Transcatheter left atrial appendage occlusion in patients with atrial fibrillation

Przezskórne zamknięcie uszka lewego przedśśionka u pacjentów z migotaniem przedśśionków

INTRODUCTION

Atrial fibrillation is one of the most common significant heart arrhythmias. It affects 1-2% of the total population, and the frequency of its incidence increases with age (1-4). A triple increase in the incidence of this disorder is projected by 2050 (5). There occurs particularly high risk of peripheral embolism and, in particular, ischemic stroke in patients with atrial fibrillation. The risk of stroke in patients with atrial fibrillation of non valvular origin is about 5% per year (6). In the research by Framingham, it has been shown, however, that the mortality rate of patients due to a stroke resulting from the atrial fibrillation is significantly higher in comparison to the strokes not connected with arrhythmia (7). This fact indicates the necessity of effective treatment and prevention in case of the occurrence of stroke in these patients. There are two main types of preventing the impact on the brain associated with occurrence of atrial fibrillation. The first is the use of chronic anticoagulant therapy, and the second is closing the left atrium appendage as a source of embolic material. The paper presents systems for transcatheter closing of the left atrial appendage in patients with atrial fibrillation. Describes the indications for this type of treatment and the results of available randomized trials.

Streszczenie

Migotanie przedsionków jest jedną najczęściej występujących arytmii serca. Obserwuje się go u ok. 1-2% ogólnej populacji, a częstość jego występowania wzrasta wraz z wiekiem. Do roku 2050 przewiduje się trzykrotny wzrost zachorowalności na to schorzenie. U pacjentów z migotaniem przedśśionków występuje szczególnie duże ryzyko wystąpienia zatorowości obwodowej a w szczególności niedokrwiennego udaru mózgu. Wyróżnia się dwa główne sposoby zapobiegania udarom mózgu związanym z występowaniem migotania przedśśionków. Pierwszy z nich to stosowanie przewlekłej terapii przeciwzakrzepowej, a drugi to zamknięcie uszka lewego przedśśionka jako źródła materiału zatorowego. W pracy przedstawiono systemy służące do przeszkórnego zamykania uszka lewego przedśśionka u chorych z migotaniem przedśśionków. Opisano wskazania do tego typu zabiegów oraz wyniki dostępnych randomizowanych badań.
This method, however, is recommended only for patients unable to use chronic anticoagulant therapy.

THE ANATOMY OF THE LEFT ATRIAL APPENDAGE

The left atrial appendage is the remnant of the embryological left atrium. It is a tubular structure with various patches and very variable morphology. Its complicated structure is conducive to the blood retention. It is especially evident during atrial fibrillation. The appendage consists of a very soft and thin “paper wall” and its ostium of very variable size from 5-40 mm is located between the mitral ring and the left upper lung vein. Its morphology can be very diverse and may resemble a shape of: a cactus, hen comb, sleeve or a cauliflower (14, 15). Echocardiographic studies have shown that in patients with atrial fibrillation of non-valvular origin, in 90% of cases the thrombus locates in the left atrium appendage. It results from the decrease in the speed of the blood flow, its stagnation, enlargement of the cavity and the increased activity of the platelets adhesion molecules (16-18).

THE HISTORY OF LEFT ATRIAL APPENDAGE OCCLUSION

The concept of closing the left atrium appendage in patients with atrial fibrillation of non-valvular origin is based on the assumption that only 10% of the thrombi does not arise in the left atrium appendage. In conclusion, its exclusion as a potential source of embolic materials should greatly reduce the risk of ischemic stroke and pulmonary embolism. This is confirmed by the observations of patients with atrial fibrillation and congenital absence of the left atrial appendage, where the risk of embolic episodes is relatively small, though it has not been exactly estimated (19-27). Incidental occlusion treatments or resection of the left atrium appendage during the cardio surgery operations have been carried out for many years. In the literature the first of such cases was described by Madden already in 1949 (28). The effectiveness of the surgical resection of left atrium appendage methods in the prevention of stroke was described in patients undergoing coronary artery bypass surgery in a randomized study of LAAOS (LAA Occlusion Study) (29). However, this method is only additional, on the occasion of other cardio surgeries rather than as a standalone procedure. In recent times, occlusion systems have been developed using the electrocardiographic guided thorascopic technique (30), and special epicardial stitches led by the magnet (31). At different stages of the research there are other minimally invasive surgical and transcatheter systems such as Aegis, AtriClips, Cardioablate.

The first transcatheter device for left atrial appendage occlusion was the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion device). It was designed as a nitinol valve mask frame covered with a polytetrafluoroethylene membrane. The system was introduced to the left atrial appendage by venous system and interventricular septum through appropriately profiled interatrial vascular sheath of diameter of 12F. Settling in the appendage was enabled due to the hooks located on the wires of occluder and passing out through the membrane.

The first implantation of the PLAATO system in a man took place on 30 August 2001 and was conducted by Sievert and Lesh (32). The efficiency of the system has been confirmed in small clinical trials, however, due to the difficult technique of implantation and observed side effects of the system it has been withdrawn from the market in 2006. The second system which was used for the transcatheter left atrium appendage occlusion was AMPLATZER, designed for atrial septal defect occlusion with two opposite disks. The first treatment with the use of this system was conducted on June 16, 2002 by Bernhard Meier. The treatment was carried out with a local anesthesia (33). In the following years, AMPLATZER was redesigned to match left atrium appendage. In 2008 a dedicated to the left atrial appendage occlusion Cardiac Amplatzer was introduced (ACP, St. Jude, USA) together with a specially developed bringing catheter. The system received CE mark in December 2008. The ACP system is built with nitinol meshwork covered with polyester material. It consists of three parts: central panel, carpal tunnel and disc. The disc has the task of ostium left atrium appendage occlusion. With the usage of the lobe, the position of the ocluder stabilizes on the surface of small hooks. The system is available in sizes from 16 to 30 mm. In 2012, a new version of the ocluder ACP called AMULET was introduced. The old platform remained the same but the lobe and isthmus was redesigned increasing the amount of catches so as to improve the fixation of the system and its effectiveness to reduce the risk of formation of thrombi. The AMULET system was, however, withdrawn from the market to successive improvements.

July 12, 2002 in Leipzig first human implantation of the system of WATCHMAN LLA Occluder (Boston Scientific, USA) was performed. The surgery was conducted by Eugen Hauptmann and Eberhard Grube. The system was designed to occlude the left atrium appendage and it consisted of nitinol self-expansible frame covered with a special material, held in the appendage due to the radial force and small anchors. The device is available in 5 sizes from 21 to 33 mm, allowing an exact match to a variable of the anatomy of the appendages. The system is fully repositionable. WATCHMAN LLA Occluder is currently the best system tested system to left atrial appendage occlusion. There are currently many other systems dedicated to left atrial appendage occlusion at different stages of design and research. The stage of development of technology to left atrial appendage occlusion is presented in table 1.

RESEARCH

The best tested occluder to the left atrium appendage occlusion is a WATCHMAN (34-38). As the only
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Table 1. The state of development of technology for left atrial appendage occlusion.

<table>
<thead>
<tr>
<th>The company</th>
<th>The device</th>
<th>Description</th>
<th>Implantation method</th>
<th>The advancement of the process of implementation of the clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aegis Medical</td>
<td>Aegis Appendage Grasper</td>
<td>Transcutaneous system, epicardial ligation of LAA; deep ligation of LAA, based on a record of ECG, including navigation, identification and localization of the tissue</td>
<td>Transcutaneous</td>
<td>Implantations outside the US.</td>
</tr>
<tr>
<td>Atricure</td>
<td>AtriClip FLEX</td>
<td>Elimination of LAA with very flexible aluminium ligature system</td>
<td>Met 510 (k) of the FDA</td>
<td></td>
</tr>
<tr>
<td>Atricure</td>
<td>AtriClip Long</td>
<td>LAA elimination system with a long wire (25 cm)</td>
<td>Used during open heart surgery (bypass grafting)</td>
<td>Met 510 (k) of the FDA</td>
</tr>
<tr>
<td>Atricure</td>
<td>AtriClip Pro</td>
<td>The next generation of the version of AtriCure 1-generation (for use on an open heart) clip for the isolation of LAA. This version is articulated, “robot friendly” and dedicated to small invasive access (right side thoracotomy)</td>
<td>A small invasive cardiac bypass surgery access</td>
<td>Met 510 (k) of the FDA</td>
</tr>
<tr>
<td>Atricure</td>
<td>AtriClip Standard</td>
<td>A platform based on a dacron clip to epicardial closing and elimination of LAA; has been developed for both open and small invasive access cardiac surgery; similar to 1-generation developed for the use during open heart treatments</td>
<td>The use of an open heart bypass grafting during surgery</td>
<td>Met 510 (k) of the FDA</td>
</tr>
<tr>
<td>Atricure</td>
<td>MIS AtriClip</td>
<td>LAA clamping technology using transcutaneous, suprasternal access</td>
<td>Minimally invasive cardiac surgery access</td>
<td>In the study</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>WATCHMAN</td>
<td>Self-expandable device constructed with permeable polyester fabric covered with scaffolding nitinol, equipped with hooks for fixation, implanted from the left part of left atrial appendage by transseptal puncture of interatrial septum</td>
<td>Transcutaneous</td>
<td>Requested PMA/ Given the CE mark. Approved for use by the FDA (13.03.2015)</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>WATCHMAN FLX</td>
<td>The new generation of device WATCHMAN to percutaneous isolation of LAA</td>
<td>Transcutaneous</td>
<td>Completed research FIM</td>
</tr>
<tr>
<td>Cardia</td>
<td>Ultracept</td>
<td>The soft cap for closing LAA, which adapts to the shape of the LAA; can be entered and withdrawn from the LAA by the original guided system</td>
<td>Transcutaneous</td>
<td>FIM study in progress</td>
</tr>
<tr>
<td>Coherex</td>
<td>Wavecrest</td>
<td>Occluder LAA, which enables occlusion regardless of the anchoring. There is a possibility of multiple repositioning and withdrawal of the device, it is characterized by a leading edge fabricates more easily</td>
<td>Transcutaneous</td>
<td>Given the CE mark. In preclinical studies in the United States</td>
</tr>
<tr>
<td>Custom Medical Devices</td>
<td>Sideris Path</td>
<td>Bio-absorbent of LAA occluder, available in 2 models. Traditional transcatheter patch delivery system without guide, with a balloon to implantation, has got matching properties and adhesion to surrounding tissues, with immediate release combined with a balloon catheter</td>
<td>Transcutaneous</td>
<td>During the procedure of transmitting the CE mark</td>
</tr>
<tr>
<td>Berlin</td>
<td>Tiger Paw II</td>
<td>Disposable device with snap closure/implantation for LAA</td>
<td>Minimally invasive cardiac surgery</td>
<td>Met 510 (k) of the FDA. Approved by the CE mark</td>
</tr>
<tr>
<td>Gore</td>
<td>Gore LAA Closure Device</td>
<td>LAA closure system in the early stages of the project. In the United States during the patent procedure, the patent number: 20130018414. The company describes the device as a system consisting of a balloon covered with an adhesive substance stimulating the growth of tissue</td>
<td>Transcutaneous</td>
<td>Work on the development of the idea</td>
</tr>
<tr>
<td>IDX Medical</td>
<td>IDX Medical LAA Occlusion Device</td>
<td>Device for closing LAA consisting of terminals, which form a closed ring form matching to a occlusive structure</td>
<td>The use of an open heart bypass grafting during surgery</td>
<td>Work on the development of the idea</td>
</tr>
</tbody>
</table>
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600
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WATCHMAN as chronic anticoagulant therapy with
warfarin (a non-inferiority study). The study included
707 patients with atrial fibrillation and non-valvular with at
least one risk factor for peripheral embolism such as the
earlier stroke, transient episode of ischemia CUN, heart
failure, diabetes, hypertension, age ≥ 75. Patients ran-
domly picked 2:1 to transcutaneous left atrium append-
age occlusion using WATCHMAN (463) and chronic
warfarin therapy with the target indicator of INR between
2 and 3 (244). Patients undergoing intervention received
warfarin for 45 days. If transeosophageal echocardiogra-
phy performed after this period showed no leaks around
the closing device, the medicine was gradually replaced
by clopidogrel and aspirin. Clopidogrel treatment lasted
for 2 weeks during the first 6 months and every month
thereafter. Observation period amounted to a total
of 1588.4 per day (1025.7 in the treatment group and
562.7 in the warfarin group). The left atrium appendage
was occluded successfully in 90.9% of patients. Com-
plex endpoint performance evaluation (ischemic stroke, sudden death or heart, hemorrhagic stroke, pulmonary
embolism) occurred in 3.0% of patients with treatment
group/year and 4.3% in group of warfarin/year (RR 0.71;
95% CI 0.44-1.30, the probability of at least equivalence
> 0.999). In assessing the safety of the therapy, the orig-
inal endpoint was 5.5% in the/year group, in which left
atrium appendage was occluded in comparison to 3.6% of
the/year in the group treated with warfarin (RR 1.53;
95% CI 0.95-2.7). After excluding the incidents that oc-
curred on the day of the intervention, fewer patients
from occluler group have experienced primary perfor-
ance assessment endpoints than the group treated
pharmacologically (2.5%/year vs 4.3%/year; probability
of superiority = 0.953). Similar results were obtained in
the evaluation of patients treated with procedures who
stopped the warfarin treatment (2.3%/year vs 4.1%/year;
probability of superiority = 0.955). After the extension
of the analysis to the patients who have completed the
therapy both with warfarin and clopidogrel and those
treated only with aspirin, resulted in the incidence of end
point security 2.3%/year in the group treated with pro-
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Conclusions

The European Society of Cardiology now recommends transcatheter treatment for the left atrium appendage occlusion in patients with a high risk of ischemic stroke and administered to chronic oral anticoagulant therapy (class IIa recommendation/B) (39). Absolute contraindication to surgery is unfavorable anatomy or the thrombus present at the left atrial appendage. These recommendations are based on early research results of PROTECT AF and it seems that now they require verification. The data obtained from long observation trial of PROTECT AF registry and CAP suggest the advantage of transcatheter left atrium appendage occlusion over the chronic oral anticoagulant therapy and decrease the amount of surgery-related complications with the increase in the amount of procedures preformed, the experience of the centre and operators. This treatment may become an alternative to pharmacological therapy. There is a constant increase in the patients who may become candidates for this type of treatment. These include people with a risk of bleeding, those who do not feel convenient with the prospect of admitting a lifetime of oral anticoagulant medicines, patients with a renewed strokes in spite of the use of oral anticoagulants, patients badly tolerating those medicines, as well as individuals with ischemic heart disease requiring triple anticoagulant therapy, for example after stent implantation DES. The modernization of already existing, as well as the development of new systems of mechanical trombectomy of left atrial appendage can also cause reduced contraindications to these types of treatments. It is also necessary to perform research comparing the effectiveness of different systems to occlude the appendage and the types of therapies used after surgery.


40. www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApproval/P- MA/ucm046719.htm.