Evaluation of the severity of right-to-left shunt in PFO patients after systemic embolism (MEASURE-PFO study): Study design

Josef Stasek[1], Josef Bis[1], Jaroslav Dusek[1], Karel Medilek[1], Jiri Dostal[1], Marian Branny[2], Jan Mrozek[2], Martin Porzer[2], Martin Mates[5], Karel Kopriva[5], Michael Zelizko[6], Vladimir Karmazin[6], Martin Poloczek[4], Petr Kala[4], Tomas Kovarnik[3], David Zemanek[3], Ales Linhart[3], Petr Parizek[1], on behalf of the MEASURE-PFO Investigators

[1]1st Department of Internal Medicine — Cardioangiology, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic
[2]Cardiovascular Department, University Hospital Ostrava, Ostrava, Czech Republic
[3]2nd Department of Internal Cardiovascular Medicine, General University Hospital in Prague, Prague, Czech Republic
[4]Department of Internal Medicine and Cardiology, University Hospital Brno, Brno, Czech Republic
[5]Department of Cardiology, University Hospital Na Homolce in Prague, Prague, Czech Republic
[6]Institute of Clinical and Experimental Medicine in Prague, Cardiocenter, Prague, Czech Republic

Correspondence to:
Josef Stasek, MD, PhD, Assist. Prof., 1st Department of Internal Medicine — Cardioangiology, University Hospital Hradec Kralove, Sokolska 581, 50003 Hradec Kralove, Czech Republic, phone: +420 495 832 248, e-mail: josef.stasek@fnhk.cz

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INTRODUCTION AND MOTIVATION

Patent foramen ovale (PFO) is a cardiac abnormality — a channel 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 transoesophageal 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 right-to-left (R-L) shunt through PFO led to clinically significant desaturation [1–4].

Nowadays, PFO is usually detected by TEE. The passage of contrast substance bubbles at rest or under strain using the Valsalva maneuver represents 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 the case of an inducible R-L shunt. It has not been determined whether the presence of an R-L shunt can affect the functional status of a PFO patient or which morphological variants of PFO are burdened with higher risk of the R-L shunt. Our ability to identify patients with a higher risk of systemic embolism through the PFO and a 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 with 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 [1–4].

More precise knowledge of the R-L shunt size could be used in the future to identify high-risk PFO patients, in whom 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. It aims to measure precisely hemodynamic parameters, in particular, of the inducible R-L shunt in PFO patients using the Inntherm® system (Innova Medical Inc, Chrastany, Czech Republic) [5]. The study also includes a standard examination of PFO patients using 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 percutaneous PFO closure on the quality of life. The study enroll patients with an indication for percutaneous

PFO closure after suffering a systemic embolism event to prevent its recurrence [6, 7].

OBJECTIVE OF THE STUDY

The study objective is to find a new risk marker for PFO patients 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 measure accurately the blood flow through the PFO at rest and after performing a standardized Valsalva maneuver. 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 PFO closure on exercise tolerance and quality of life.

METHODOLOGY

We planned to enroll 150 PFO patients eligible for the PFO closure to prevent the recurrence of systemic embolism and to identify 30 patients with a significant R-L shunt (20% of the target population). This multicenter study is conducted in 6 cardiology centers in the Czech Republic. The patients must be 18 to 60 years old and sign informed consent. Study recruitment started in October 2020. The COVID-19 pandemic significantly slowed patient recruitment. The article was sended on November 15, 2023. Currently 151 patients are enrolled, the follow-up of all patients is completed in January 2024. Further data are completing subsequently and the publication will be prepared for autumn 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 PFO diagnosis with a detailed assessment of the 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 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 before PFO closure.
5. A hemodynamic catheterization examination performed through femoral access — measurement of the pressures in the heart chambers, aorta, and pulmonary artery, measurement of the systemic and pulmonary blood flow, and L-R and R-L shunts using the original Inntherm® system before PFO closure in one catheterization procedure.
6. An assessment of the clinical condition 6 months after PFO closure.
7. A follow-up TEE ultrasound examination 6 months after PFO closure.
8. A follow-up standardized spiroergometric examination with oxygen measurement and blood saturation measurement using the pulse oximeter NONIN Avant® with the head reflection sensor 6 months after PFO closure.
9. An assessment of the impact of percutaneous PFO closure on the quality of life using the EQ-5D-5L questionnaire (before the procedure and 6 months after).

Inclusion criteria:

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

Exclusion criteria:

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

Follow-up 6 months after the PFO closure:

1. A detailed clinical examination.
2. An assessment of the impact of 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 PFO closure.
4. A standardized spiroergometric examination using the same procedure as before PFO closure.

Statistical analysis

Power analysis performed with an expected endpoint occurrence of 30% and a sample size of 151 patients reached power with a 95% confidence interval. Based on the data, we will correlate the amount of R-L shunt measured by cardiac catheterization, TEE, and basic spiroergometry

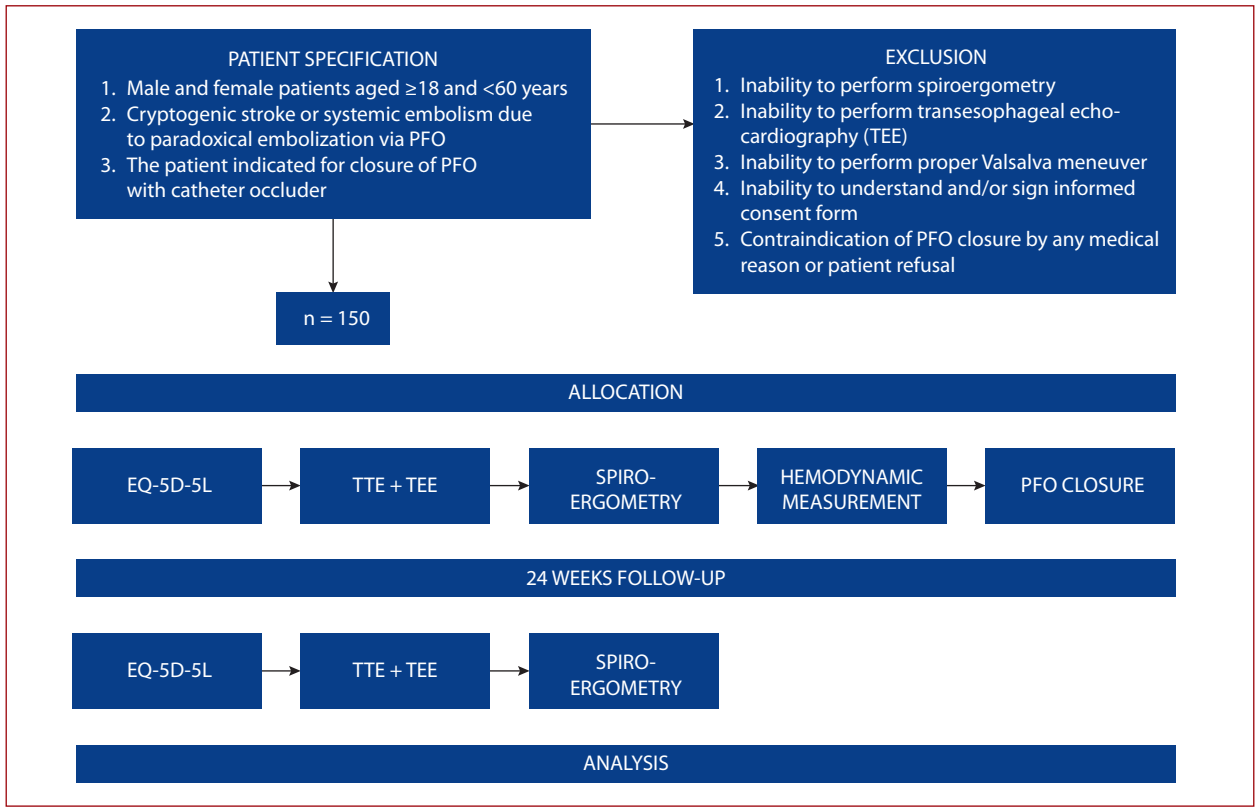

Figure 1. Chart of the study

values (VO_2 max, desaturation). At follow-up, we will compare the efficacy of occlusion and the change in exercise test parameters. Quality of life will be analyzed by baseline and follow-up EQ-5D-5L questionnaires. 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 to measure the right-to-left shunt in PFO patients. The project aims 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 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 the literature. The project will also include an evaluation of the impact of 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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