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Heart-Stroke Team: A multidisciplinary assessment of patent foramen ovale-associated stroke

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Abstract

Introduction: Patent foramen ovale (PFO) closure prevents recurrent ischemic stroke in selected patients with a cryptogenic stroke. Trial results tend to be generalized to daily practice, often extending original trial inclusion criteria. This may result in unnecessary closure without benefit, but with risk of complications. We therefore introduced a standardized and structured evaluation by an interdisciplinary Heart-Stroke Team (HST). Our aim was to investigate the proportion of actual PFO closure of all referred patients with a cryptogenic stroke, after evaluation by the HST.

Patients and methods: We conducted a single-center, retrospective cohort study. Patients with an assumed cryptogenic ischemic stroke or transient ischemic attack (TIA) and a PFO who were referred for PFO closure were analyzed. As part of the HST approach, all patients underwent a standardized work-up, first to demonstrate the ischemic event on neuroimaging, second to evaluate all potential causes of stroke and finally, to assess the possible relation between the PFO and stroke. Outcome was the proportion of patients treated with PFO closure after referral.

Results: A total of 195 patients were included. In 124 patients (64%) PFO closure was advised. Fourty-two (22%) patients had a clear alternative cause of stroke and in 13 (7%) patients the initial stroke diagnosis could not be confirmed.

Conclusion: After careful analysis of patients referred for PFO closure a relationship between the PFO and stroke could not be demonstrated in 32% of referrals, and 3% preferred best medical treatment over percutaneous closure. This stresses the need for a complete neurovascular work-up and multidisciplinary assessment.

Keywords

Heart-Stroke Team, patent foramen ovale, PFO closure

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Introduction

A PFO is a common finding, with a prevalence of up to 25% in the general population.[1] In young patients with a cryptogenic stroke a prevalence as high as 40%–50% has been reported.[2,3] Randomized controlled trials (RCT) demonstrated a lower risk of recurrent ischemic stroke after PFO closure in selected patients,[4–6] however it is difficult to demonstrate a causal relation between highly prevalent findings in healthy individuals, such as PFO and stroke. In the randomized clinical trials, this relation was operationalized as evidence of a cortical infarct on imaging without any other cause of the stroke than a PFO. Over time, trial results tend to be generalized, with the risk of indications for PFO closure becoming extended. This is illustrated in a study that reported that 33% of all PFO closures were performed in patients over the age of 60 years, even though such patients had been excluded from the RCTs.[7] Extrapolating trial results to the general population is a cautious, deliberate and inevitable process. This requires a standardized work-up and individualized assessment to

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determine in which patients the PFO is deemed the cause of stroke and consequently which patients will benefit most from PFO closure, since unnecessary closure has no benefits and may cause complications.[8]

The European Association of Percutaneous Cardiovascular Interventions (EAPCI) and The Society for Cardiovascular Angiography and Interventions (SCAI) have each published position papers on the management of patients with PFO and stroke.[9,10] These papers advocate the installment of an interdisciplinary Heart-Stroke Team (HST) including at least a neurologist and an interventional cardiologist, to investigate whether the stroke can be attributed to the PFO. However, HSTs have not been implemented in every stroke unit and limited data are available on the effects of the introduction of an HST on the proportion of PFO closures of all referred patients. Only one previous study, conducted after the positive closure RCTs, investigated the added value of an HST.[4–6] That study showed that in 20% of PFO-patients, the HST diagnosis was discordant from that of referring physicians. Fourteen percent were stroke misdiagnoses and the authors advised against closure in 53% of patients. However the investigators did not describe in detail the reasons for rejection of PFO closure, neither specifying why patients with a cryptogenic stroke and PFO did not have a PFO-associated stroke, nor showing how echocardiographic data influenced the decision-making on PFO closure.[11] We therefore investigated what proportion of patients with a cryptogenic stroke referred to a tertiary stroke center (Radboudumc, Nijmegen, The Netherlands) for PFO closure, were actually closed after HST evaluation. Furthermore, we planned to state clearly the reasons for rejection and show the value of variables like RoPE Score, anatomical-, stroke- and patient characteristics in deciding on PFO closure. Additionally, we explored group differences between the patients who underwent PFO closure before versus after the instigation of the HST.

Methods

Study design and patients

We conducted a single-center, retrospective cohort study. Patients with a cryptogenic ischemic stroke or transient ischemic attack (TIA) and a PFO, who were referred to the Radboudumc (Nijmegen, the Netherlands) for consideration of PFO closure between November 2016 and December 2021, were included. Patients were referred because in the referring centers the PFO was concluded to be the cause of stroke.

Before the HST

Before the instigation of the HST (2016 until 2018) all patients who were referred for PFO closure were accepted for closure when criteria of the RCTs (a cryptogenic stroke, below the age 60 years and with any type of PFO) were fulfilled. All investigation for the cause of stroke was done within the referring hospitals, and according to their local guidelines.

After the introduction of the HST

The Radboudumc HST started in June 2018. It comprises a congenital interventional cardiologist, a vascular internal medicine specialist, stroke neurologist and a specialized nurse. This composition is based on the Dutch guideline for PFO closure.[12] The inclusion criteria for evaluation by the HST are: (1) a presumed cryptogenic stroke according to the referring neurologist, (2) demonstration of a PFO, and (3) a probable relation between the PFO and the stroke. Patients were excluded when another, more likely, cause of stroke was present.

The HST evaluates all data collected during the standardized work-up to determine the relationship (or its absence) between the PFO and the stroke.

Standardized work-up after installment of the HST

Relevant data on prothrombotic state, cardiac arrythmia, neuroimaging (including cervical artery angiography) and vascular risk factors were retrieved from the patient files. If the available information was considered insufficient, additional testing or imaging was performed. Before a decision regarding PFO closure, all patients underwent the following standardized assessment on the cause of their stroke: imaging proof of the ischemic lesion (preferably an MRI), prothrombotic testing (Supplemental Table 1), electrocardiogram, a minimum of 72 hours' heart rhythm registration, a transthoracic echocardiogram (TTE) with agitated saline contrast to demonstrate a right-to-left shunt and preferably measurements of PFO characteristics (e.g. presence of an atrial septal aneurysm, tunnel length), imaging of the cervical arteries and a comprehensive cardiovascular risk profile. Any tests missing were subsequently performed in our hospital or in the referring hospital if considered of importance for the decision-making. Following the SCAI guideline, PFO closure is performed in most patients with thrombophilia, except for those with uncertain benefits of PFO closure and a concomitant higher risk of periprocedural risks. Taking into account the lifelong need for oral anticoagulation in patients with anti-phospholipid syndrome and the low level of evidence for PFO closure in these patients, non-closure of the PFO can be considered and would always be discussed with the patient.

The relation between stroke and the PFO was deemed causal when the stroke diagnosis was verified by the HST without any other cause of stroke, except the PFO. If the

stroke was not attributed to the PFO, the etiology was classified according to the TOAST-criteria.[13,14]

Vascular risk factors

Classical cardiovascular risk factors were obtained from the medical files. The first LDL-value available was used for analysis. This was preferably a statin naive value; if this was not available the first available LDL-value was used. Hypertension was defined as a systolic blood-pressure of >130 mmHg on at least two occasions during out-patient visits. When a 24 h blood-pressure recording was available this was used. Diabetes mellitus was defined as the need for medication to control blood glucose levels.

Cardiac work-up

All patients underwent a minimum of 72 hours' heart rhythm registration, but preferably 7 day heart rhythm monitoring for atrial fibrillation. Atrial fibrillation as cause of stroke was defined as any atrial fibrillation on heart rhythm monitoring lasting more than 15 min, independent of patient symptoms.

Echocardiographic work-up

All patients underwent a TTE with agitated saline contrast to demonstrate a right-to-left shunt. An additional transesophageal echocardiogram (TEE) was left to the discretion of the referring neurologist and cardiologists. All TTE and TEE were re-evaluated by the same cardiologists (TtC/AvD). When the available images from the referring center were inconclusive, a TTE with agitated saline contrast was repeated in the Radboudumc. At least three contrast runs without and with Valsalva maneuvers were conducted. When the patient was unable to perform a proper Valsalva maneuver, a TEE was performed to visualize the atrial septum.

PFO was defined as a right-to-left shunt when the contrast was visible in the left atrium within five heart beats after its administration. Atrial septal aneurysm (ASA) was defined in three different ways: (1) at least 10 mm of excursion from the midline as used by the Systematic Collaborative, PFO closure Evaluation (SCOPE), (2) at least 15 mm protrusion of interatrial septum used by Hanley et al., and (3) protrusion of saccular redundant tissue.[15,16] Shunt size was defined as (0) None, (1) Small, <5 bubbles, (2) Moderate, 5–30 bubbles, (3) Large, >30 bubbles, (4), Opacification, near immediate opacification of the left ventricle.[17]

Statistical analyses

Statistical analysis was done using IBM SPSS Statistics 26. Data are shown as number (%) for categorical data or as mean ± SD or median and range for continuous data depending on the Gaussian distribution. Categorical data was analyzed using the Chi-squared test. Two-sided independent Student's *t*-test and Mann-Whitney *U* test were used to analyze differences between the groups for continuous data. Differences within the groups were analyzed by repeated measures ANOVA.

A *p*-value of <0.05 was considered statistically significant. In general, data were considered missing if the item was not explicitly mentioned in the medical files.

Results

Patient characteristics

We included 240 patients, of whom 45 were evaluated before the introduction of the HST (2016–2018) and all 45 had PFO closure.

After the introduction of the HST, 195 patients were included with a mean age of 46 years (SD 12.2); 96 (49%) were female. Patients accepted for PFO closure were younger (mean age 43 years (SD 10.6)), had fewer classical cardiovascular risk-factors and less often a history of stroke or TIA (Table 1) than those rejected for closure.

Patients' characteristics with PFO closure prior to the existence of the HST

Patients who underwent PFO closure before the presence of a HST were younger (mean age 38 years SD 9.1vs 43 years SD 10.6; $p=0.005$), had a higher RoPE Score (8–10, 67% vs 39%; $p=0.001$) and fewer high-risk PFO features on echocardiography (Supplemental Table 2) than those who underwent PFO closure after HST installment.

Echocardiographic features of PFO

Patients accepted for PFO closure, compared to those who were rejected, had a significantly larger shunt, both with (3 [IQR 2–4] vs 2 [IQR 1.25–3]; $p=0.028$) and without Valsalva maneuver (2 [IQR 1–3] vs 1 [IQR 0.25–2]; $p=0.022$). Their tunnel lengths were longer (8.8 mm SD 3.3vs 7.7 mm SD 2.0; $p=0.027$) and the opening of the PFO was larger (5.4 mm SD 2.6vs 3.6 mm SD 1.5; $p\leqslant 0.001$) (Supplemental Table 3).

Reasons not to close the PFO

In total, 76 (39%) patients did not undergo PFO closure. Seventy-one (36%) patients were rejected for closure and five (3%) patients were accepted but preferred best medical treatment over surgery. The most common reasons included rejection of stroke diagnosis (13 patients (7%)), another cause of stroke (large artery atherosclerosis (5%), small vessel disease (4%), atrial fibrillation (1%),

Table 1. Baseline characteristics.

Characteristics	All patients *N* = 195	Accepted for closure *N* = 124	Rejected for closure *N* = 71	*p*-Value
Mean age at time of referral, years [SD]	45.9 [12.2]	42.7 [10.6]	51.5 [12.8]	<0.001¤
Age groups, *N* (%)				
18–29	21 (10.8)	18 (14.5)	3 (4.2)	0.026
30–39	31 (15.9)	23 (18.5)	8 (11.3)	0.181
40–49	68 (34.9)	48 (38.7)	20 (28.2)	0.137
50–59	49 (25.1)	31 (25.0)	18 (25.4)	0.956
60–65	16 (8.2)	4 (3.2)	12 (16.9)	0.001¤
>65	10 (5.1)	0 (0.0)	10 (14.1)	xΩ
Male, *N* (%)	99 (50.8)	63 (50.8)	36 (50.7)	0.989
Mean BMI, kg/m^2 [SD]	25.4 [4.0]	25.1 [4.0]	25.9 [4.0]	0.232
History of smoking,* *N* (%)	82 (42.7)	48 (39.0)	34 (49.3)	0.168
Mean LDL-value without medication, mmol/L [SD],*	2.42 [0.81]	2.36 [0.87]	2.54 [0.65]	0.408
History of stroke or TIA,* *N* (%)	34 (17.6)	10 (8.1)	24 (34.3)	<0.001¤
History of hypertension, *N* (%)	41 (21.0)	18 (14.5)	27 (38.0)	<0.001¤
Mean systolic blood pressure without medication,* mmHg [SD]	124.1 [15.1]	122.6 [14.2]	127.6 [16.5]	0.063
History of diabetes mellitus, *N* (%)	8 (4.1)	1 (0.8)	7 (9.9)	0.004¤
Family history of vascular disease,* *N* (%)	74 (38.5)	43 (35.0)	31 (44.9)	0.173
Antithrombotic therapy at evaluation,* *N* (%)				
Anticoagulant	13 (6.7)	11 (8.9)	5 (7.1)	0.654
Antiplatelet	157 (80.9)	112 (90.3)	62 (88.6)	0.516
None	3 (1.5)	1 (0.8)	3 (4.3)	0.105

BMI: Body Mass Index; SD: standard deviation; LDL: low-density lipoprotein; TIA: transient ischemic attack; HST: Heart-Stroke team.
Five patients were deemed eligible for PFO closure but did not undergo PFO closure due to their own preference (these patients are included in the "Accepted for closure" group).
*Information was missing in the following number of patients: 8 patients in "LDL-value before medication," 2 patients in "History of stroke or TIA," 3 patients in "Family history of vascular diseases," 3 patients in "Smoking," 11 patients in "systolic blood pressure," 1 patient in "Antithrombotic therapy at evaluation." Missing variables have been excluded from the calculated percentages.
ΩCould not be calculated due to presence of "0."
¤Reached significance level of 0.05. *p*-Values were calculated two-sided using a chi-squared test to assess the equality of proportion.

antiphospholipid syndrome (2%), cervical artery dissection (1%) and vasculitis (1%)) or the presence of multiple classical cardiovascular risk factors that made the PFO less likely the cause of stroke (9%). Finally, in 6 (3%) patients the stroke – HST evaluation time-interval was considered too long, by both patients and the HST (mean 8.5 years; range of 5–16 years) to proceed with PFO closure, also because of a lack of data on the efficacy on PFO closure several years after index event (Supplemental Table 4).

Missing data

Due to the retrospective design there was a considerable amount of missing data. All missing data are noted in the legends below each table.

Discussion

After installment of the HST, 71 (36%) patients were rejected for PFO closure as the team found no relation between the PFO and the stroke. Patients who might have been accepted for PFO closure prior to the installment of the HST were now rejected based on several reasons, especially the presence of another, more likely stroke diagnosis.

Conversely, patients who in the past would have been excluded for PFO closure because they would not match the inclusion criteria of the RCTs may now be accepted after careful HST evaluation. In the past, patients older than 60 years and patients with a TIA as index event were excluded, while in our cohort 37 (19%) patients who were accepted for closure either had a TIA or were older than 60 years (Table 2).

PFO closure in patients with a cryptogenic stroke is cost-effective compared to medical therapy, based on the RCTs on PFO closure.[18] Avoiding unnecessary PFO closure will not only diminish surgical risks but also reduce healthcare costs. In addition, there is a high risk of overlooking the true cause of stroke (which will then be left untreated) in cases where PFO closure is performed before completing a comprehensive work-up and evaluation by an HST.

Patients accepted and rejected for PFO closure have different characteristics. Patients who underwent PFO

Table 2. Clinical characteristics.

Characteristics	All patients $N=195$	Accepted for closure $N=124$	Rejected for closure $N=71$	p-Value
Index event at referral				
Ischemic stroke	130 (66.7)	91 (73.4)	39 (54.9)	0.009[¤]
TIA	65 (33.3)	33 (26.6)	32 (45.1)	0.009[¤]
Etiology based on TOAST criteria PFO excluded				
Large artery atherosclerosis	18 (9.9)	0 (0.0)	18 (25.4)	x[Ω]
Small-vessel occlusion	12 (6.6)	0 (0.0)	12 (16.9)	x[Ω]
Cardio embolic stroke	2 (1.1)	0 (0.0)	2 (2.8)	x[Ω]
Other	12 (6.6)	4 (3.2)[α]	8 (11.3)	0.016[¤]
Undetermined	16 (8.8)	0 (0.0)	16 (22.5)	x [Ω]
Multiple affected vascular territories,*	42 (24.0)	26 (21.7)	16 (29.1)	0.491
Cortical infarction,*	95 (52.5)	70 (56.5)	25 (43.9)	0.115
RoPE score,*				
0–5	35 (19.1)	6 (4.9)	29 (48.3)	<0.001[¤]
6	51 (27.9)	37 (30.1)	14 (23.3)	0.339
7	44 (24.0)	33 (26.8)	11 (18.3)	0.207
8–10	53 (29.0)	47 (38.2)	6 (10.0)	<0.001[¤]
PFO-related medical history				
Pulmonary embolism,*	12 (7.8)	12 (10.5)	0 (0.0)	0.033[¤]
Deep venous thrombosis,*	6 (4.9)	6 (7.3)	0 (0.0)	0.079
Migraine,*	52 (40.9)	35 (41.7)	17 (39.5)	0.817
Use of oral contraceptives,*~	37 (38.1)	24 (40.0)	13 (35.1)	0.632

PFO: patent foramen ovale; TIA: transient ischemic attack; TOAST: trial of org in acute stroke treatment; RoPE: risk of paradoxical embolism.
*Information was missing in the following amount of patients: 20 patients in "Multiple affected vascular territories," 14 patients in "Cortical infarction," 12 patients in "RoPE Score," 41 patients in "pulmonary embolism," 73 in "deep venous thrombosis," 68 in "migraine," 98 patients in "use of oral contraceptive medication." Missing variables have been excluded from the calculated percentages.
[α]In four patients who underwent PFO closure an additional possible cause for stroke was present: antiphospholipid syndrome in three patients and atherosclerosis in one patient.
~Male patients have been excluded from the calculated percentages.
[Ω]Could not be calculated due to presence of "0."
[¤]Reached significance level of 0.05. p-Values were calculated two-sided using a chi-squared test to assess the equality of proportion.

closure after HST evaluation were significantly younger than those without closure, supporting the notion that PFO-associated stroke is predominantly prevalent in young adults.[19] Apart from being older, patients rejected for PFO closure were more likely to have hypertension and diabetes. These factors subsequently increase the risk of developing (subclinical) atherosclerosis, which is more likely to be a risk factor or cause of stroke than the PFO.[20] Patients accepted for PFO closure were more likely to have a history of pulmonary embolism (PE) compared to patients who were rejected, which supports the notion that the presence of a venous embolism may convert a PFO into a stroke causing PFO. The guideline published by EAPCI also stresses careful history taking, including enquiries on PE.[5,9,21] Several studies have identified anatomical features which increase the risk of a causal relationship between PFO and stroke.[22] A High-risk PFO includes the presence of an atrial septal aneurysm and a large right-to-left shunt.[23] Our study added a large diameter of the opening and long tunnel length to that. However, in contrast to previous studies[23,24] we could not replicate the presence of ASA as a factor that converted a PFO into a stroke causing PFO, perhaps due to our small sample size. (High risk) PFO characteristics played a minor role in the decision-making on PFO closure, but recent studies indicate that this could be a useful approach as illustrated by the PASCAL classification which combines the RoPE Score with high-risk PFO features.[25,26]

Prior to the HST (June 2018), patients received PFO closure based on the evaluation of the referring centers. The decision to refer patients was based on their age, a high RoPE Score, the presence of PFO and an apparent cryptogenic stroke. The patients who underwent PFO closure prior to the HST did have a significant higher RoPE Score and were younger compared to the patients accepted for PFO closure by the HST. Furthermore, the patients accepted for closure after HST evaluation had more high risk PFO features (e.g. larger shunt size and longer tunnel) compared to patients accepted for PFO closure prior to the HST. Taking into account the number of patients rejected for PFO closure after additional work-up and HST evaluation it is possible that several patients referred for PFO closure (and actually closed) before HST installment would nowadays not be considered eligible for PFO closure.

PFO closure can be considered in patients who do, apart from older age, fulfill the RCT inclusion criteria as recent studies suggests PFO closure to be beneficial also in patients older than 60 years of age,[27–29] provided that the PFO is deemed causal to the stroke by the HST. On the contrary, patients who are being referred for PFO closure may get rejected after a thorough work-up and evaluation by the HST, for example when misclassification or other causes of stroke are identified. Nevertheless, caution is warranted when deviating from the inclusion criteria on which the RCTs are based and future research should indicate if extension of the inclusion criteria is justifiable.

A strength of our study is the re-evaluation of all echocardiographic data by the same experienced interventional cardiologist to prevent measurement bias and to look in detail at the anatomical echocardiographic characteristics of PFO. Three studies have evaluated the added value of a multidisciplinary approach to PFO closure. Two were executed (mainly) before the results of the positive RCTs, showing PFO closure to be superior over best medical treatment, and before the existence of the RoPE Score.[30,31] One more recently performed study did not clearly state the reasons for rejection of PFO closure.[11] Our study is the first to evaluate the added value of a multidisciplinary HST in the decision process of PFO closure or not, combining RoPE Score, re-evaluated echocardiographic data, stroke- and patient characteristics.

A limitation of this study is the considerable amount of missing data due to the retrospective design. Also, outcome regarding the recurrence of stroke has not been noted.

Future research should therefore preferably entail long-term follow-up of patients rejected and accepted for PFO closure, collecting all outcomes and adverse events like atrial fibrillation.[32,33]

In conclusion, we found that a thorough, standardized assessment complemented by an evaluation in a multidisciplinary team is paramount in deciding on PFO closure. Furthermore, centralizing the HST in a tertiary stroke center builds expertise on the decision-making. We advise to evaluate all patients in a centralized HST when PFO closure is considered.

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Informed consent

The Ethics Committee of the Radboudumc, Nijmegen, Netherlands waived the need to obtain informed consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this non-interventional study.

Guarantor

M.H.M. Immens

Contributorship

V and TJ researched literature and conceived the study together with TJF and FE. TJ and V did the first part of the data collection and wrote the first draft of the manuscript. AD and TJF evaluated all the echocardiograms and attributed to the Heart-Stroke team together with FE. MHM did the second part of the data collection, did the data analysis and wrote all the other drafts of the manuscripts. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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