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Novel Insights from Clinical Experience

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Post-Mortem Analysis of a Left Atrial Appendage Occlusion Device (PLAATO™) in a Patient with Permanent Atrial Fibrillation

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Established Facts

- Percutaneous transcatheter occlusion of the left atrial appendage with an implant is feasible and maybe an alternative to anticoagulation in high-risk patients suffering from atrial fibrillation.

Novel Insights

- Surprisingly and contrary to prior reports, we did not find endothelialization of the luminal side of the PLAATO™ device 2.5 years after implantation.

Key Words
Atrial fibrillation · Endothelialization · Left atrial appendage · Occlusion system · PLAATO™

Introduction

Atrial fibrillation (AF) is associated with a high cardioembolic risk and is responsible for about 20% of all strokes [1–4]. Randomized clinical trials have demonstrated the efficacy of anticoagulation to reduce the rate of stroke in patients with AF [1]. Unfortunately, it is often difficult to achieve a well-controlled therapeutic range of anticoagulation over long periods of time [1, 4] and contraindications to oral anticoagulation exist in a considerable number of patients [2, 3].

In a review by Blackshear and Odell [5], 17% of 1,288 nonrheumatic AF patients had a left atrial thrombus, and 91% of these 222 were isolated to the left atrial appendage (LAA). Because more than 90% of thrombi are located in the LAA, an elimination of the appendage – either by resection or occlusion – seems to be an attractive alternative to oral anticoagulation. In many centers, it has become routine practice to ligate the LAA at the time of mitral valve surgery, and the American Heart Association guidelines for mitral valve surgery recommend LAA amputation to reduce the risk of stroke [6].

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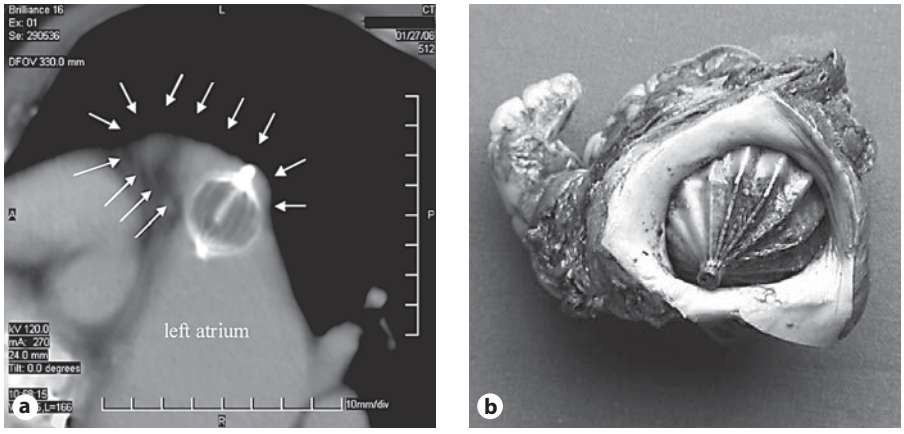

Fig. 1. Position of the PLAATO™ device in the LAA. **a** Cardiac CT of the PLAATO™ device 3 months after implantation. The arrows frame the LAA. The device was rotated off axis of the LAA and showed a slight partial protrusion into the left atrial cavity. This phenomenon was already seen in TEE directly after implantation and is due to the angulated appendage. A further migration of the device could not be observed. **b** Position of the implanted PLAATO device in the left atrial appendage. Autopsy specimen of the patient.

Some years ago, an implantable device for percutaneous LAA transcatheter occlusion (PLAATO) has been developed for clinical use [3, 7]. We report the autopsy findings of a 54-year-old man who died 2.5 years after successful PLAATO implantation.

Case Report

The patient was admitted to the Hoyerswerda Hospital due to an acute left-sided hemiparesis, aphasia and right-sided preorbital headache. The examination of the patient, including neurological, neuroradiological (CT and MRI) and cardiovascular [ECG, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and extracranial Duplex] evaluations, revealed a cardiac thromboembolus from the LAA as the most probable cause of stroke. The patient suffered from hypertrophic non-obstructive cardiomyopathy. ECG showed AF. A dilated left atrium (57 mm) could be demonstrated by TTE. TEE revealed spontaneous echos predominantly in the LAA.

The neurological symptoms of the patient completely recovered during the following days and, finally, he reached full vocational rehabilitation as a butcher. An attempt of electrical cardioversion after 4 weeks of phenprocoumon therapy (international normalized ratio 2.5–3.5) failed. Due to his occupational hazard, the patient asked for an alternative to oral anticoagulation. After two detailed explanations, the patient signed a written consent and a PLAATO device was successfully implanted using the standard approach. Thereafter, the patient received clopidogrel 75 mg once daily for 6 months.

The PLAATO system (ev3, Roissy, France) consists of an implant and a delivery catheter [7]. The implant is a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene membrane, which is laminated directly to the frame structure of the nitinol cage so that the perimeter has close contact with the inner wall of the appendage. Small hooklets along the struts passing through the membrane allow a firm anchoring of the device within the LAA. The device is delivered through a custom 14-french transseptal sheath curved to point at the LAA.

In our patient, the device completely occluded the LAA, confirmed by the injection of contrast medium, of which no trace could be found around the device.

The LAA including the PLAATO was preserved in 2% formalin immediately after explantation. For further processing, the autopsy specimen was transported in formalin-saturated wet compresses. After microscopic investigation and documentation using a stereo microscope, the LAA was prepared for immunohistology. Using confocal laser scanning microscopy, the presence of endothelial cells on the surface of PLAATO was investigated by fluorescence microscopy.

Simultaneously, it could be demonstrated, that the endothelium of the adjacent left atrial endocardium was completely intact. A triple staining procedure was applied to assure the presence of endothelial cells at the PLAATO surface. The endothelial cell surface was labelled immunohistochemically by anti-CD31 antibodies and histochemically by ulex-I lectin. Cell nuclei were stained histochemically by the DAPI method. In confocal laser scanning microscopy, DAPI staining gave the cell nuclei a blue color. Ulex-I presented the endothelial cell surface in green color and cell surface structures labelled by anti-CD-31 antibodies were shown in red color.

Results

De novo thrombus formation at the surface of the PLAATO device adjoining the left atrial lumen was excluded by repeated TTE and TEE. There was no reported neurological clinical event during the follow-up period of 2.5 years.

Dislocation or migration of the device was excluded by cardiac CT 3 months after implantation. Figure 1 shows the location of the PLAATO device within the LAA.

The autopsy specimen showed perfect positioning of the PLAATO device in the LAA (fig. 1). Even at low magnification (fig. 2a), thrombotic depositions were visible in

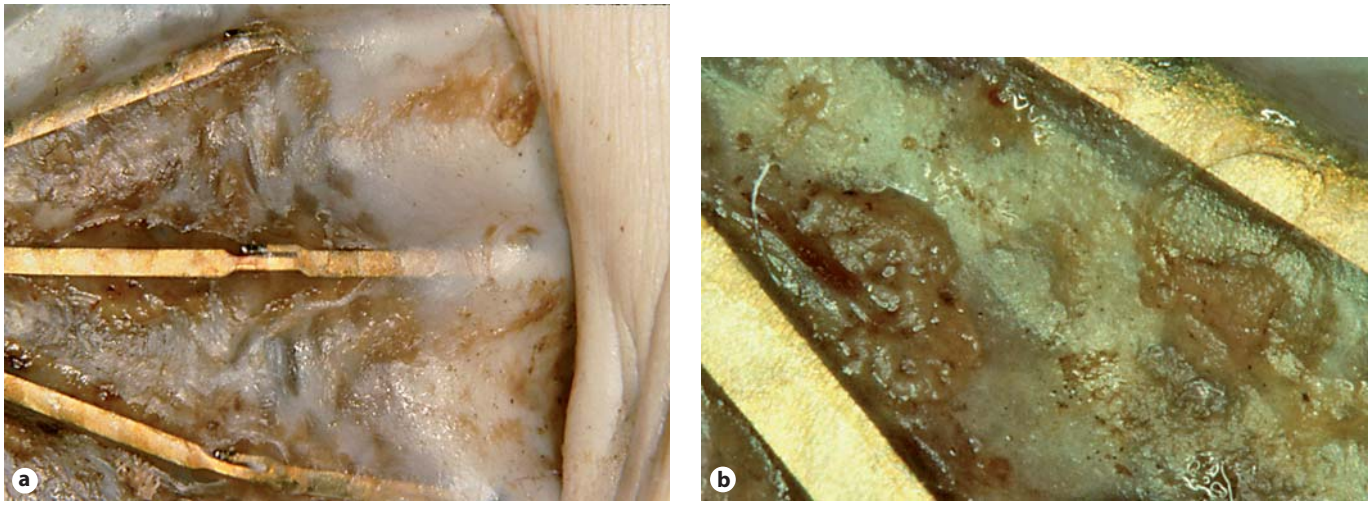

Fig. 2. Thrombotic deposition on the atrial sided surface of the PLAATO system. **a** 1:8 primary magnification. **b** 1:18 primary magnification.

the contact zones between the PLAATO device and the endocardium as well as on and near the umbrella struts of the PLAATO device. The PLAATO device axis was twisted in relation to the LAA axis, resulting in loss of contact of the hooklets of the first row. This row was rotated towards the free cavity of the left atrium. A further dislocation or migration of the device was not observed during clinical follow-up with TEE and CT. At higher magnification (fig. 2b), areas with massive adhesion of thrombotic material can be seen on the surface of the device between the umbrella struts adjoining the left atrial lumen.

The patient died (most likely) due to a sudden cardiac arrest in the course of lung cancer in our hospital 2.5 years after PLAATO implantation. Autopsy confirmed the diagnosis of hypertrophic non-obstructive cardiomyopathy. There were no signs of thromboembolism, and pericardial effusion was excluded.

Based on single color channel (RGB) display, triple staining could demonstrate whether differently stained cell structures were either co-localized and the overlapping colors, e.g. red (CD31) and green (UlexI), result in a new color (e.g. orange) or are grouped together with the DAPI (blue)-stained cell nuclei. Ulex1 (green) was present in a fine/medium-grained staining pattern more or less evenly distributed over the surfaces (also covering the nuclei) of unlesioned endothelial cells of the neighboring endocardium.

Application of the same tissue processing method allowed the discrimination of endothelial cells also on the surface of the PLAATO system. There were only few distantly located single endothelial cells. This was further demonstrated by the almost complete lack of the finely dispersed homogenous pattern of green color which is typical of a functionally dense endothelial layer. Finally, the absence of a typical red-stained pattern (CD31) has to be taken as critical evidence that endothelial cells in relevant numbers and cell densities were absent. Quite a number of blue (DAPI)-stained nuclei were found, however, which were identified as cells of the monocytic lineage. There were high numbers of small and big green spots identified as adherent platelets or platelet aggregates, respectively.

Discussion

The PLAATO device was not fractured and completely occluded the ostium of the LAA. The device was rotated off axis of the LAA and showed a slight partial protrusion into the left atrial cavity. This phenomenon was already seen immediately after implantation and was due to the underlying anatomical angulation of the LAA. A further migration of the device was not observed during the clinical follow-up investigations.

As described in an earlier post-mortem study, the atrial luminal surface of the PLAATO system was covered by a so-called neointima [8]. Between the PLAATO device and the LAA a crevice had formed, which showed signs of thrombogenicity. Sparse thrombocoagulant layers ap-

peared, including erythrocytes now and then. Significant thrombi, however, were not found. At a few spots, where the PLAATO device surface was in close contact to the adjacent atrial surface, bridge-like layers of endothelial cells overgrew the crevasse.

A complete endothelial neoformation, as described earlier [9], could not be demonstrated on the PLAATO surface. The immunofluorescent visualization of endothelial cells showed a complete endothelial layer on the atrial endocardium, but only singular endothelial cells – mostly in parts of the PLAATO surface adjacent to the aforementioned contact zones between the PLAATO device and the atrial endocardium.

Although a complete endothelialization of the PLAATO surface could not be demonstrated, no clinical episodes of neurological deficits occurred during the 2.5 years after the implantation of the PLAATO system. It seems obvious that a so-called neointima, as described for vascular prostheses of greater diameter [10], had developed. In terms of thrombogenicity, this thin layer was compared to intact endothelium [9] and hence may have prevented clot formation.

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