Interventional approach to reduce thromboembolic risk in patients with atrial fibrillation ineligible for oral anticoagulation

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The annual incidence of stroke in patients with nonrheumatic atrial fibrillation averages 5% per year and increases with age, left ventricular dysfunction, hypertension, diabetes or prior stroke. Since in nonrheumatic atrial fibrillation 91% of left atrial thrombi are located in the left atrial appendage, in patients ineligible for oral anticoagulation it was suggested the percutaneous closure of left atrial appendage as a therapeutic option to reduce embolic risk. In this article we report our initial experience with this procedure, which was uneventful and efficacious at short-term follow-up. In conclusion, the interventional approach in patients with atrial fibrillation ineligible for oral anticoagulation seems feasible and promising, and deserves further investigation.

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Case description

A 76-year-old male with chronic atrial fibrillation (AF) since 1999 and hypertension, on oral anticoagulation (OA) developed two episodes of hematemesis and melena in 2001 and 2003, which required blood transfusion. Therefore, he was not considered any longer a candidate for OA, and he was switched on aspirin.

A 69-year-old male on OA treatment for chronic AF since 2001 and previous myocardial infarction, on September 2003 developed subdural hematoma, successfully treated with surgical decompression. His OA therapy was discontinued and he was switched on aspirin.

A 78-year-old male with chronic AF since 2001, hypertension, diabetes, hypercholesterolemia, obesity, and previous myocardial infarction treated with OA, on May 2003 developed hemoptysis, petechiae and ecchymosis on the upper limbs. Thereafter, warfarin therapy was discontinued.

A 69-year-old male with chronic longstanding AF, congestive heart failure, and hypertension developed a hemorrhagic stroke on August 2002 while on OA treatment, with left hemiplegia as neurological sequelae. Therefore, he was not considered any longer a candidate for OA and he was switched on antiplatelet therapy.

All these 4 patients at high risk of stroke and not suitable for OA, were enrolled in the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) trial, aiming at reducing the risk of stroke with the occlusion of the left atrial appendage (LAA) by the deployment of the PLAATO device with a percutaneous approach. Eligibility criteria were the presence of nonrheumatic AF, contraindications to long-term OA, and high risk for thromboembolism based on the presence of at least one of the following: congestive heart failure, diabetes mellitus, hypertension, history of transient ischemic attack/stroke, or spontaneous echocontrast in the LAA at transesophageal echocardiography (TEE).

Before the procedure the patients underwent a physical and neurological examination, routine blood tests, ECG, and chest X-ray. Moreover, transthoracic echocardiography and TEE were performed to exclude the presence of thrombus formation in the left atrium or LAA, which contraindicated the device deployment by protocol.

The typical procedure is performed under TEE guidance, local groin anesthesia and conscious sedation. Heparin is administered to keep the activated clotting time > 250 s. After venous femoral access and transseptal puncture a 14F transseptal sheath is delivered into the left atrium, its

tip is advanced into the LAA for the dye injection to obtain information on the diameter of the ostium, the length of the LAA, and its shape (Fig. 1). The size of the device is chosen to have a diameter 20 to 40% larger than that of the LAA ostium, measured at TEE and angiography, to secure a complete sealing of the LAA from the left atrial cavity. The shape of the LAA is important to select the correct position of the device. The length of the LAA in relation to the diameter of its ostium is a crucial measurement, in order to permit the complete deployment of the device into the LAA. When the delivery catheter and transseptal sheath are withdrawn, the device is allowed to expand and fill the appendage (Fig. 2). The dye is then injected both distally (through a special lumen in the device) and proximally to assess for leaks and positioning (Fig. 3). Since the device is completely retrievable, if sealing is not adequate, it could be collapsed, repositioned, and re-expanded, or completely removed and replaced with another one of different size until final release. Finally, after demonstration of adequate positioning, sealing and stability of the PLAATO, the delivery system and the transseptal sheath are withdrawn from the left atrium.

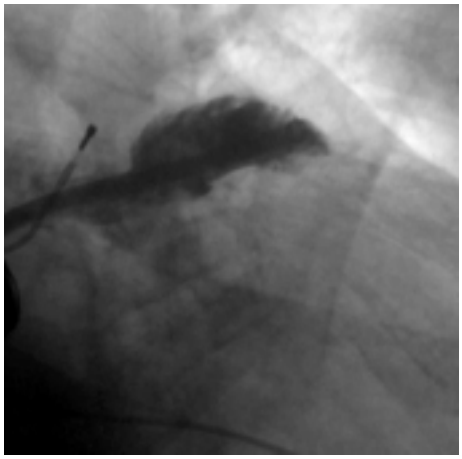

Figure 1. *Dye injection in the left atrial appendage to obtain information on the diameter of the ostium, the length of the left atrial appendage, and its shape.*

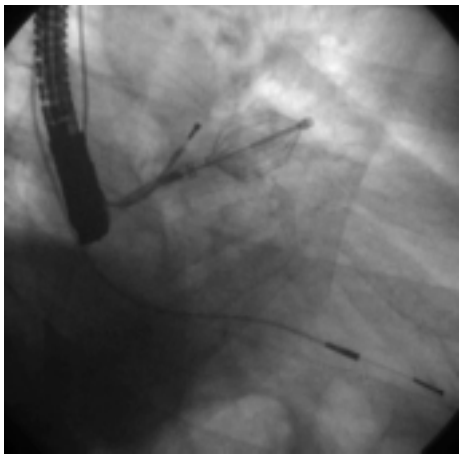

Figure 2. *Completely expanded device filling the appendage after the withdrawal of the delivery catheter and transseptal sheath.*

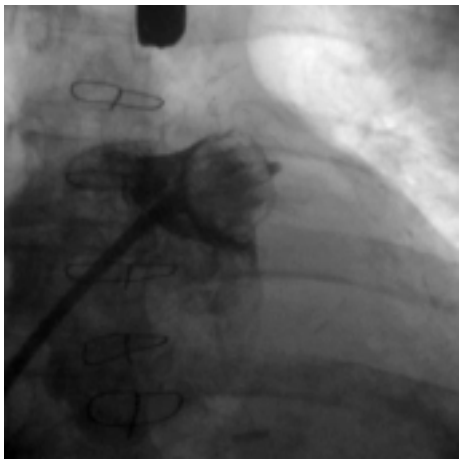

Figure 3. *Dye injection proximal to the device, demonstrating its correct positioning and only a minimal leak.*

The post-procedure therapeutic regimen consists of aspirin, 300 mg/day indefinitely, clopidogrel 75 mg/day as well as bacterial endocarditis prophylaxis for the following 6 months.

Follow-up. All the implant procedures were uneventful. After 6 months of follow-up for the first 3 patients, and 1 month for the last patient no adverse events occurred and they were all in good health. After 2 months TEE confirmed in the first 3 subjects the persistent correct positioning of the devices, the virtual complete closure of the LAA, the absence of thrombotic material adhesion to its surface.

Discussion

Prospective studies suggest that the incidence of AF ranges between < 0.1% per year in subjects < 40 years to > 1.5-2% per year in subjects > 80 years[1-3]. The annual stroke rate among patients with nonrheumatic AF averages 5% per year, between 2 and 7 times that of subjects without AF[4,5] and increases with age, left ventricular dysfunction, hypertension, diabetes or prior stroke[6].

As proposed by the American College of Cardiology/American Heart Association/European Society of Cardiology[7] and American College of Chest Physicians guidelines[8], unless contraindicated, OA targeting an international normalized ratio of 2 to 3 is the preferred therapy in patients with AF at high risk of stroke. However, anticoagulation increases the frequency and severity of major extracranial and intracranial hemorrhage (1.8% per year in patients > 75 years[2]) and the suggestions of the guidelines, as stated by the authors, were driven by clinical trials that excluded patients

considered at high risk of bleeding. This could explain why anticoagulation is inadequately implemented in the treatment of AF[9]. Moreover, it has been estimated that ≥ 20% of patients with AF at high risk of stroke have a contraindication to anticoagulant therapy[10]. In these subjects we could offer antiplatelet therapy, which is almost unanimously recognized to be less efficacious than anticoagulant therapy in reducing the stroke risk, or occlusion of the LAA as an adjunct to the aforementioned medical therapy.

Blackshear and Odell[11] reported their conclusions based on a meta-analysis of 23 studies in which the LAA was examined at TEE, autopsy, or direct intraoperative inspection: 57% of atrial thrombi in rheumatic mitral valve disease occurred in the LAA, whereas in nonrheumatic AF 91% of left atrial thrombi were located in the LAA. Moreover, in the recent ALFA study[12] it was stated that < 20% of chronic AF is due to rheumatic disease[13]. Therefore the vast majority of patients with AF and unsuitable for OA could benefit from LAA occlusion.

LAA occlusion was first suggested as an adjunct to mitral valvotomy in the 1930s through the 1950s, in an attempt at reducing the risk of stroke[14]. Despite the possible advantage derived by LAA closure during mitral valve replacement or repair as recommended by the American College of Cardiology/American Heart Association guidelines in patients with valvular heart disease undergoing cardiac operation[15], to date this procedure has not gained universal consensus. This is probably due to: a) uncertainties to exclude the LAA from the circulation (appendectomy, endocardial or epicardial closure of the LAA[16-18]) and closure not always complete and durable[19]; b) invasiveness of the surgical approach; c) role of the LAA in the regulation of intravasal volume by neurohumoral regulation[20]; d) controversies in the real efficacy of this measure in reducing the thromboembolic risk.

Since 2001 another option is available, i.e. the percutaneous delivery of the PLAATO device. It consists of a self-expandable nitinol cage (range of diameters 15 to 32 mm), which is covered with expanded polytetraflouroethylene. The membrane occludes the LAA orifice and allows tissue incorporation into the device, favoring the endothelialization of its surface, guaranteeing a nonthrombotic surface. Animal studies confirmed a complete endothelialization at 2-3 months[21]. Small anchors along the struts help in stabilizing the device in the LAA. Up to date, although CE-approved, the PLAATO device is only available within the multicenter homonymous study, in which > 90 patients were enrolled. To be eligible patients had to be unsuitable for long-term OA, and have chronic nonrheumatic AF and at least one additional risk factor for thromboembolism besides AF.

The procedure of PLAATO device delivery, although not complex, requires skills that make it safely affordable only by experienced interventional cardiologists. Besides vascular access complications, the most critical part of the procedure is the transseptal puncture, which has an adverse event rate of 5% in experienced hands. Associated complication is needle puncture of an adjacent structure as the posterior wall of the right atrium, the coronary sinus, or the aortic root, which could lead to hemopericardium. The last may also be determined by perforation of the heart during LAA access. Possible risks associated with the PLAATO device *per se* are represented by its dislodgment from the original location and peripheral embolization. Accurate sizing, test stability before final release, and cage's anchorage system seem to be able to prevent this complication that has not been reported to date. A study recently published by the PLAATO trialists[22] underscores the feasibility and safety of the PLAATO device implantation in the first 15 treated subjects: the procedure was done successfully in all patients and at 1-month follow-up the implant position was stable without erosion or encroachment in the surrounding structures. Among the first 31 patients, considering the patients reported in the notes added in proof, in 2 subjects a hemopericardium was reported as complication without sequelae.

Another important issue is the possibility of the PLAATO of acting as a foreign body, promoting thrombosis or fibrosis of the LAA, which could affect the left atrial structure and function, the mitral leaflet excursion, and cause pulmonary vein stenosis. A recent paper published by Hanna et al.[23] demonstrated that, at least at 6-month follow-up, these structures were devoid of significant changes in function. Furthermore, the smooth appearance of the device surface without any thrombotic material adhesion *in vivo*[23] and the experimental demonstration of its complete endothelialization[21] testify its biocompatibility and justify the interruption of clopidogrel.

In conclusion, the interventional approach in patients with AF ineligible for OA seems feasible, promising and more appealing compared to surgery, because of its minimally invasive nature. Therefore, it deserves further investigation because conclusive data on the efficacy of this approach could be derived only by longer-term results of the PLAATO trial.

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