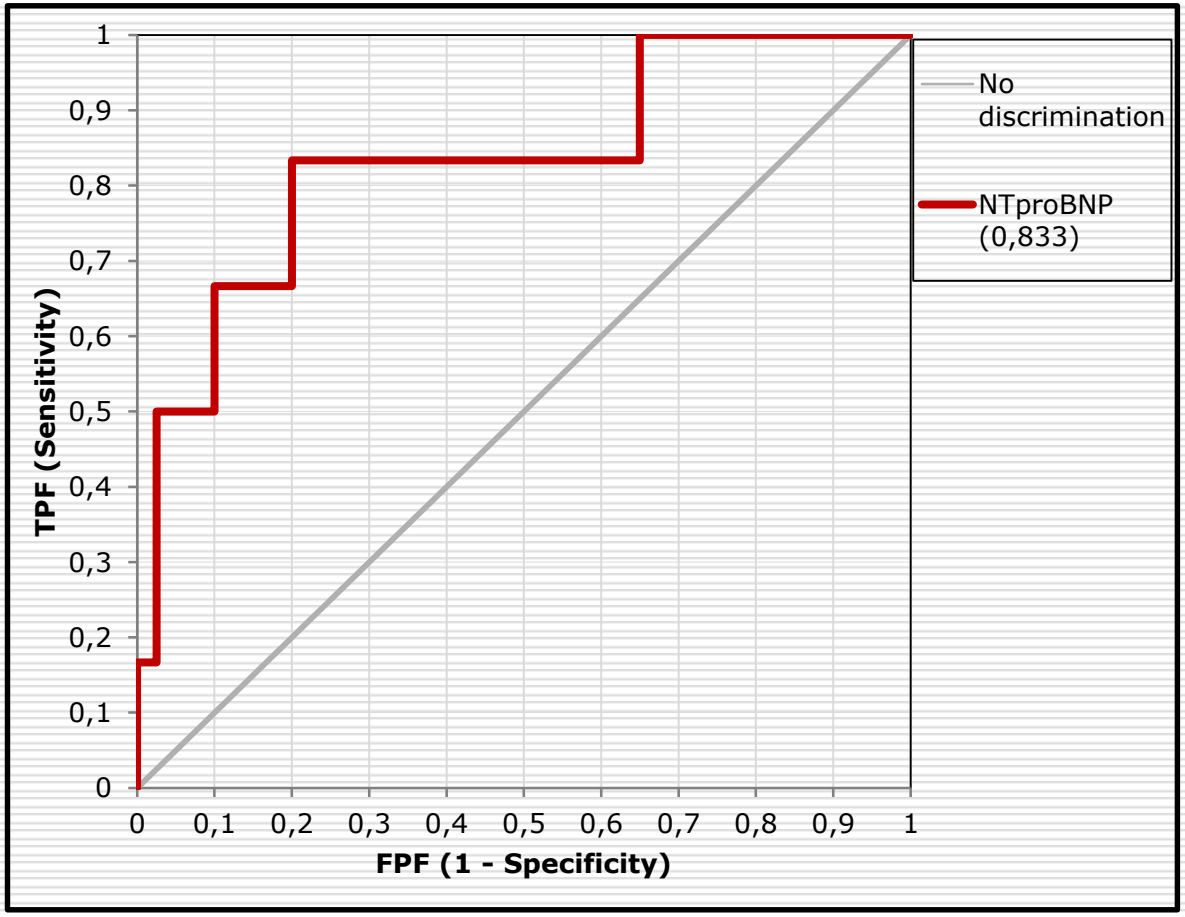
		OR (95% CI)*	*P*	Sensitivity	Specificity
Baseline [3]MRI ischemic brain lesions					
	*PFO	1.536(1.048;6.849)	***0.024***	0.645	0.596
	‡RLS	1.415(0.956;6.463)	***0.033***	0.643	0.580
New [3]MRI ischemic brain lesions at follow-up					
	*PFO	4.575(1.616;47.386)	***0.008***	0.333	0.946
	‡RLS	6.190(2.190;66.767)	***0.002***	0.389	0.950

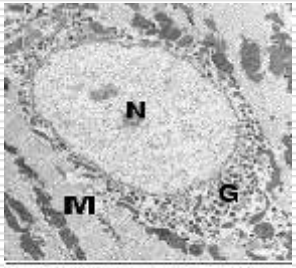
* Odds ratio (OR) for models based on logistic regression, * PFO – patent foramen ovale, ‡ RLS – right to left shunt





Prediction of clinically presented IS events using baseline NR-proBNP during follow-up period in ROC analysis





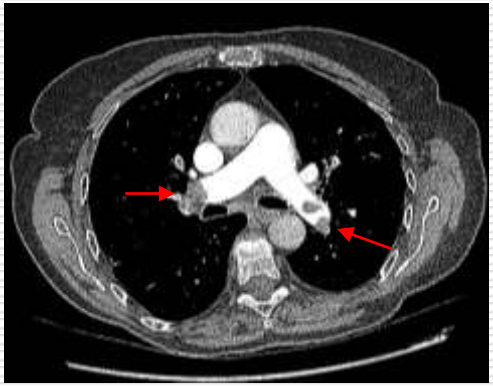
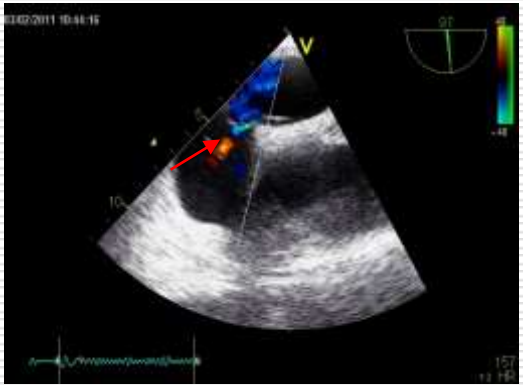
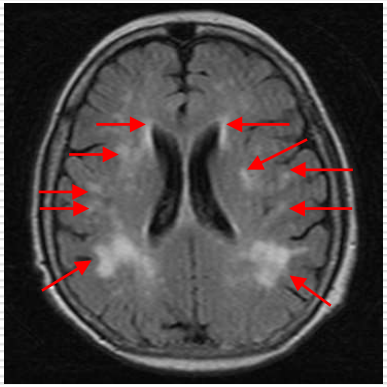
* NT-proBNP - N-terminal fragment of brain natriuretic peptide, †AUC – area under curve, ‡CI – confidence interval
*optimal NT-proBNP cut-off value 2473 ng/L (sensitivity 83%, specificity 80%, odds ratio 20.0, AUC 0.83 [0.32 to 1.0]; *P*=0.008)

Conclusions

1. The presence of PFO and RLS is associated with a higher risk of new brain ischemic lesions on MRI in patients with PE during a 12-month follow-up period despite effective anticoagulation therapy.

2. Paradoxical embolism may be an important cause of ischemic cerebral events, which has to be ruled out in patients with no other evident stroke etiology. The detection of PFO and RLS can identify patients with PE who might profit from the closure of PFO.

3. For diagnostic purposes, we recommend the use of contrast-enhanced TEE. Thus, TEE should be a standard part of the diagnostic management of patients with acute PE.

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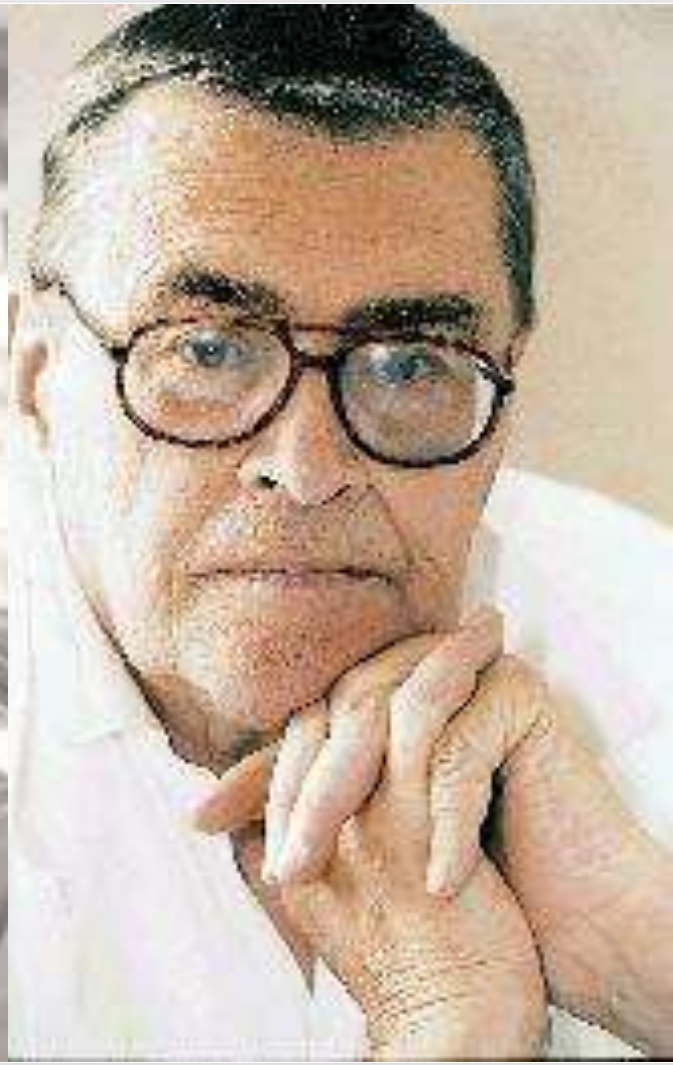

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