

Clinical outcomes of secondary prevention strategies for young patients with cryptogenic stroke and patent foramen ovale

INTRODUCTION

The Foramen Ovale is necessary during fetal life to facilitate the shunting of blood from the right atrium to the left atrium, thereby bypassing the high resistance pulmonary circuit. At birth or shortly thereafter, the septum primum and the septum secundum usually fuse, closing the interatrial septum to the flow of blood. A Patent Foramen Ovale (PFO) occurs when fusion of the septum primum with the septum secundum is inadequate (1). In a significant number of individuals the foramen ovale remains somewhat patent during adult life, approximately 20 %, but in young adult (less than 55 years old) with stroke is about 50 % (2).

Some anatomical characteristics seem to confer an additional risk of transient ischemic attack (TIA) or stroke in young people by facilitating the right-to-left passage: these are the presence of an atrial septal aneurysm (greater than 10-mm septal excursion during a cardiac cycle) (3,4); a PFO more than 4 mm in diameter (5); the presence of Eustachian Valve or Chiari's network.

Paradoxical embolism can be promoted by 1) inherited or acquired thrombophilia; 2) conditions predisposing thrombosis in the pelvic and lower extremity veins such as cancer, recent surgery, pregnancy; 3) all those situations entailing the Valsalva maneuver (1).

So far, 3 randomised controlled trials have compared medical therapy and percutaneous closure of the PFO in patients aged between 18 and 60 years old as strategies for the secondary prevention of patients with cryptogenic stroke/TIA and PFO. CLOSURE I (6) enrolled 909 patients with cryptogenic stroke or TIA investigating the STARFLEX device (NMT Medical) during a 2 years follow up. The PC TRIAL (7) analyzed 414 patients treated with the Amplatzer PFO Occluder (St.

Jude Medical, St. Paul, MN, USA) or medical therapy in a follow-up period of 4 years. The most recent RESPECT TRIAL (8) enrolled 980 patients comparing the Amplatzer PFO Occluder (St. Jude Medical, St. Paul, MN, USA) with medical therapy. All these trials, taken individually, were not able to prove the superiority of PFO closure over the medical management. **With a different design and endpoint, the MIST trial evaluated the efficacy of the PFO occluder in patients with migraine (add). /In discussione esplicita l'incidenza globale in questi studi di recidive ischemici nei gruppi medico e occlusion per confrontarlo con i nostri dati, sicuramente molto più bassi/**

The aim of our study was to assess the clinical outcomes of patients younger than 55 years old presenting cryptogenic stroke and PFO and treated with secondary prevention strategies tailored on individual characteristics as analyzed by an expert and dedicated by a multi-disciplinary team.

MATERIALS AND METHODS

All the patients admitted or referred to the Neurology, Cardiology or Internal Medicine Divisions of the University Hospital of Verona from January 2006 to January 2015 with the diagnosis of cryptogenic stroke, according to the TOAST classification (9), and patent foramen ovale were included in our analysis and prospectively followed.

All the patients were discussed in the setting of a multidisciplinary approach, according to the decision algorithm of the VEROSTROKE group (Group of the diagnosis and treatment of Atrial Septal Abnormalities in Patients of 55 years or less and Stroke of unknown origin). The VEROSTROKE group of the University Hospital of Verona is a multidisciplinary group constituted by neurologists and cardiologists regularly meeting to discuss patients with cryptogenic stroke and patent foramen ovale as previously detailed (10).

A diagnostic evaluation was performed in all patients, according to the flow chart of the VEROSTROKE group (Figure 1), including cerebral imaging (brain magnetic resonance imaging and computerised tomography), vascular imaging (carotid/transcranial ultrasound, angio-brain magnetic resonance imaging or angio-computerised tomography, lower limb venous ultrasounds),

cardiac evaluation (contrast-enhanced transcranial doppler, transthoracic echocardiography, 24-hour arterial blood pressure recording, 24-hour ECG recording) and blood test for thrombophilia screening (Table 1).

The diagnosis of Patent Foramen Ovale was made using contrast-enhanced transcranial Doppler (ceTCD), based on intravenous injection of agitated saline (9 ml of saline mixed with 1 ml of air) as contrast-enhancing agent, according to the current guidelines (11). Transcranial Doppler signals were recorded in the middle cerebral artery, both at rest and after Valsalva strain. Standard classifications were used: grade I (1-10 micro-embolic signals or MES), grade II (> 10 MES); “persistent” if present at rest, “latent” if present only under Valsalva strain.

Transoesophageal echocardiography (TEE) was usually performed to understand the anatomical characteristics of the PFO, including diameter, atrial septal aneurysm, the presence of Chiari Network or Eustachian valve and finally the amount of right-to-left shunt using agitated saline as contrast-enhancing agent. The examination was performed according to the standard practice guidelines (12).

After having analysed the clinical documentation, the VEROSTROKE group took a decision about the most appropriate therapeutical management (medical therapy or a PFO closure) for each patient, on the basis of the decision algorithm (Figure 1). In the “medical therapy” group the first choice was Acetilsalicylic Acid (75-160 mg/day), however in case of allergy or intolerance Clopidogrel (75 mg/Day) or Ticlopidine (250 mg twice/day) were used. In patients with coagulation disorders, Warfarin was considered as first choice.

After percutaneous atrial septal repair, Acetilsalicylic Acid (100 mg/day) plus Clopidogrel (75 mg/day) were prescribed for six months. If a residual shunt persisted 6, 12 or 24 months after the intervention, patients were prescribed to continue with Acetilsalicylic Acid therapy.

Follow up

Patients having undergone percutaneous PFO closure were followed with transthoracic echocardiography 24 hours after procedure, and then ce-TCD and TEE at 1, 6, 12 and 24 months; a

telephonic interview was performed every year by a neurologist in order to assess the occurrence of ischaemic events. Patients belonging to the “medical therapy” group underwent a neurological examination in our outpatient clinic and/or phone interview done by a neurologist or cardiologist every year.

Endpoints

Primary and secondary endpoints were defined as follows:

Primary endpoints. Recurrent cerebrovascular accidents (TIA/stroke).

Secondary endpoints. Persisting migraine after the PFO closure or under medical treatment alone.

Percutaneous device-related complications: these include, surgical removal because of migration in acute, or surgical repair, erosion of a cardiac or vascular structure in chronic. Drug-related or procedure-related side effects such as **bleeding according to the BARC classification** [/vedi e aggiungi ref/](#), gastric intolerance to aspirin, blood dyscrasias related to thienopyridines; persistence of right-to-left shunt, as assessed by contrast-enhanced transcranial Doppler at 6 and 12 months in patients who had undergone atrial septal repair, grade I or more [/defini e metti ref/](#) ; persistent cardiac arrhythmia of new onset.

Statistical methods

Data are given as mean and standard deviation (SD) or as absolute values and percentages as appropriate. Continuous variables were compared using the Student's t-test or Mann-Whitney as appropriate and categorical variables were compared using Chi-square or Fisher test. A probability value of less than or equal to 5% was considered significant. Statistical analyses were conducted using SPSS software (SPSS v21, Chicago, IL, USA).

RESULTS

Qui come ti dicevo, incomincerei dichiarando il numero di casi sottoposti al gruppo come “strokes” in PFO che poi non sono stati confermati, e descriverei le diagnosi emerse al posto di stroke.

Dopo questo dato molto importante passerei a:

In 159 patients (98 males, mean age: 49.7 ± 9.7 years) the group confirmed the diagnosis of ischemic embolic disease (TIA or stroke) and this constitutes the study population. According to the therapeutic flow chart, 77 patients with cryptogenic stroke and PFO less than 55 years old underwent percutaneous atrial septal repair and 82 patients were addressed to medical therapy.

At baseline, the two groups diverged only as to the presence of interatrial septal aneurysm and Valsalva strain before the ischemic event which were more prevalent in the “atrial septal repair” group (respectively, 22% vs 64.9%, $p=0.00004$ and 2.4% vs 16.9%, $p=0.001$). Furthermore, patients having undergone percutaneous septal repair exhibited an higher prevalence of anterior stroke compared with the “medical therapy” group (respectively, 70.1% vs 53.7%, $p=0.03$); otherwise, patients belonging to the “medical therapy” group presented more frequently an involvement of both vascular territories if compared with the other group (respectively, 7.3% vs 0%, $p=0.01$). The mean follow-up period was 51.6 ± 34.8 months, both in medical and in the atrial septal repair group (Table 2 and 3).

The proper device was chosen on the basis of intraprocedural TEE, according to PFO morphology and atrial septal aneurism entity. Amplatzer Patent Foramen Ovale Occluder 18/25, Amplatzer Cribriform Occluder 25 or 35 millimetres (AGA Medical Corporation, Golden Valley, Minnesota, USA) were chosen accordingly (13). For only three patients aged less than 25 years, BioSTAR (NMT Medical, Boston, Massachusetts, USA) bioabsorbable devices were chosen. Finally for the last five patients Nit Occluder Device were used. None of the patients required multiple devices deployment.

Primary endpoint. Two patients belonging to the “medical therapy” group had a recurrent ischemic event (2.4%). One experienced a first stroke recurrence while receiving 100 mg of Aspirin, and a second recurrent stroke under oral anticoagulation. Subsequently, he was treated with a percutaneous PFO closure procedure with no further events. A second case of recurrence occurred under treatment with 75 mg of Clopidogrel and was then switched to the interventional procedure.

Alessandra: hai incluso anche l'ultimo caso di ricorrenza della Sgra. Savazza?

In the “atrial septal repair” group no relapses occurred (2.4% vs 0%; $p=0.16$).

Secondary endpoint. Among the overall population 34 patients had migraine (21.4%), 26 of them (16.3%) with aura and the remaining 8 of them (5.1%) without aura.

In the “medical therapy” group, 8 out of 19 patients (36.8%) with migraine did not complain it anymore during the follow-up period compared with 12/15 patients with migraine of the “atrial septal repair” group who benefited from the interventional procedure (80%; $p=0.02$). Of note, patients with migraine presenting with aura benefited more from the PFO closure compared with the medical therapy (11 out of 12 patients, 92%, were free from migraine after the procedure vs 5 out of 14 patients, 36%, in the “medical therapy” group; $p=0.005$) (Figure 2). Among patients with migraine presenting without aura, no differences were observed at follow-up between groups (1 out of 3 patients, 33%, were free from migraine after the procedure compared with 3 out of 5 patients, 60%, in the “medical therapy” group; $p=0.5$). Moreover, among patients with migraine having undergone the PFO closure, those with aura presented a better outcome than those without aura (11 out of 12 patients with migraine and aura, 92%, were free from migraine after the procedure vs 1 out of 3 patients with migraine and no aura, 33%; $p=0.08$). Among patients with migraine in medical treatment, no differences in outcome were seen between patients with aura and those without (5 out of 14 patients with migraine and aura, 36%, were free from migraine after the procedure vs 3 out of 5 patients with migraine and no aura, 60%; $p=0.6$). In the interventional group, 4 patients (5.2%) had a residual right-to-left shunt persisting after 12 months /di quale entità?/ from the procedure, but only 1 patient had still migraine.

In the “atrial septal repair” group no percutaneous device-related complication occurred. One patient had a transient episode of acute pericarditis after the procedure, one had a peri-procedural minor bleeding at the access site (BARC 1) and a symptomatic traumatic intracerebral haemorrhage

occurred in a patient while taking aspirin in the post-procedural phase ($p=0.76$: *cosa è questa p?*).

Drug-related side-effects occurred in 4 out of 82 patients (4.9%) treated with medical therapy: a case of gastric pyrosis with aspirin, 2 cases of diffuse haematomas with aspirin and clopidogrel and a case of increased liver enzymes secondary to low weight molecular heparin administration.

Alessandra: controlla che non manchino eventi dichiarati nella precedente pubblicazione

Persistence of right-to-left shunt was also analysed in the interventional treatment group, using contrast enhanced transcranial Doppler. At 6 months follow-up, 27% of patients showed a residual shunt: 18% showed latent I grade shunt, 4% latent II degree shunt, 4% persistent I degree shunt and 1% persistent II degree shunt. At 12 months, only 8% of patients showed a latent I grade shunt, and 6% a latent II degree shunt, and none had a persistent shunt. Atrial fibrillation was observed only in 1 patient 5 months after PFO closure.

DISCUSSION

The VEROSTROKE group is active at our Center since April 2006 aiming at a standardization of the clinical management of young patients with stroke and PFO based on current scientific evidence applied to each individual case.

The present study analysed 159 patients with cryptogenic stroke and PFO who were discussed and addressed to medical therapy or interventional procedure, according to the above-mentioned protocol. *Of note, this population represents the ...% of the cases referred to the attention of the group as cryptogenic strokes related to PFO. This data reinforces the importance of a dedicated multi-disciplinary team to evaluate the real ischemic nature of events that may be mis-interpreted and put in a false correlation with the stochastic presence of a “benign” PFO. The lack of an accurate diagnosis would certainly impact the number of treatments, both medical and interventional, indicated in cases that may not benefit from it. The young age of these patients and*

their long live expectancy render even more critical the indication of a wrong long-lasting therapy.

During the follow-up period only 2 patients in the medical group had a recurrent ischemic event, and they consequently were switched to the septal repair group. No recurrent strokes occurred in the PFO closure group. This finding is consistent with data reported by the literature and suggests a higher efficacy of the invasive treatment. However, this superiority cannot be detected statistically given the low incidence of recurrence in general and in each treatment group.

In previous randomized trials, the incidence of recurrent stroke in patients allocated to medical therapy ranged between 3.3% (Respect) and 6.4% (Closure 1) and the procedural complications of the PFO closure between 3.2% (Closure1) to 4.2% (Respect).

In our experience, recurrence of ischemic events in medically managed patients was low (2.4%) /controlla che non ti manchi una paziente, altrimenti diventa uguale a gli altri studi... This finding suggest that the selection criteria applied to advice a medical therapy or a trans-catheter closure in each single patient is safe and effective. On the other hand, the complication rate of our experience is lower than that reported in the trials.

In our patient population, 34 (21.4 %) had an history of migraine (76.5 % with aura). As reported in several studies PFO has been shown to be more common in migraineurs with aura than in general population (16, 17, 18). A recent systematic review found that PFO ranged from 46.3 to 88.0 % in patients with migraine with aura (MA), from 16.2 to 34.9 % in patients with migraine without aura (MO) and was 27.3 % in the general population (19). Even if MA is strongly associate with PFO, it is an independent risk factor for ischemic stroke, especially in patients under than 45 years old (20). The mechanism that underlies the possible relationship between PFO and migraine remain speculative. Right-to-left shunt allows to vasoactive substances (like serotonin), that are usually present in the venous circulation, to bypass the pulmonary filter and reach the cerebral circulation, and then activities triggering migraine (like exertional activities) lead also to a greater right-to-left

shunt (21). Moreover, paradoxical cerebral embolism is a mechanism that may be involved in inducing aura phenomenon: a possible explanation might be that platelet aggregates create a focal ischemia inducing a cortical spreading depression (22).

Among our patients with migraine, 15 underwent to atrial septal repair procedure and 19 were treated with medical therapy. During the follow up, 80 % (92 % MA) in the interventional group did not complain anymore migraine after the procedure compared with 42.1 % (62 % MA) who had benefit from the medical therapy only ($p= 0.02$). Several studies have been carried out to determine whether closure of PFO is able to affect migraine frequency. The initial report by Wilmshurst et al. (23) found that the closure of the atrial septal defect significantly reduced attack frequency in migraine patients. In the following years, some other non-controlled observational studies have reported an improvement of the migraine after PFO closure (24-32). However, the Migraine Intervention with STARflex Technology (MIST) trial (33), a prospective, randomised, double-blind and sham-controlled trial, failed to demonstrate a superiority of PFO closure on migraine cessation. Therefore PFO closure is not indicated as a treatment of migraine in the clinical practice.

Our study found a considerable benefit in migraine in the “atrial septal repair” group compared with the “medical therapy” group, according to the previous non-randomised trial. A possible limitation of our study was that the amount of patient with migraine was quite low (34 patients with migraine) that it was not randomized. Moreover, the degree of migraine was not evaluated with appropriate scales to understand the decrease entity.

Two other trials (European Percutaneous Closure of PFO In Migraine with Aura (PRISMA) trial, Northern American Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using Amplatzer PFO Occluder Compared to Medical Management (PREMIUM) trial) are still ongoing. Further randomised controlled trials are necessary to confirm the positive interaction of PFO closure for the treatment of migraine, focusing on MA group.

Persistence of right-to-left shunt was also analysed in the interventional treatment group, using contrast enhanced transcranial Doppler, which has proven to be more sensitive in detecting residual shunt (34). Our cohort showed a similar prevalence of post-procedural residual right-to-left shunt when compared with the previous study (35, 36, 37). The entity of shunts was mainly small and with a latent pattern; none was persistent at 12 months. Furthermore, such residual shunts seem to have any prognostic implications (38).

Atrial fibrillation was observed only in 1 patient after five months from atrial septal repair procedure. The incidence of paroxysmal atrial fibrillation in patient with cryptogenic stroke after PFO closure is between 2 and 3 % (39,40,41). Other study found a greater incidence of atrial fibrillation (35, 42-44), up to 8 %. The reasons for these differences is that the arrhythmia was not systematically ruled out with 24-h Holter recording, as also in our study. Some authors hypothesized that patients presenting an atrial septal abnormality might hypothetically have an increased atrial vulnerability (45,46); another potential mechanism lies in a device-related atrial irritation that can be a trigger for the development of newly diagnosed atrial fibrillation (47).

Limitations of our work are represented by the non-randomized nature of the study and the relatively low number of patients.

CONCLUSION

The low incidence of recurrence in our medically managed patients as well as the low rate of complications related to PFO trans-catheter closure observed in our study confirms the usefulness of a dedicated multi-disciplinary group to advice on the therapeutic strategies of this delicate patient's category. Furthermore, the large number of patients referred as "ischemic" that were not confirmed by the group indicates the need for a thorough evaluation of these patients.

Despite the better clinical outcome obtained with the trans-catheter treatment, no statistically significant advantage could be shown given the relatively small number of patients and the very low

incidence of ischemic events.

Of note, in the present study migraine significantly improved in patients who underwent the interventional procedure, although the amount of patients with migraine is quite low. Interestingly, patients with migraine presenting with aura benefited more from the PFO closure compared with the medical therapy group. Further randomised trials are warranted to understand if PFO closure might play a role in migraine improvement.