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Evaluation of the severity of right to left shunt in PFO patients after systemic embolism (MEASURE-PFO study). Design of the study

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INTRODUCTION AND MOTIVATION

Patent foramen ovale is a cardiac abnormality — a channel opening between the right and left atrium. While PFO is functional in the prenatal stage of life, it should close after birth. PFO can be found in about 15% to 30% of autopsies and has been reported in 10% to 25% of patients examined by transesophageal echocardiography (TEE). In most cases, PFO does not result in any adverse effects, but may occasionally cause severe disabilities. It is generally believed that

PFO has no hemodynamic significance, but situations have been described in which the R–L shunt through PFO led to a clinically significant desaturation.

Nowadays, PFO is usually detected by TEE. The passage of contrast substance bubbles at rest or under strain using the Valsalva manoeuvre represents a clear evidence of the R–L shunt in PFO patients. However, quantitative assessment of the R–L shunt by contrast TEE examination is imprecise and semiquantitative. To date, no precise knowledge exists about the volume of blood flow through the PFO in case of an inducible R–L shunt. It has not been determined whether the presence of a R–L shunt can affect the functional status of a PFO patient or which morphological variants of PFO are burdened with a higher risk of the R–L shunt. Our ability to identify patients with a higher risk of systemic embolism through the PFO and higher risk of systemic desaturation is also limited. Data from previous research and clinical practice suggest that there is a certain group of PFO patients who have a higher risk of the R–L shunt in stress situations (e.g., physical stress, static stress, sleep apnoea), and thus higher risk of systemic embolism and desaturation.

More precise knowledge of the R–L shunt size could be used in the future to identify high-risk PFO patients, in whom a preventive PFO closure could be medically justified in terms of preventing severe systemic embolism or severe cases of desaturation.

This study focuses on abnormalities of the interatrial septum in PFO patients. Its aim is a precise measurement of hemodynamic parameters, in particular of the inducible R–L shunt, in PFO patients using the Inntherm® system (Innova Medical Inc, Chrastany, Czech Republic). The study also includes a standard examination of PFO patients using the TEE and stress tests, and a comparison of non-invasive findings with invasive hemodynamic examination. Using the EQ-5D-5L questionnaire, the study also assesses the impact of the percutaneous PFO closure on the quality of life. The study are enrolled patients indicated for the percutaneous PFO closure after suffering a systemic embolism event to prevent its recurrence.

OBJECTIVE OF THE STUDY

The objective of the study is to find a new risk marker for patients with PFO based on a newly developed technique to accurately measure the size of the R–L shunt, even in cases where it is present only intermittently. To detect the R–L shunt, the original Inntherm® system will be used, which works on the principle of thermodilution. An essential premise of the study is the hypothesis that the R–L shunt size is a risk factor for the development of paradoxical embolism potentially leading to ischemic stroke or systemic embolism and occasional desaturation states. A measurement as precise as proposed herein has never been performed before, since the

technology making it possible was not available. After correlation with commonly used methods, accurate quantification of the R–L shunt will allow for more precise identification of risk patients.

The primary priority of the study is to accurately measure the blood flow through the PFO at rest and after performing a standardized Valsalva manoeuvre. Another goal is to identify a subgroup of patients with a significant R–L shunt (>20% of systemic blood flow). Hemodynamic findings verified by catheterization will be compared with standard TEE. The R–L shunt size will be assessed in patients in whom systemic desaturation occurred in stress tests. Last but not least, we will assess the impact of the PFO closure on the exercise tolerance and quality of life.

METHODOLOGY

We plan to enrolled 150 patients with PFO eligible for the PFO closure to prevent the recurrence of systemic embolism, with the aim of identifying 30 patients with a significant R–L shunt (20% of the target population). This multicentric study is conducted in 6 cardiology centres in the Czech Republic. The patients must be 18 to 60 years old and sign an informed consent. Study recruitment started on October 2020. The “COVID 19” pandemic significantly slowed patient recruitment. Currently, 150 patients are enrolled. Follow-up will be completed in January 2024.

Planned examinations:

1. A detailed neurological clinical examination to confirm paradoxical embolism as the most likely cause of the cardioembolic event.
2. A standardized cardiac ultrasound examination (transthoracic echocardiography [TTE] + TEE) for the PFO diagnosis with a detailed assessment of morphology of the interatrial septum and a semi-quantitative assessment of the shunt using contrast.
3. A detailed medical history focused on symptoms potentially related to systemic desaturation.
4. A standardized spiroergometric examination with the oxygen consumption measurement and measurement of blood saturation with the pulse oximeter NONIN Avant® 9600 (Nonin Medical Inc, Plymouth, MN, US) using the head reflection sensor prior to the PFO closure.
5. A hemodynamic catheterization examination performed through the femoral access — measurement of the pressures in heart chambers, aorta and pulmonary artery, measurement of the systemic and pulmonary blood flow, and the L–R and R–L shunts using the original Inntherm® system before the PFO closure in one catheterization procedure.

6. An assessment of the clinical condition 6 months after the PFO closure.
7. A follow-up TEE ultrasound examination 6 months after the PFO closure.
8. A follow-up standardized spiroergometric examination with the oxygen measurement and blood saturation measurement using the pulse oximeter NONIN Avant® with the head reflection sensor 6 months after the PFO closure.
9. An assessment of the impact of the percutaneous PFO closure on the quality of life using the EQ-5D-5L questionnaire (before the procedure and 6 months after).

Inclusion criteria:

Patients with cryptogenic stroke/transient ischemic attack or systemic embolism.
Patients indicated for the percutaneous PFO closure.
Patients between 18 and 60 years of age.

Exclusion criteria:

Patients under 18 years of age or above 60 years of age.
Prior known inability to complete a TTE/TEE.
Prior known inability to complete a relevant stress test.
Prior known inability to perform appropriately the Valsalva manoeuvre.
Inability or unwillingness to sign an informed consent.
Failure to complete the percutaneous PFO closure.

A follow-up 6 months after the PFO closure:

1. A detailed clinical examination.
2. An assessment of the impact of the percutaneous PFO closure on quality of life using the EQ-5D-5L questionnaire.
3. A standardized cardiac ultrasound examination (TTE+TEE) using the same procedure as before the PFO closure.
4. A standardized spiroergometric examination using the same procedure as before the PFO closure.

Statistical analysis

Power analysis has been performed with expected endpoint occurrence 30% and sample size of 150 patient reached power with 95% confidence interval. Based on a data, we will correlate amount of R-L shunt measured by cardiac catheterization, TEE and basic spiroergometry values

(VO_2max, desaturation). At follow up we will compare efficacy of occlusion and change of exercise test parameters. Quality of life will be analyzed by basic and follow up EQ-5D-5L questionnaire. Expected statistical tests will be conducted: Fisher's exact test, McNemar's test, Mann–Whitney U test, related-samples Wilcoxon signed rank test.

CONCLUSIONS

The subject of the MEASURE-PFO study is the right-to-left shunt in patients with PFO. The aim of the project is to identify a subgroup of high-risk PFO patients using an accurate hemodynamic measurement of the R–L shunt in combination with non-invasive tests (TTE, TEE, spiroergometry). No other commercially available system enables measuring of the blood flow in shunt defects at rest and under stress. No data on precise quantitative measurement of R–L shunts in PFO patients are available in literature. The project will also include an evaluation of the impact of the percutaneous PFO closure on exercise tolerance and quality of life using the EQ-5D-5L questionnaire.

Article information

Conflict of interest: None declared.

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REFERENCES

1. Endrys J, Stasek J. New precise thermodilution method for measurement of intracardiac shunts. Eur Heart J. 2006; 27: 399.
2. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000; 55(8): 1172–1179, doi: 10.1212/wnl.55.8.1172, indexed in Pubmed: 11071496.

3. Devendra GP, Rane AA, Krasuski RA. Provoked exercise desaturation in patent foramen ovale and impact of percutaneous closure. JACC Cardiovasc Interv. 2012; 5(4): 416–419, doi: 10.1016/j.jcin.2012.01.011, indexed in Pubmed: 22516398.
4. Pristipino C, Germonpré P, Toni D, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. EuroIntervention. 2019; 14(13): 1389–1402, doi: 10.4244/EIJ-D-18-00622, indexed in Pubmed: 30141306.
5. Pristipino C, Germonpré P, Toni D. European position paper on the management of patients with patent foramen ovale. Part II - Decompression sickness, migraine, arterial deoxygenation syndromes and select high-risk clinical conditions. Eur Heart J. 2021; 42(16): 1545–1553, doi: 10.1093/eurheartj/ehaa1070, indexed in Pubmed: 33507260.
6. De Cuyper C, Pauwels T, Derom E, et al. Percutaneous closure of PFO in patients with reduced oxygen saturation at rest and during exercise: Short- and long-term results. J Interv Cardiol. 2020; 2020: 9813038, doi: 10.1155/2020/9813038, indexed in Pubmed: 32265599.
7. Mojadidi MK, Ruiz JC, Chertoff J, et al. Patent Foramen Ovale and Hypoxemia. Cardiol Rev. 2019; 27(16): 34–40, doi: 10.1097/CRD.0000000000000205., indexed in Pubmed: 29570476.

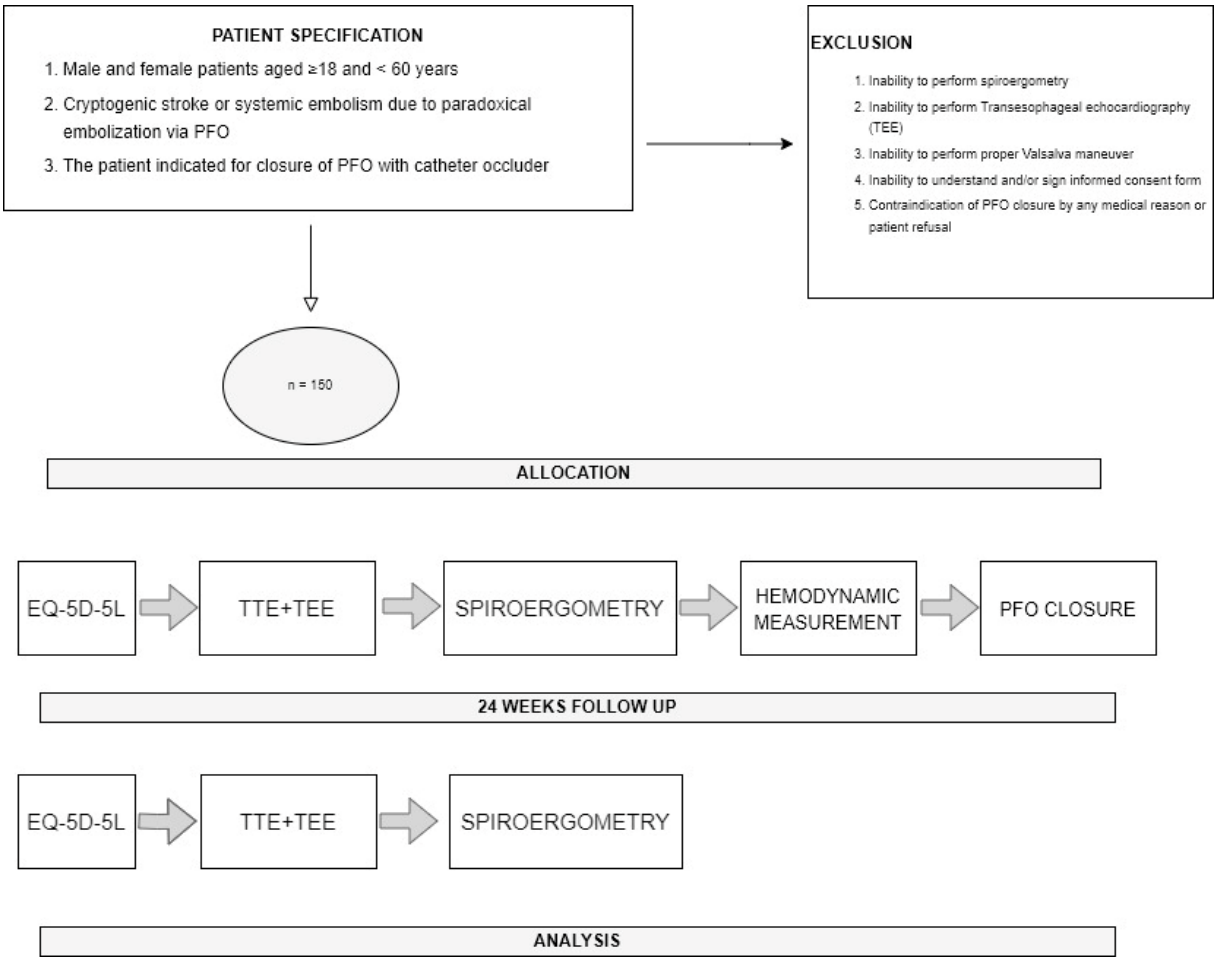

Figure 1. Chart of the study