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ORIGINAL ARTICLE

Fetal trans-apical stent delivery into the pulmonary artery: prospects for prenatal heart-valve implantation

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Abstract

OBJECTIVE: The purpose of this study was to assess the technical feasibility of a fetal trans-apical stent delivery into the pulmonary artery using a novel hybrid-intervention technique as a possible route for prenatal minimally invasive heart-valve-implantation approaches.

METHODS: Pregnant Pre-Alp sheep between 122 and 128 days' gestation (n = 3) underwent a midline laparotomy. The fetus was left *in utero* or partially externalized and its chest was opened via a left-sided minithoracotomy. The fetal heart was cannulated and a guide wire was introduced through the ductus arteriosus into the aorta. A 14-French delivery system was then mounted onto the guide wire and advanced to the landing zone in the pulmonary artery, where the stent was deployed. The position of the stent was confirmed using echocardiography, angiography as well as computed tomography.

RESULTS: The trans-apical implantation was successful in all animals. However, at necropsy in one animal, the stent was found to partly occlude one of the pulmonary valvular leaflets. Bleeding at the antero-apical incision occurred in all animals but could be managed without fetal demise. No fetal cardiopulmonary bypass was performed. In all animals, contrast angiography displayed normal perfusion of the pulmonary vasculature as well as the ductus arteriosus.

CONCLUSIONS: Our study demonstrates the principal technical feasibility of a prenatal stent delivery into the pulmonary artery using a novel trans-apical hybrid-intervention technique. This approach demonstrates the first step towards possible future minimally invasive prenatal heart-valve-implantation procedures.

Keywords: Fetal • Trans-apical • Stent • Heart valve • Congenital

INTRODUCTION

Based on advanced fetal-imaging techniques, there is an increasing interest in performing prenatal cardiac interventions, in particular in severe anatomic cardiac obstructions, such as pulmonary or aortic-valve stenosis [1–5]. Both lesions can induce irreversible ventricular malformation and dysfunction as well as hypoplasia of the adjacent great arteries, leading to severe cardiac malformation and decompensation [1,4]. The resulting insufficient growth of the ventricle has a substantial impact on postnatal treatment options, as in most cases only palliative surgical procedures may be offered and common treatment options might be limited, that is, univentricular strategies [1,5,6]. Moreover, heart failure may develop during late gestation, leading to either fetal loss or delivery of a premature infant who requires urgent interventions [5,6].

The reduction of intrauterine progression of fetal cardiac malformations is desirable to minimize consecutive congenital maldevelopment of cardiovascular structures. Therefore, the relief of obstructive malformations, such as heart-valve stenoses, using interventional procedures has been suggested to promote functional recovery of the affected ventricle [4,6,7]. The principal feasibility of fetal cardiac interventions has been proven in both, in selected human fetuses 4] as well as in various experimental animal models involving minimally invasive fetoscopic- as well as catheter-based approaches [2,3,8,9]. In humans, successful fetal cardiac catheterization and balloon valvuloplasty by ultrasound-guided direct puncture of the obstructed ventricle have been reported by several groups [1,4,7,10–13]. Although encouraging, these indirect percutaneous interventions were associated with a high risk for major complications including

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pericardial tamponade, hematothorax, cardiac arrhythmia, prenatal birth, and even fetal death [1,5,14,16]. Furthermore, restenoses of the obstructed segments have been repeatedly reported after prenatal cardiac-balloon interventions [4,14].

The implantation of a stented heart valve into the orthotopic valvular position, as currently performed in elderly patients [15], could potentially overcome these limitations by dilating the obstructive segment, restoring normal valvular functionality as well as preventing valvular restenosis. While the reported balloon-dilation approaches often aimed at a bridging of affected fetuses until birth, prenatal heart-valve implantations could allow for a more flexible follow-up period by fully restoring native valvular functionality. Besides that, an open-chest closed-heart *in utero* intervention technique could combine optimal control of peri- as well as acute postoperative bleeding complications with a minimally invasive catheter-based intervention.

The purpose of this acute study in fetal sheep was to assess the technical feasibility of a minimally invasive trans-apical stent implantation into a defined landing zone of the pulmonary artery (PA) using a novel fetal hybrid-intervention technique. This approach could serve as a potential future route for minimally invasive prenatal heart-valve implantation procedures.

MATERIALS AND METHODS

Experimental protocol

We studied three pregnant Pre-Alp sheep between 122 and 128 days' gestation (term 145 days, mean weight 1500 g). All animals received humane care in compliance with the Principles of Laboratory Animal Care as well as with the 'Guide for the Care and Use of Laboratory Animals' published by the National Institutes of Health (NIH publication no. 85-23, revised 1985). After overnight fasting, each animal was sedated by intravenous injection of pentothal (10 mg kg^{-1} body weight). The sheep were placed in supine position, intubated, ventilated with 100% oxygen and 1–2% isoflurane, and monitored continuously throughout the entire procedure. Fetuses were heparinized prior to stent deployment (0.5 mg heparin i.a. per fetus, Heparine Choay®, Sanofi Synthelabo). No anti-arrhythmic agents were used during or after the procedure. All procedures were approved by the Institutional Ethics Committee (10-16QRF30A).

Imaging modalities

Prior to implantation, major cardiac structures and thoracic vessels were located with transuterine ultrasound equipment (Philips Healthcare iE33® xMATRIX Ultrasound System; the Netherlands) with sterile packed 3–5-MHz broadband transducers. PA and pulmonary valve annulus (PVA) diameters were determined: PA diameter 10.0 ± 0.1 mm; and PVA diameter 9.78 ± 0.5 mm. Intra- and postoperative imaging included contrast angiography (OEC® 9900 Elite General Electric, Fairfield, CT, USA; intraventricular contrast injection) as well as computed tomography (CT, Siemens, Munich, Germany). Three-dimensional CT reconstruction and volume rendering were performed using the OsiriX Image Processing Software (OsiriX Mac OS X; Version 3.8.1).

Operative technique

After transuterine sonographic assessment, the uterus was exteriorized through a maternal midline laparotomy and the fetal heart was approached using two different routes: (1) the fetus was left *in utero* and, after thoracotomy, its skin was sutured to the uterine wall or (2) it was partially externalized from the uterus and thoracotomy was performed – the upper part of the body remained within the maternal uterine cavity. The amniotic fluid (415 ± 334 ml) was collected and stored. The fetal chest was opened via a left-sided 4th intercostal space minithoracotomy. Following pericardiotomy and optimal cardiac exposure, a 5/0 pledged purse-string suture was placed on the right antero-apical region (TI-CRON® 5/0, Syneture Suture, IPP Pharma, France). Next, the fetal heart was cannulated to perform pressure measurements as well as contrast angiography prior to deployment. Thereafter, a 16-gauge catheter was inserted into the apex of the right ventricle and a 0.35-mm guide wire was introduced into the catheter and through the ductus arteriosus into the aorta (see Fig. 1 for detailed anatomy). The 14 French delivery system (Zenith Flex® Catheter, Cook Medical, Bloomington, IN, USA) was then mounted onto the guide wire and advanced to the landing zone. We aimed to deploy the stent (1.0/1.2 × 1.0 cm; self-expanding nitinol stent, Sinus-Repo-Visual-6F, OptiMed, Ettlingen, Germany) supravalvular into the PA of the fetus. After delivery, the position of the stent was confirmed using echocardiography as well as angiography. At the end of the procedure, the delivery system was removed and the right-ventricular implantation site was closed with the 5/0 pledged pre-placed purse-string suture (four to five pledges; TI-CRON® 5-0, Syneture Suture, IPP Pharma, France). At post-mortem examination, the stent position in the PA as well as the artery wall integrity was assessed macroscopically and compared to *in vivo* findings.

Disclosures and freedom of investigation

The equipment and technology used in the study were purchased using academic funds. The authors had full control of the

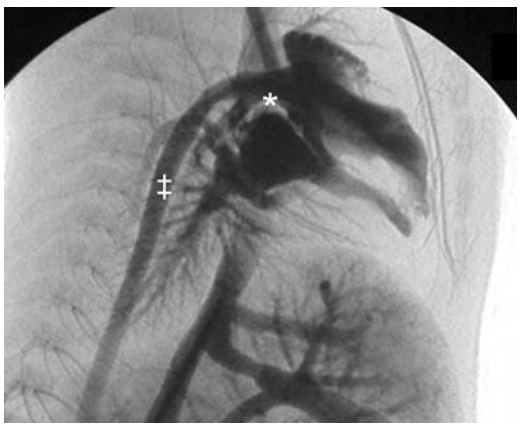

Figure 1: Fetal cardiac anatomy. Post-mortem angiography through umbilical vein including descending aorta (‡) and the ductus arteriosus at its entry into the aortic arch (*).

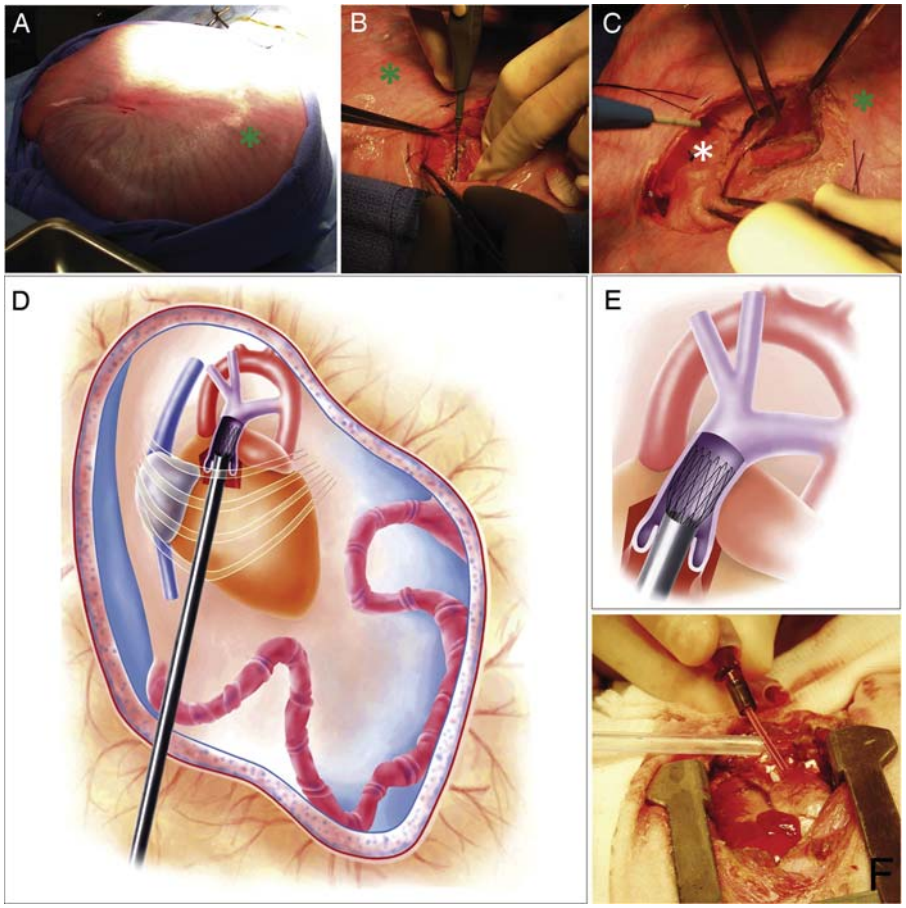

Figure 2: The fetal open-chest *in utero* trans-apical hybrid technique. After exteriorization of the uterus (A), a small incision was made in the uterine wall (B, *A–C: uterus), and the fetal chest was opened (C). The 16-gauge catheter was inserted into the apex of the right ventricle (F) and the delivery system is advanced to the landing zone. The stent is then deployed supravalvular into the distal portion of the pulmonary artery (D–F).

design of the study, methods used, analysis of data, and production of the written report.

Statistical analysis

Quantitative data are presented as mean ± standard deviation (Statistical Package for Social Sciences (SPSS) 17.0, IBM, Somers, NY, USA).

RESULTS

Trans-apical implantation

After mounting onto the guide wire, the delivery system was introduced into the ventricle via the antero-apical incision (Fig. 2 ; Suppl. Video 1) and advanced to the defined landing zone located 3.0–5.0 mm distal to the PVA (Fig. 3). The stent deployment was successful in all three animals, and all fetuses survived the surgical procedure of approximately 60 min, lasting from maternal laparotomy to the end of post-deployment *in vivo* evaluation. The mean distance from the ventricle entry point to the proximal stent margin after delivery was 19.7 ± 0.6 mm (Fig. 4). However, the introduction of the delivery device into the right ventricle was difficult in all fetuses, and significant blood loss occurred in one of the animals. No fetal cardiac arrhythmia or bradycardia was observed during the procedures, and no fetal cardiac bypass was used.

Stent deployment and positioning

The stent position and the perfusion of the adjacent vessels was verified using Doppler sonography as well as contrast angiography (Fig. 5). In one of the fetuses (F1), the stent was deployed supravalvular into the PA, and initial sonographic assessment indicated a stent position clearly proximal to the ductus arteriosus Botalli (DAB). However, at angiography the distal stent ending was found to reach into the proximal part of the DAB. Although still located within the predefined lading zone, this indicated a slight stent migration after deployment (Fig. 5). As confirmed by Doppler sonography and angiography, this migration did not result in an impairment of DAB or PA perfusion in this fetus (Suppl. Video 2, Fig. 5). In another fetus (F2), echocardiography revealed that one of the pulmonary valvular leaflets could not be fully identified, suggesting some impairment of the cusp by the proximal stents' struts. In the third fetus (F3), no signs of migration or pulmonary cusp impairment could observed *in vivo*, indicating optimal positioning. In all fetuses (F1–3), contrast angiography as well as transepicardial echocardiography displayed normal perfusion of the pulmonary vasculature as well as of the DAB (Fig. 5).

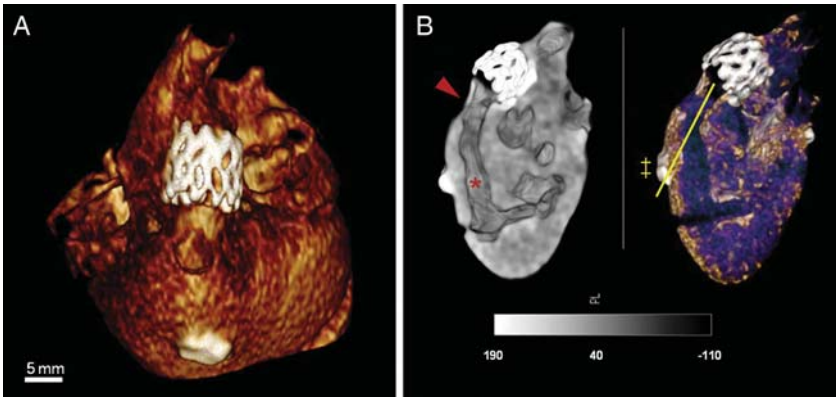

Figure 3: A three-dimensional CT reconstruction of the fetal heart verifies the position of the self-expanding nitinol stent in the distal pulmonary artery (A). The delivery system was advanced through the right ventricle (B, *) to the landing zone and the stent was deployed supravalvular distal to the pulmonary valve annulus (arrow, B). The ventricular insertion site was closed using a pledged purse-string suture (B, †).

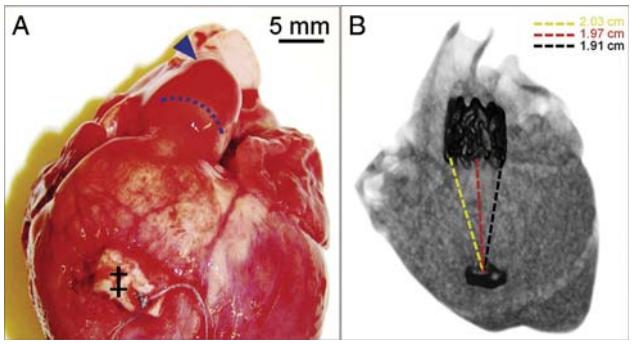

Figure 4: Post-mortem analysis confirmed the stent position in the pulmonary artery (A, line: proximal end; arrow: distal end) ~2 cm distal from the antero-apical entry point (A, † entry point; B, distance to entry point).

Post-mortem examination

After *in vivo* assessment, fetuses were harvested and examined with regard to stent position, native leaflet impairment, or further procedural complications. In all fetuses, post-mortem analysis revealed strut impregnations on the wall of the PA but lacking any laceration or perforation of the vessel wall (Fig. 4). In one fetus (F2), the intra-operative sonographic finding of a too-proximal stent positioning could be confirmed, as one of the native pulmonary leaflets was partly impaired by one of the proximal stent strut endings. In addition, in fetus F1, the angiographic stent position could be confirmed with the distal stent ending reaching into the proximal DAB. In fetus F3, the stent was situated in the distal PA not covering any of the native pulmonary leaflets. No signs for thoracic bleeding or stent-associated obstruction were observed.

DISCUSSION

Congenital heart disease (CHD) affects almost 1% of all newborns [16] and represents a major cause for spontaneous abortion and stillbirth [17]. Fetal cardiac intervention has thus emerged as a novel treatment concept for a selected group of patients with CHD [1,5]. In particular, balloon valvuloplasty of heart valves has been established as a routine clinical procedure in several centers worldwide. The patients of these interventions mainly include either fetuses with high-grade aortic stenosis with evolving hypoplastic left-heart syndrome (HLHS) or patients with pulmonary atresia with evolving hypoplastic right-heart syndrome (HRHS) (reviewed by McElhinney et al. [1]). The prenatal correction of these congenital cardiac defects, as a definite surgical repair at the earliest time point, could be associated with several therapeutic advantages, including prevention of fetal demise in selected cases [1,5], prevention of intrauterine cardiac maldevelopment and reduction of severity of postnatal disease [1], enhanced (scarless) healing reactions in early-gestational fetuses [18], capacity for myocyte proliferation [19] as well as a high regenerative capacity [20] in fetuses promoted by high blood levels of progenitor cells [21]. Although first clinical experiences of fetal heart-valve intervention, including balloon valvuloplasty, seem highly promising [1,5], restenoses of the obstructed segments have been repeatedly reported after prenatal cardiac-balloon interventions [4,14].

The orthotopic fetal implantation of stented heart valves with growth-adaptive capacities could combine an optimal and sustained dilation of the stenotic regions and full restoration of valvular functionality with the advantages of a catheter-based minimally invasive implantation approach. The presented study demonstrates for the first time the principal technical feasibility and acute safety of a fetal stent implantation into the PA via a catheter-based trans-apical hybrid technique in the ovine fetal model.

Recent experimental as well as pioneering clinical attempts have focused primarily on percutaneous and/or transuterine interventional approaches for treating severe aortic and pulmonary stenoses [1–13]. While several experimental studies have also addressed the feasibility of using fetal cardiac bypass [22,23], open-fetal-cardiac surgery for valvotomy has not yet been successfully achieved. Although allowing for a definite repair of the structural defect, fetal loss following fetal open-heart interventions has been reported [1].

In 2008, Schmidt et al. [24] already demonstrated the feasibility of percutaneous ultrasound-guided cardiac stenting of the atrial septum in the ovine fetal model. Although they claimed the principal feasibility of this percutaneous stent delivery *in utero*, they observed severe complications by laceration of adjacent fetal organs. While they experienced unsuccessful implantation via the transhepatic route, they also reported major

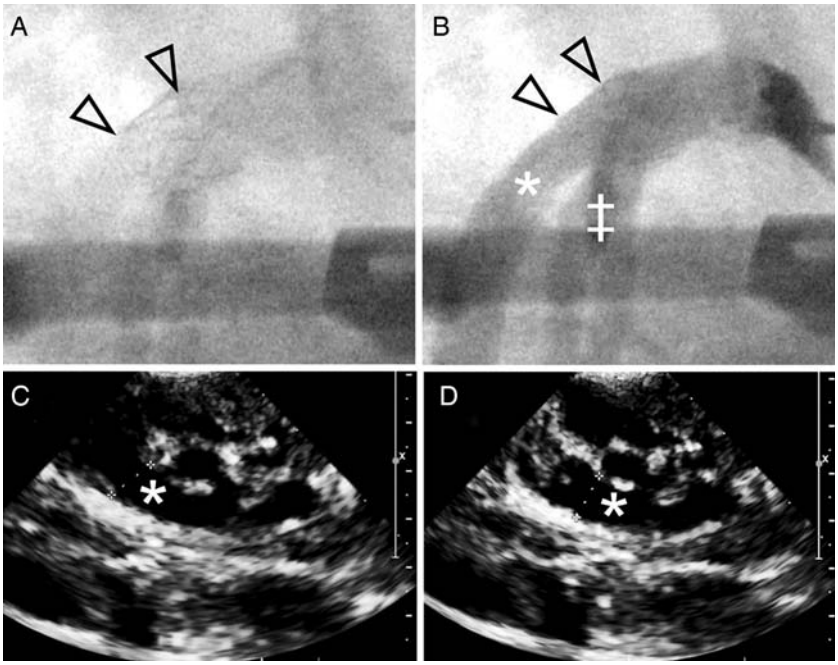

Figure 5: The stent (A and B, arrows) was deployed into the pulmonary artery (C and D, *). After delivery adequate perfusion of the ductus arteriosus Botalli (B, *) as well as the pulmonary arteries (B, ‡) was observed using contrast angiography (A and B).

laceration of the inferior vena cava via the transpulmonary route. Given their optimal device diameters of <4 French, percutaneous-valve-implantation attempts, by requiring significantly larger devices (present study: 14 French), would certainly result in even more extensive fetal complications when using these routes. Although aiming at the lowest perioperative trauma, possible fetal-heart-valve implantations will have to strike the balance between large device diameters and minimally invasive delivery routes.

Also with regard to minimizing the perioperative trauma for the fetus and the mother, several previous experimental studies in the ovine model on fetal cardiac catheterization have mainly focused on the establishment of noninvasive catheterization techniques [2,3,8,9]. Kohl et al. [2] first assessed a fetoscopic and open transumbilical cardiac-catheterization procedure. Although their indirect approach was minimally invasive, fetal bleeding at the time of sheath removal or dislodgment was described as a serious complication. Also in further investigations in the same model assessing a fetoscopic direct cardiac access, bleeding occurred and the acute loss of fetuses during the procedure could not be prevented [9]. In a further ovine experimental study by Jouannic et al. [3], a fetal transhepatic ultrasound-guided cardiac catheterization was investigated as a potential alternative route for fetal cardiac intervention. In this indirect, closed approach, again several fetuses were lost due to acute bleeding complications. When using the ultrasound-guided cardiac puncture and balloon dilation in human fetuses with anatomic cardiac obstructions, also several complications including pericardial tamponade, hematothorax or even fetal death have been reported [1,5,7,25]. In addition, in some cases, repeated punctures of the heart were necessary to optimize positioning of interventional devices [4], which further increased the risk for complications.

Although having the limitation of a uterine incision, no major extracardiac complications occurred in the presented study using a hybrid intervention. Only – as previously reported [4,5] – perioperative bleeding during the insertion and removal of the delivery device occurred and was substantial in one animal. Even if these hemorrhagic complications can partly be attributed to the prototypic design of the implantation device, bleeding at the insertion site certainly displays also a major hurdle for future prenatal trans-apical-valve implantations. These bleeding complications, however, could clearly be reduced because of the experience gained in the first animal, suggesting a steep procedural learning curve, as reported by previous studies [7,14]. The long-term fate of the bleeding complications will have to be addressed in longer follow-up investigations. In the end, it seemed that acute hemorrhagic complications could eventually be fully avoided when using a more technically mature device for trans-apical fetal implantations.

A further procedural complication observed in the presented interventions was the suboptimal positioning of one of the stents (F1) in the PA. According to the steep learning curve reported above, the other stents could be deployed within the landing zone. Besides the difficulty of the beating-heart approach and the diminutive dimensions of the fetal heart, the exact positioning was further challenged by the narrow landing zone, allowing for only 2 mm proximal and distal tolerance.

The presented study demonstrates the principal technical feasibility and acute safety of a fetal-stent implantation via a catheter-based technique using the trans-apical route. Even if percutaneous or fetoscopic trans-apical cardiac approaches would be desirable, they lack control of direct fetal cardiac hemorrhage – a major issue in fetal cardiac catheterization. The presented transuterine open-chest closed-heart hybrid technique represents a possible alternative for future approaches on the route to prenatal heart-valve repair, also allowing for the insertion of large devices, such as heart-valve delivery systems. Further long-term studies are necessary to evaluate fetal myocardial tolerance and long-term survival of the presented technique before it may be applied to the clinical setting.

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Conflict of interest: L.B. is an employee of IMM Recherche, Paris, France.

SUPPLEMENTARY DATA

Supplementary material (Video 1 and Video 2) is available at *EJCTS* online.

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