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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Temporal healing patterns and coverage dynamics after new Polish transcatheter PFO occluder implantation in a swine

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Abstract

Background: Although currently used devices for interventional closure of patent foramen ovale (PFO) are widely used due to the minimally invasive nature of this technique and high success rate, there is still a need to look for new materials and designs in order to improve the treatment outcomes.

Aim: To evaluate the safety, biocompatibility, temporal healing patterns, and coverage dynamics of the new Polish PFO occluder (Balton, Warsaw, Poland) in a swine model — an observation that may assist the decision with regard to its first-in-human use and duration of anticoagulation therapy.

Methods: In total, 12 pigs were scheduled for 28-day (n = 6) and 90-day follow-up (n = 6). In each animal, using a standard femoral venous approach, one PFO occluder was implanted and subsequently, in order to verify device position stability, the Minnesota manoeuvre was performed. At follow-up, all devices underwent a comprehensive evaluation with the use of high-resolution radiography (Faxitron MX-20 system), scanning electron microscopy (SEM), and standard histopathological techniques.

Results: All PFO occluders were implanted successfully with no complications. The Faxitron revealed that all nitinol portions of the frame appeared intact and breaks were not detected at both studied time points. Overall, the device appeared to be well deployed in the atrial septum. At 28 days the average neointimal coverage of the right side of the PFO occluder by SEM was 92%; while in contrast the left side had less coverage, at 63%. At 90 days, the coverage of the right side of the occluder was 96.8%, while the left side of the PFO occluder improved and had similar coverage of 93.3%. By histology the endothelialisation process was virtually complete at 90 days. At the early time-point the overall inflammatory infiltrate was moderate and subsequently it diminished and was only mild or occasionally moderate at 90-day follow-up. At both time points the inflammatory reaction was limited to the neointimal tissue surrounding the device.

Conclusions: Our study confirmed safety and good overall biocompatibility of the new Polish PFO occluder, which is comparable to other devices available on the market — an observation that supports the decision with regard to its first-in-human application. Neoendothelialisation was virtually completed at 90 days, suggesting that similarly to other widely used devices a minimum of three to six months of anticoagulation therapy should be recommended.

Key words: PFO occluder, porcine, biocompatibility

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INTRODUCTION

Transcatheter interventional closure of patent foramen ovale (PFO) is a broadly applied procedure due to the minimally invasive nature of this technique and its high success rate [1]. Safety and long-term efficiency appear satisfactory in the majority of patients; nevertheless, in some of them transcatheter therapy may be suboptimal [2]. This could be induced by impaired healing with thrombi formation on the nitinol-based device implanted into the atrial septum [3]. Incomplete neointimal coverage of the device with impaired endothelialisation and persistent inflammation could lead to these suboptimal results. Therefore, we sought to evaluate the safety, biocompatibility, temporal healing patterns, and coverage dynamics of the new Polish PFO occluder (Balton, Warsaw, Poland) in a swine model — an observation that may assist the decision with regard to its first-in-human use and duration of anticoagulation therapy.

METHODS

Device description

The PFO occluder is a self-expandable, symmetrical, double-disc device made from a nitinol wire. The two discs are linked together by a short connector. The discs contain thin polyester fabric. The polyester fabric is sewn to each disc by a polyester thread. The materials used for its production have been widely used for years in implantology, having acceptable biocompatibility and mechanical parameters including elasticity. The occluder size ranges from 18 mm to 35 mm. It is compatible with a 9 F delivery sheath.

Experiment design and procedure

The study was performed in the Centre for Cardiovascular Research and Development of American Heart of Poland. Histopathological evaluation was conducted in the independent AccelLAB laboratory (Montreal, Canada). The study protocol was approved by the local ethics committee for animal research. All animals received standard care outlined in the study protocol and in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" [4].

Six pigs were scheduled for 28-day and six for 90-day follow-up. All animals were fasted overnight before the PFO closure procedure. Animals were pre-medicated, sedated, intubated and anaesthetised using standard procedures described elsewhere [5]. A vascular sheath (9 F) was placed in the right or left femoral vein utilising the Seldinger technique. Thereafter, the delivery sheath was advanced through the septum to the left atrium. In cases in which this approach was impossible due to closed foramen ovale, the puncture of the septum was achieved with a stiff guidewire. Then, a PFO occluder was deployed. In order to verify position stability, the Minnesota manoeuvre was performed and the device was released. At the end of the procedure the tightness and completeness of the closure between the atriums was checked with the application of contrast media. Anticoagulation with heparin was achieved (3000–10,000 U) to maintain a coagulation time ≥ 250 s. All animals received dual antiplatelet therapy consisting of oral acetylsalicylic acid (300 mg loading dose and 150 mg subsequently) and clopidogrel (300 mg initial dose and 75 mg subsequently), starting five days prior to intervention and continuing until the last day of the study.

At follow-up the treated segments were carefully harvested, flushed, and stored in formalin and sent to the pathology laboratory. All devices underwent evaluation with the use of high-resolution radiography (Faxitron MX-20 radiography system). Images were taken at two angles, approximately perpendicular. Subsequently, scanning electron microscopy (SEM) was used to evaluate the presence of endothelial/neointimal percentage area coverage, inflammatory cells, and thrombus formation. Specimens were visualised using a JEOL JSM-6460LV low vacuum SEM (LVSEM). For histopathological analysis, the implanted devices were embedded in methyl methacrylate (MMA). After embedding, one block was cut from each implanted device at mid-point. From each block, one section was cut, ground, and polished, to a final section thickness of 60 μm or less. Each section was stained with haematoxylin and eosin (H&E). Images of each H&E-stained section (low and high magnification) were digitally captured. All H&E stained sections were examined by the pathologist for descriptive histopathology.

Statistical analysis

The categorical variables are presented as mean ± standard deviation (SD). The continuous data are presented as mean ± SD or medians (interquartile range) after data distribution was analysed. Graph Pad Prism 6 was used as statistical software.

RESULTS

All PFO occluders were implanted successfully with no complications; moreover, good visibility in fluoroscopy and deliverability were noted. In all animals position stability and tightness between atriums were confirmed immediately after baseline procedure. At 28 days of follow-up incomplete coverage was seen on both sides of the PFO occluders in all animals; however, the left side appeared to be less covered. At 90 days of follow-up the coverage appeared to be complete. At both time points no thrombi were noted on gross specimen evaluation.

High-resolution radiography

On high-resolution radiography, all nitinol portions of the frame appeared intact and breaks were not detected at either of the time points. Overall, the device appeared to be well deployed in the atrial septum. The right and left sides of the nitinol frame were parallel to each other, and the connector, which crossed the septum, was perpendicular to the two sides of the device (Fig. 1).

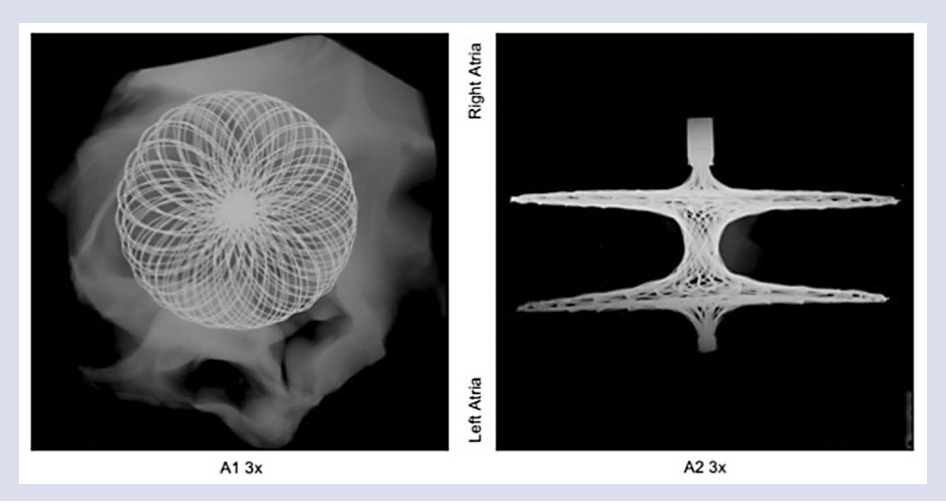

Figure 1. High-resolution radiography of tested occluder at 90-day follow-up. All nitinol portions of the frame appeared intact and breaks were not detected. Overall, the device appeared to be well deployed in the atrial septum. The right and left sides of the nitinol frame were parallel to each other, and the connector, which crossed the septum, was perpendicular to the two sides of the device

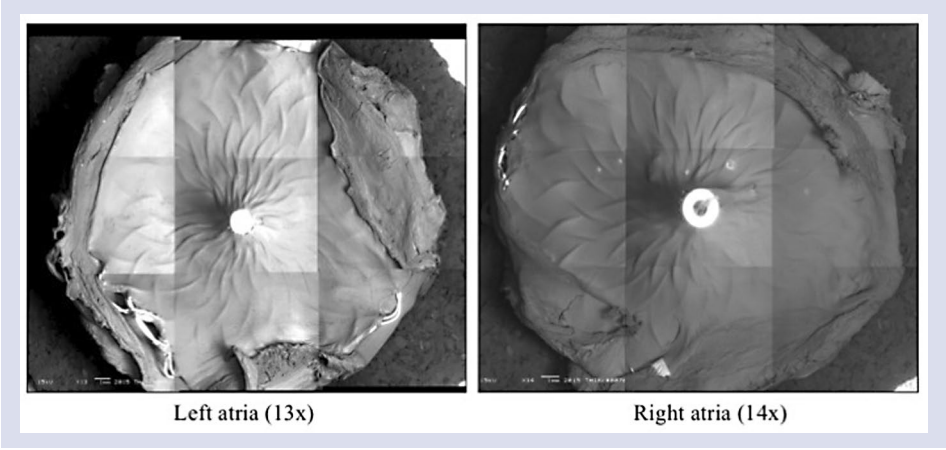

Figure 2. Scanning electron microscopy images of PFO occluders at 90 days. Very few areas of the device were devoid of endothelial coverage, primarily seen in the peripheral portion of the device, although a few areas were seen near the centre. In the bare areas seen at the edges, the nitinol mesh was partially exposed. Note that the atrial tissue surrounding the PFO occluder curled up over the edges of the devices. These areas of the device covered by surrounding atrial tissues were not included in the endothelial coverage calculations

Scanning electron microscopy

At 28-day follow-up the average neointimal coverage of the right side of the PFO occluder by SEM was 92% (range of 76–98%). In contrast, the left side of the PFO occluder had much less coverage, at 63% (range 47–87%). The majority of endothelium covering the device was mature; nevertheless, in some areas it was still immature.

At 90-day follow-up the average neointimal coverage of the right side of the PFO occluder was 96.8% (90.2–99.8%), while the left side of the PFO occluder had similar coverage of 93.3% (range of 76.5–98.4%). At this time-point the endothelium covering the device was already mature (Fig. 2).

Histology

At 28-day follow-up the nitinol frame and surrounding woven mesh were partially covered with a thin layer of maturing neointima with incomplete endothelialisation. The endothelialisation process was virtually complete at 90 days with only small areas devoid of endothelium. Despite the presence of some empty spaces between the left-side and right-side disks, the nitinol frame was mostly well apposed to the atrial septal wall (Fig. 3); however, the apposition appeared to be greater on the right side at both studied time points.

At the early time-point the overall inflammatory infiltrate was moderate. The nitinol wire evoked a more pyogranuloma-

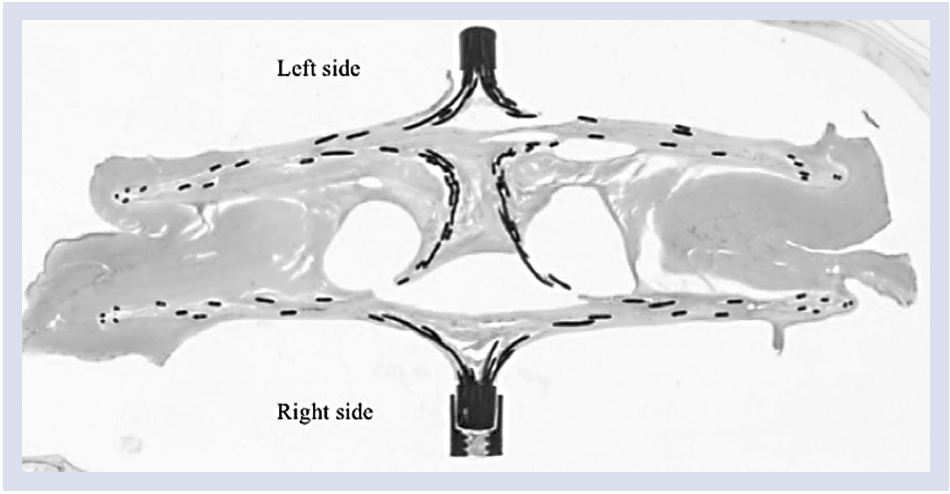

Figure 3. Low-magnification histology scan made at 90-day follow-up (haematoxylin and eosin). This section included a portion of the screw of the device (right side), its nitinol wire frame, and a pin (left side). The nitinol frame was mostly covered with a thin endothelialised neointima. Only few small areas were devoid of neointima close to the pin. The tips of the pin, of the screw, and their edges were bare and not incorporated into the neointima. Despite the presence of some empty spaces on both sides of the connector, the nitinol frame was mostly well apposed to the atrial septal wall

tous response with increased numbers of neutrophils. The mesh evoked granulomatous infiltrate rich in multinucleated giant cells. At 90-day follow-up the inflammatory reaction diminished and was only mild or occasionally moderate. At both time points the inflammatory reaction was limited to the neointimal tissue surrounding the device and did not extend appreciably into the atrial septal wall. Within the device, inflammation was most prominently seen underneath the screw and pin structure, close to the connector region and along the nitinol frame where the woven mesh material was also present. Overall, the device surfaces were largely devoid of fibrin or thrombus at one and three months post implant. On the last day of the study, evidence of myocardial degeneration in the connector region was observed in most of the animals.

DISCUSSION

Complications after transcatheter PFO closure are rare; nevertheless, they occur and may cause death or neurological deficits [6]. The delayed neointimal coverage, impaired endothelialisation, and persistent inflammation in the nitinol-based devices could play a role in suboptimal long-term results after transcatheter PFO closure by leading to thromboembolic events, including ischaemic stroke. In addition, microthrombi that can develop on the incompletely covered device might penetrate through left chamber to the distal part of brain circulatory bed. This may lead to silent strokes visible in magnetic resonance imaging that can be associated with worsening cognitive functions, similary to undiagnosed, asymptomatic atrial fibrillation [7]. For this reason, it is crucial to know and understand the timing and healing pattern after PFO closure device placement in order to adjust the length of antithrombotic treatment. Although there are no strict guidelines with regard to the type and length of optimal antithrombotic treatment after transcatheter PFO closure, the reduction of thromboembolic events in clinical practice is usually achieved by the six-month antiplatelet therapy or in some cases by anticoagulation administration [6]. This, however, may increase the probability of bleeding events. In our study we tested the safety, biocompatibility, temporal healing patterns, and coverage dynamics of the new Polish PFO occluder (Balton, Warsaw) in a swine model in order to not only assist the decision with regard to its first-in-human use but also to decide about the duration of anticoagulation therapy.

Although at 28-day follow-up the nitinol frame and surrounding woven mesh were only partially covered with a thin layer of maturing neointima with incomplete endothelialisation, the healing process was virtually complete at 90-day follow-up. In most previously published studies the complete neoendothelialisation process was achieved within three months after implantation [8–11], which is in line with our observations.

The interesting finding of our study is that temporal healing patterns and coverage dynamics significantly vary between left and right atrium. A similar finding was described earlier in a study of Krizanic et al. [12], in which the authors reported asymmetrical healing between left and right side of the occluder in a swine model; however, the assessment was based only on macroscopic evaluation (the mean implantation time was 127 ± 46 days). In contrast, in our study we used precise methods utilising SEM with quantitative measures of the coverage. At 28-day follow-up the left-side neointimal coverage appeared significantly lower as compared to the

right-side (63% vs. 92%). At three-month follow-up, although the difference of the coverage was still noticeable it was virtually complete on both sides (93.3% vs. 96.8%).

There are several theoretical explanations for delayed coverage on the left side of the device at earlier time-point. Firstly, this finding could be attributable to a higher systolic and diastolic pressure in the left atrium. Secondly, the blood flowing from posteriorly situated ostia of pulmonary veins passes through the septum [13], theoretically affecting the healing pattern. Thirdly, the blood in the left atrium is oxygenated and refined from biologically active molecules (including growth factors) that are metabolised in the lungs, thus potentially delaying endothelialisation process [14]. In addition to these theoretical factors, protrusion of implant material, asymmetrical design of the device, as well as apposition discrepancy between the right or left side and the arterial septum could be identified as a risk factor for uneven healing on both sides of a device with subsequent thrombus formation [15–17]. However, the device tested in our study has a symmetrical design in which two identical discs are linked together by a short connector, and both of these discs contain identical polyester fabric. Thus, it seems that this factor should be rejected as the source of asymmetrical healing, and the only possibility to explain this finding would be the apposition that tended to be slightly greater on the right side; this finding is not surprising because the porcine PFO anatomy may not perfectly imitate human conditions.

It would be interesting to validate whether the asymmetrical healing pattern found in our experimental study is also present in a clinical setting, especially in the case of symmetrical apposition of both discs. In previously published studies in which human explants were tested no such findings were described [10].

In our study the inflammatory reaction in all tested devices was mild to moderate at both studied time-points, and most importantly it was identical on both sides of the device, suggesting no effect on delayed endothelialisation seen on the left side. Moreover, inflammation was limited to the neointimal tissue surrounding the device. It is hard to state if the incidental findings of fibrin in our study were the result of the healing process of a previously injured myocardium or simply incidental. However, even in the case where the fibrin would have been due to a healing process, it was not suspected to be related to any functional problem of the heart in these animals. The myocardial degeneration changes observed in the connector region were suspected to have been caused at implantation during the passage of the device through the atrial wall. Similar findings with regards to inflammatory reactions were described previously [11].

Limitations of the study

Porcine PFO exhibits a microscopic structure similar to that in humans. However, care should be taken when interpreting data from the porcine model to clinical settings [18]. In our study we selected two time-points of 28 and 90 days because, as shown previously, these time-points provide the most relevant pathological findings after nitinol device placement in the interatrial septum [9]. An important limitation is the relatively small number of animals that are justified by the requirements of the Ethics Committee to maximally limit the size of tested samples. Another parameter that deserves comment and should be treated as a study limitation is the lack of routinely performed tests to evaluate completeness of PFO closure (like transoesophageal echocardiography examination). The only "indirect" evidence of closure completeness utilised in our study was the shape and symmetry of the device. Finally, the dual antiplatelet therapy used in our study was more restrictive as compared to the routine clinical practice and theoretically could influence the results.

CONCLUSIONS

Our study confirmed the safety and good overall biocompatibility of the new Polish PFO occluder, which is comparable to other devices available on the market — an observation that supports the decision with regard to its first-in-human application. An important finding of our study is the asymmetrical healing pattern between the left and right side of the occluder at an early time-point. This finding seems to be related to the disk's apposition, which tended to be slightly greater on the right side — as expected, taking into account the fact that the porcine PFO anatomy used for human device evaluation may not perfectly imitate clinical conditions. Most importantly, at 90-day follow-up neoendothelialisation was virtually complete. This observation suggests that, similarly to other widely used devices, a minimum of three to six months of anticoagulation therapy should be recommended.

Conflict of interest: *none declared*

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Sposób gojenia i dynamika pokrycia nowego polskiego okludera PFO na eksperymentalnym modelu świni

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Streszczenie

Wstęp: Mimo że obecnie stosowane urządzenia do interwencyjnego zamykania przetrwałego otworu owalnego (PFO) są powszechnie stosowane w praktyce klinicznej z uwagi na ich minimalnie inwazyjny charakter oraz wysoki odsetek powodzeń, ciągle istnieje potrzeba poszukiwania nowych materiałów i konstrukcji w celu dalszej poprawy wyników leczenia.

Cel: Celem badania była ocena bezpieczeństwa, biokompatybilności, sposobu gojenia i dynamiki pokrycia nowego polskiego okludera PFO (Balton, Warszawa, Polska) na modelu świni, aby potwierdzić możliwość dopuszczenia go do testów klinicznych, jak również by dobrać czas trwania terapii przeciwzakrzepowej.

Metody: Po uzyskaniu zgody lokalnej Komisji Etycznej do badania włączono łącznie 12 świń domowych, którym implantowano okludery PFO na okres 28 (n = 6) oraz 90 dni (n = 6). U każdego ze zwierząt okludery implantowano w przegrodzie międzyprzedsionkowej z dostępu przez żyłę udową i następnie, w celu weryfikacji stabilności pozycji okludera, wykonywano manewr Minnesota. W kontrolnych punktach czasowych zwierzęta usypiano, a wszystkie okludery badano, stosując obrazowanie z użyciem radiografii o wysokiej rozdzielczości (system Faxitron MX-20), technikę skaningowej mikroskopii elektronowej (SEM) oraz metodę histopatologii wykorzystującej zatapianie próbek w twardej żywicy (metakrylan metylu; MMA), ich cięcie na grubość poniżej 60 μm i wybarwianie hematoksyliną-eozyną.

Wyniki: Wszystkie badane okludery implantowano z powodzeniem, bez komplikacji. Obrazowanie z użyciem systemu Faxitron wykazało, że wszystkie części konstrukcji nitinolowej były nienaruszone, nie stwierdzono również pęknięć ani złamań. Urządzenie było implantowane prawidłowo w obrębie przegrody międzyprzedsionkowej. W 28-dniowej obserwacji na podstawie analizy SEM wykazano, że prawa strona okludera była pokryta w 92%, podczas gdy strona lewa była pokryta znacznie słabiej (63% pokrycia powierzchni). Po 90 dniach pokrycie po stronie prawej wyniosło 96,8% powierzchni, natomiast po stronie lewej odsetek pokrycia uległ znacznej poprawie i wyniósł 93,3%. Na podstawie analizy histopatologii stwierdzono, że proces endotelializacji był praktycznie zakończony po 90 dniach. We wczesnym punkcie czasowym reakcję zapalną określono jako umiarkowaną i zmniejszyła się po 90 dniach od implantacji do łagodnej lub tylko okazjonalnie umiarkowanej. W obu punktach czasowych reakcja zapalna była ograniczona do obszaru neointimy otaczającej urządzenie.

Wnioski: Zaprezentowane badanie potwierdziło bezpieczeństwo oraz biokompatybilność nowego polskiego okludera do zamykania ubytków typu PFO. Wyniki te należy ocenić jako zbliżone do innych urządzeń powszechnie stosowanych w praktyce klinicznej, wspierając tym samym decyzję o możliwości dopuszczenia okludera do prób klinicznych. Proces neoendotelializacji został praktycznie zakończony po 90 dniach od implantacji, co sugeruje, że podobnie do innych stosowanych urządzeń terapia przeciwzakrzepowa powinna być stosowana przez okres minimum od 3 do 6 miesięcy.

Słowa kluczowe: okluder do ubytków PFO, świnia, biokompatybilność

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