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CASE REPORT
Coronary heart disease

Myocardial ischaemia caused by bilateral coronary ostial stenosis from pseudointimal membranes in a full root freestyle valve: a case report

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Background Coronary artery ostial stenosis is a rare but well-known complication to aortic root replacement. The occurrence of this complication in patients with the Medtronic Freestyle bioprosthesis is poorly described. We report a case of late bilateral coronary ostial stenosis due to pseudointimal membranes within a Medtronic Freestyle bioprosthesis, resulting in acute coronary syndrome.

Case summary In 2013, a 43-year-old male patient received a Medtronic Freestyle bioprosthesis as a full aortic root implantation due to endocarditis with root abscess. Preoperative coronary angiography was normal. The patient, who had no previous symptoms of coronary ischaemia, presented with severe chest pain and acute coronary syndrome in 2017. Coronary angiography and electrocardiogram-gated contrast-enhanced cardiac computed tomography showed bilateral coronary ostial stenosis. The patient was successfully treated with coronary artery bypass grafting. Intraoperative inspection revealed pseudointimal membranes covering the coronary ostia. Histology showed fibrointimal thickening with areas of inflamed granulation tissue.

Discussion Bilateral coronary ostial stenosis is a severe, potentially life-threatening condition, and a possible complication to implantation of the Medtronic Freestyle bioprosthesis as a full root. The phenomenon may occur late and should be distinguished from arteriosclerotic coronary artery disease.

Keywords Coronary ostial stenosis • Myocardial ischaemia • Pseudointimal membranes • Medtronic Freestyle bioprosthesis • Reimplanted coronary arteries • Case report

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Learning points

- Patients with full root implantation of Medtronic Freestyle bioprosthesis are at risk of bilateral coronary ostial stenosis, due to pseudointimal membranes.
- The pseudointimal membranes can result in myocardial ischaemia even years after surgery.
- Bilateral coronary ostial stenosis in Medtronic Freestyle bioprosthesis can be difficult to treat, with high risk of further complications or death.

Introduction

Aortic root replacement can be achieved by full root implantation of the porcine Medtronic Freestyle stentless bioprosthesis (FB), which includes coronary artery reimplantation.[1] Subsequent coronary ostial stenosis is a known complication; yet its exact morphology, aetiology, and frequency are poorly described.[2,3] Case reports indicate a high mortality rate (33% among reported cases) and additionally a risk of further complications, leaving mortality due to undiagnosed cases unknown.[4–6]

We present a unique case of late bilateral coronary ostial stenosis in a full root FB occurring as late as 4 years after surgery. This report presents and discusses the intraoperative findings, with the aim to add to the understanding of pathophysiology and treatment of this unusual but potentially fatal complication.

Timeline

2007	A 37-year-old man presented in with rheumatic mitral stenosis, mild aortic insufficiency, and pulmonary hypertension. He was referred to surgical treatment in his country of residence, which was not performed.
February 2009	Presented with heart failure, signs of endocarditis, and sepsis with excessive organ failure.
	Urgent surgery with implantation of a mechanical mitral valve and a minor commissurotomy of the aortic valve cusps.
January 2013	Double valve re-endocarditis affecting the prosthetic mitral- and native aortic valve. Urgent surgery with implantation of a biological mitral valve (St. Jude Medical Epic, size 27 mm) and, due to aortic root abscess, a full root implantation of an Medtronic Freestyle stentless bioprosthesis (MFB) (size 23 mm) in the aortic position including reimplantation of the coronary ostia. Preoperative coronary angiography had shown normal coronary arteries, without stenosis.
June 2017	Diagnosed with non-ST-elevation myocardial infarction. Preoperative computed tomography and coronary angiography showed 90% ostial stenosis of both left main and right coronary artery.
	Emergent re-reoperation with coronary artery bypass grafting of left anterior descending branch of the coronary artery and right coronary artery.
	Intraoperative findings included endoluminar glass-like pseudointimal membranes covering the distal anastomosis of the MFB, as well as both of the coronary ostiae.

Case presentation

A 43-year-old Pakistani man was admitted to Rigshospitalet, University Hospital of Copenhagen, in January 2013, with complex mechanical mitral valve- and native aortic valve endocarditis, complicated by aortic root abscess. Medical history included heart failure after rheumatic fever with mitral stenosis and mild aortic insufficiency, treated with mitral valve replacement and a minor commissurotomy of his fused aortic valve cusps in 2009. The patient was otherwise healthy and had no risk factors for coronary artery disease. Preoperative coronary angiography was normal (*Figure 1A* and *B*). The patient was emergently operated with implantation of a biological mitral valve (St. Jude Medical, Epic, size 27 mm) and a full root FB (size 23 mm) in the aortic position. A FB was chosen since the tissue quality and irregularity of the revised root including the presence of a rigid biological mitral valve prosthesis did not allow for implantation of the rigid suture-ring of a stented (mechanical or biological) aortic valve prosthesis. Furthermore, a homograft was not available. Reimplantation of the coronary ostia was performed in a standard fashion with the button technique. The angle of the porcine coronary ostia is 90° relative to the centre of the aortic root, whereas the human coronary ostia assume an angle of 120°. The FB was therefore oriented so that the left coronary artery was reimplanted in the left porcine ostium, while the right coronary artery was reimplanted higher and further to the right in the right sinus of the FB, to avoid kinking or stretching of the coronary *(Figure 2)*. The patient was discharged after 6 weeks of targeted intravenous antibiotic therapy, with atrial fibrillation, and newly diagnosed diabetes mellitus

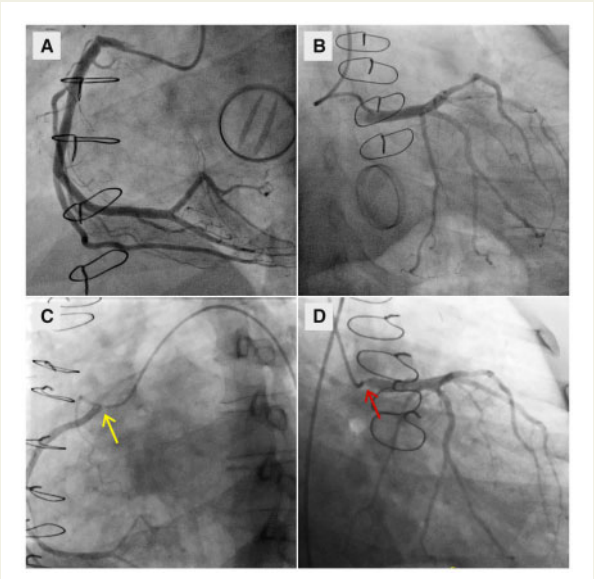


Figure 1 Coronary angiography. (*A* and *B*) Preoperative coronary angiography from 2013 showing normal coronary arteries, without stenosis. (*C* and *D*) Preoperative coronary angiography from June 2017. The yellow arrow shows 90% stenosis of the right coronary artery. Red arrow shows 90% stenosis of the main stem of the left coronary artery.

type 2. He was prescribed warfarin (target international normalized ratio 2–3), enalapril 2.5 mg, metformin 1000 mg, and metoprolol 50 mg. Follow-up transoesophageal echocardiography 41 days postoperatively showed a well-functioning FB valve in the aortic position.

In June 2017, the patient presented with chest oppression, pain in the left arm and hand, as well as shortness of breath. Physical examination revealed a discrete heart murmur along with an irregular rhythm. Lung auscultation presented normal vesicular breath sounds and extremities were without oedema. Except from the chest oppression, the general condition was good and further physical examination normal. Electrocardiogram showed atrial fibrillation and new ST depressions and T-wave inversions in I, II, V5, V6, and ST elevation in aVR (*Figure 3*). Troponin T samples showed increasing concentration reaching a maximum of 196 ng/L (normal range < 14 ng/L). A contrast-enhanced cardiac computed tomography (CT) showed significant left- and right coronary ostial stenosis but no sign of atherosclerosis (*Figure 4*). Preoperative coronary angiography confirmed this finding, showing 90% stenosis in both ostia and otherwise normal coronary arteries (*Figure 1C* and *D, Videos 1 and 2*). Preoperative transthoracic echocardiogram showed left ventricular ejection fraction of 50%, and excellent prosthetic aortic- and mitral valve function. Due to the risk of non-dilatable ostial tissue and stents protruding into the aortic lumen, the case was not found suitable for percutaneous coronary intervention (PCI). The patient underwent emergent reoperation with the aim to either replace the FB or to perform revascularization. Intraoperatively, after partial opening of the distal anastomosis between the FB and the ascending aorta, we found pseudointimal glass-like membranes, which covered the distal anastomosis between the FB and the ascending aorta as well as both coronary ostia, leaving the latter with high-grade stenoses (*Figure 5*). The membranal tissue was brittle, not invading the FB and could thus be peeled of the FB tissue in strips. Since the pseudointimal membranes extended from the anastomotic sites and into both coronary arteries, and since surgical detachment of the membrane tissue could only be done radically in the proximal parts of the vessels, we considered

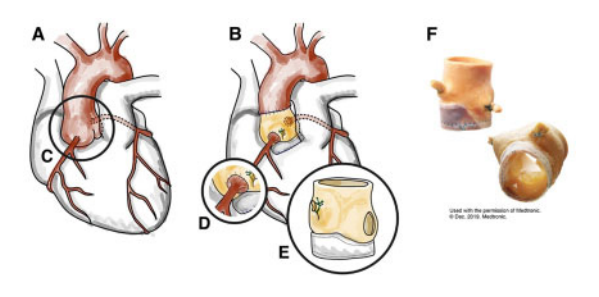


Figure 2 Full root implantation (*B*) of the Freestyle Medtronic stentless bioprosthesis (*F*—courtesy Medtronic), for replacement of the aortic root (*C*). The porcine left main stump was used for reimplantation of the left coronary artery, whereas the porcine right coronary stump was kept unused (*E*). Coronaries were reimplanted using the buttoned technique, i.e. leaving a cuff of native aortic tissue to use for suturing the anastomosis to the freestyle (*D*).

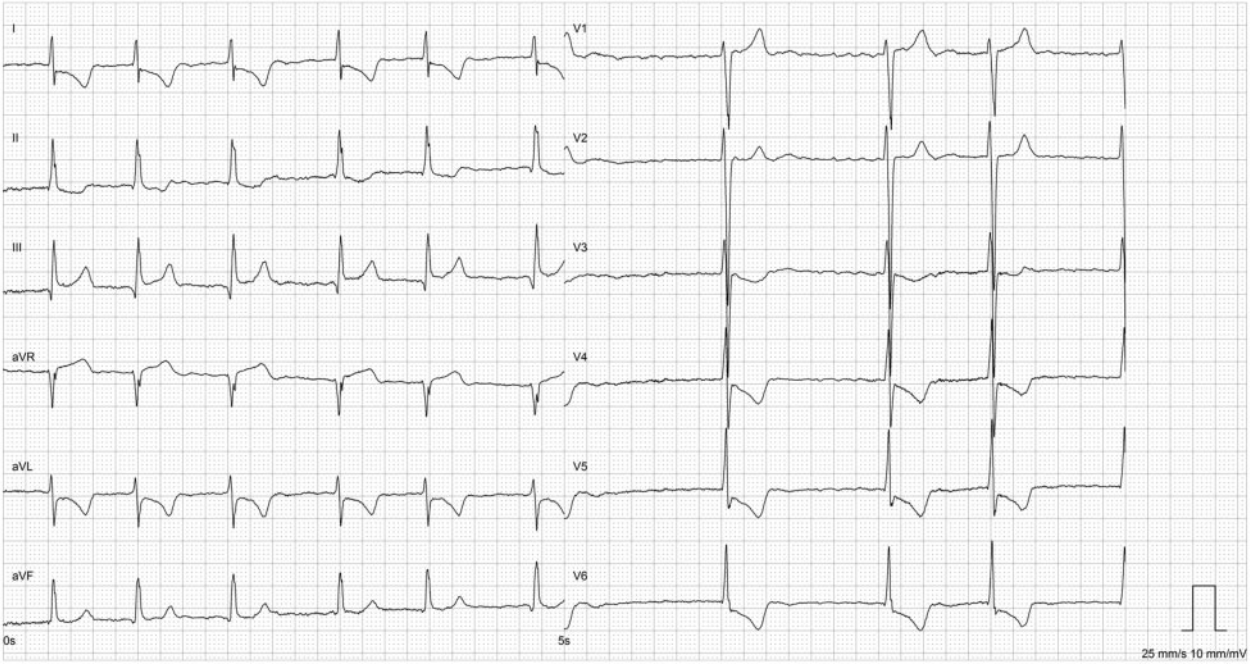


Figure 3 Electrocardiogram from the admission in June 2018. Note the ST depressions and T-wave inversions in I, II, V5, V6, and ST elevation in aVR. The patient also has atrial fibrillation.

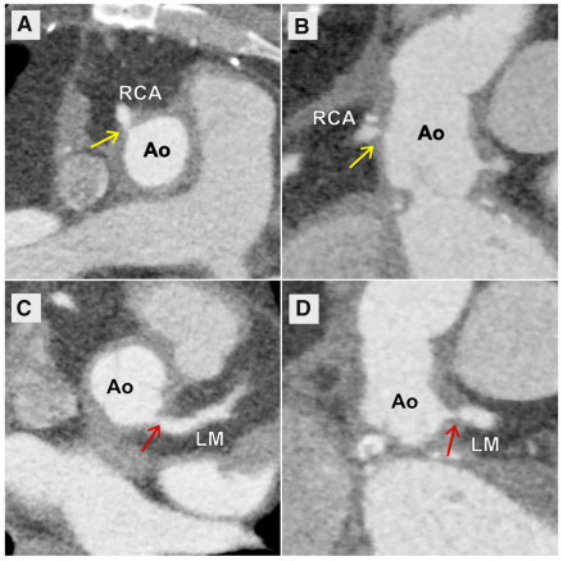


Figure 4 Preoperative 4D contrast-enhanced cardiac computed tomography from 2017 in cross-sectional (*A* and *C*) and sagittal view (*B* and *D*). The yellow arrow shows ostial stenosis of right coronary artery. The red arrow shows ostial stenosis of left main coronary artery. Ao, aorta; LM, 'left main': main stem of the left coronary artery; LVOT, left ventricular outflow tract; RCA, right coronary artery.

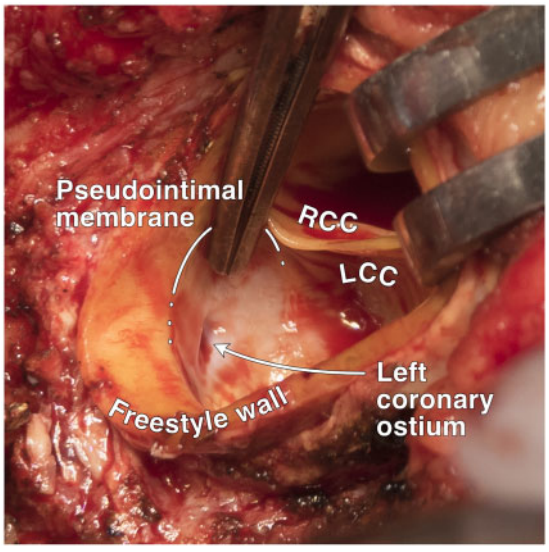


Figure 5 Preoperative photograph, from 2017, showing the ostial stenosis of the left main coronary artery. Looking down through the aortotomy, we see the aortic valve to the right and the left coronary ostium to the left. Note how the glass-like pseudointimal membrane covers the walls of the left coronary sinus and narrows the ostium circumferentially, leaving <50% of the expected orifice. LCC, left coronary cusp of the aortic valve; RCC, right coronary cusp of the aortic valve.

replacement of the FB and subsequent reimplantation to carry a considerable risk of dissection between the pseudointimal tissue and native tissue, and subsequent coronary occlusion by the remaining membrane tissue. Likewise, PCI could potentially also dislodge the membrane and cause occlusion. Therefore, after collecting a tissue sample of pseudointimal membrane, the patient had coronary artery bypass grafting (CABG) performed with separate venous grafts to the left anterior descending artery and the right coronary artery (RCA). The patient recovered uneventfully, aside from a smaller procedure due to epigastric fascial rupture.

Acetylsalicylic acid 75 mg was added to previous medication and metoprolol was reduced to 25 mg. Histological examination of the explanted pseudointimal membranes showed fibro-intimal thickening with areas of inflamed granulation tissue. There was no sign of acute inflammation, calcifications, foreign bodies, or amyloidosis.

In September 2017, a follow-up cardiac CT and transthoracic echocardiography, performed due to complaints of chest pains, showed a small (2.3 mL) pseudoaneurysm arising from partial rupture of the last opened (distal) anastomosis between the FB and the aorta (*Figure 6 and Video 3*). Due to the patient's numerous previous reoperations, and the small size of the pseudoaneurysm, we chose a conservative, non-surgical strategy. Repeat follow-up cardiac CT, performed 3 months later, showed reduction of the pseudoaneurysm to 1.4 mL. and video 3

During follow-up in November 2019, the patient still suffered from exercise-induced chest pains. Myocardial perfusion scintigraphy from 2018 showed exercise-induced myocardial ischaemia of 6–8%, probably due to previous myocardial infarction. Coronary angiography from 2018 confirmed complete revascularization. Transthoracic echo showed mild-moderate stenosis of the FB valve and well-functioning biological mitral valve.

Discussion

Previously published cases describe acute coronary syndrome due to bilateral coronary ostial stenosis between 2 and 18 months after receiving the FB.[4–7] In contrast to this, our patient presented 4 years after surgery, suggesting another pathophysiology. Furthermore, this is the first case where the mechanical cause for the bilateral coronary ostial stenosis has been identified *in vivo*, namely pseudointimal membranes covering the coronary ostia. This complication does not seem to be caused by atherosclerosis nor by technical default, since the suture lines of the anastomoses were not involved in the stenosis formation.

The mortality rate of this complication is unknown due to the limited amount of previous reports on the subject, and it is therefore not unlikely that patients may have suffered from this complication without diagnosis. In a literature search, we found four case reports describing five patients treated for bilateral coronary stenosis presenting between 2 and 18 months after aortic root replacement with FB.[4–7] In two patients, the primary treatment was CABG: one of these patients died postoperatively in the intensive care unit,[4] and one received PCI 1 year later due to unstable angina pectoris.[5] Two other patients received PCI as the primary

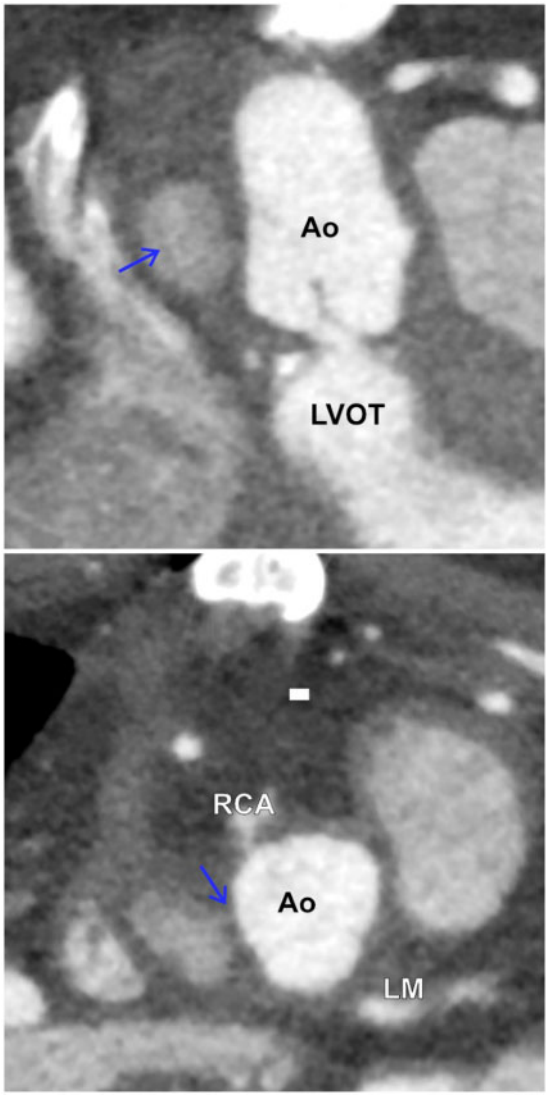


Figure 6 Pseudoaneurysm on computed tomography scan from June 2017 after CABG. The blue arrow marks the pseudoaneurysm, which is only partly contrast-filled, and the very small connection to the aortic lumen. Ao, aorta; LM, 'left main': main stem of the left coronary artery; RCA, right coronary artery.

treatment. One of these patients suffered restenosis and underwent re-PCI 7 months later,[6] while the other patient recovered without subsequent restenosis.[7] The fifth patient died during coronary angiography.[4] The patient presented in the present report received CABG, which was complicated by pseudoaneurysm formation. Thus, only one out of six patients with FB-induced coronary stenosis went through uncomplicated treatment for coronary ostial stenosis. The exact causes of these complications to reintervention are unknown, but we suspect that dissection of the pseudointimal membranes may occur due to mechanical disturbance such as catheterization during PCI. This may lead to coronary artery obstruction, which could explain the high incidence of restenosis after PCI, and one death during coronary angiography. Theoretically, from a revascularization point of view, treatment with CABG would seem as a safer solution to avoid mechanical disturbance, but this approach naturally carries the risk of an open-heart reoperation and complications such as restenosis and pseudoaneurysms (*Table 1*).

The pathophysiological mechanism causing bilateral coronary ostial stenosis in the FB remains unknown, yet several theories have been suggested: (i) local pressure necrosis and subsequent intimal proliferation due to cannulation of the coronary ostia with cardioplegia catheters[8,9]; (ii) a genetic predisposition for developing ostial coronary stenosis after aortic valve replacement[10]; (iii) turbulence in the blood flow due to aortic valve replacement invoking intimal thickening and fibrous proliferation of the ostia[8]; and (iv) an immunological reaction towards the FB causing coronary ostial stenosis.[4,5] Another potential mechanism for late occurring coronary stenosis from to pseudointimal membranes could be local fibrosis induced by mechanical tension from inappropriate stretch or 'pull' of the coronary arteries during reimplantation. This mechanism would be comparable to other situations in which fibrosis occurs from stretch of the luminal surfaces of the heart and vessels, such as left atrial fibrosis secondary to mitral stenosis or regurgitation or left ventricular fibroelastosis in aortic stenosis. We sought to elucidate this option, by comparing the placement and orientation of the left- and right coronary arteries before and after reimplantation in the FB, knowing well that this would only be indicative. As shown in *Figure 1*, the proximal part of the left coronary artery does not seem to change its spatial orientation

Table 1 Treatment options for ostial coronary stenosis by pseudointimal membrane

	Pro	Con
PCI	• Fast treatment	• Risk of 'dissection' by separation of pseudointimal tissue from FB or native tissue
		• Risk of a non-dilatable fibrotic lesion
	• Avoidance of resternotomy	• Risk of restenosis
CABG	• No mechanical disturbance of pseudointimal membranes	• Risk of future graft occlusion in patient with (potentially) otherwise healthy coronaries
	• No reaortotomy	• Resternotomy
Surgical resection of pseudointimal membranes	• No infliction of possibly limited graft patency	• Risk of 'dissection' by separation of pseudointimal tissue from FB or native tissue, occlusion, stenosis or embolism from leftover pseudointimal membrane
		• Resternotomy
		• Reaortotomy

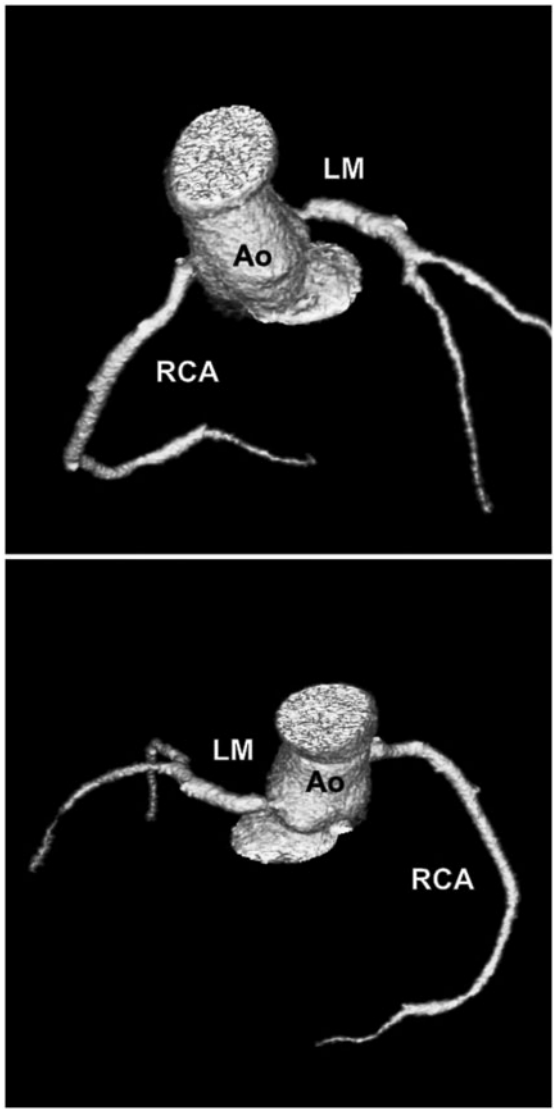


Figure 7 Three-dimensional volume rendering from the computed tomography scan in *Figure 3*, showing the aortic root and coronary arteries from different angles. Note the almost perpendicular departure of the coronary arteries from the aortic root, suggesting no tension as a consequence of the reimplantation.

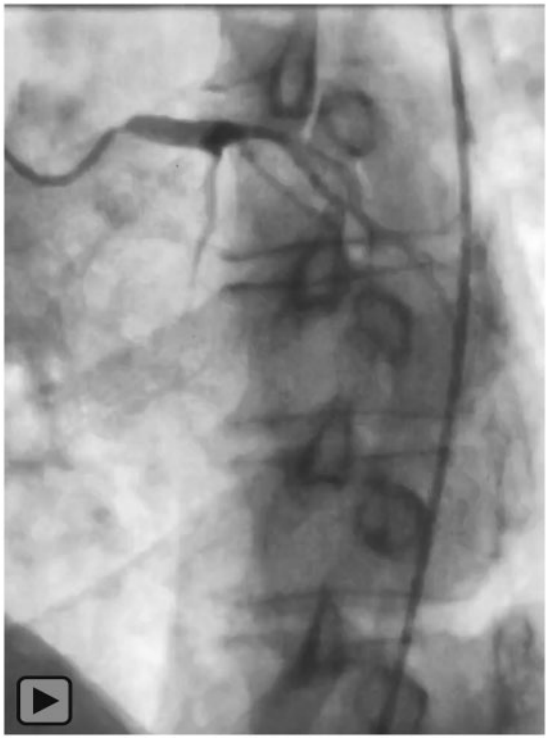
significantly after surgery, whereas the RCA does seem to assume a more transverse orientation. As opposed to this, post-surgical 3D volume rendering CT images (*Figure 7*) show that both coronary arteries depart from the FB at almost right angles. Any surplus stretch, tension or 'pull' during initial coronary reimplantation, must be assumed to translate into more acute angulation between the coronaries and the root prosthesis. Since this does not seem to be the case, we think that this hypothetical mechanism for late occurrence of pseudointimal membranes remains suggestive.

The present report is not able to establish a causal association to support or to reject the above suggestions, however, the late presentation of the phenomenon in this case suggest that initial mechanical injury is not a likely cause. The endoluminar non-invasive structure of the membranes, as well as the fibrotic and inflamed tissue could be compatible with an immunological reaction towards the FB.

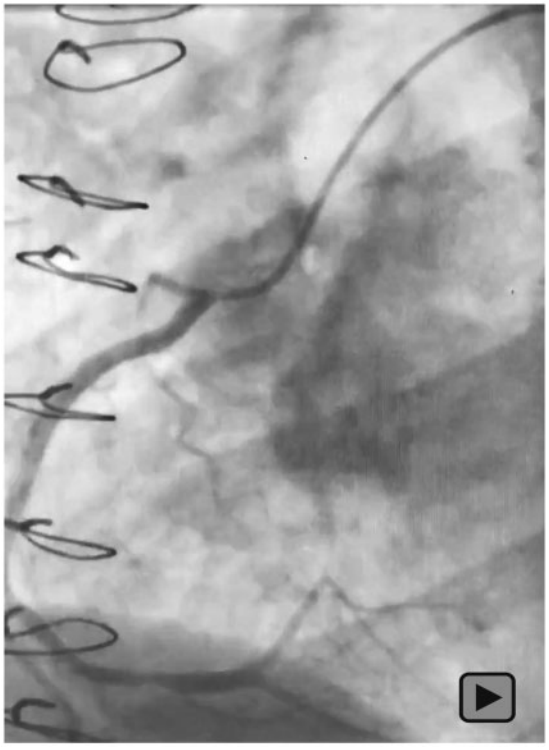
Because aortic root replacement, by virtue of the procedure, necessitates coronary reimplantation, previous aortic root replacement is an alarm sign in patients with chest pain or other symptoms of ischaemic heart disease. Coronary ostial issues must always be considered, in addition to—and in absence of—conventional atherosclerotic coronary disease and related risk factors. The clinical presentation of pseudointimal membranes is likely similar to other ostial issues such as technical or plaques, although the symptoms of pseudointimal membranes seems to present later. Whether the membranes form late postoperatively or is a result of gradual progress of an early process is to this point unknown. As we cannot know why or when membrane formation is initiated and how long it takes, we can only assume that the membranes builds up gradually and the symptoms occur as the stenosis narrows. From a purely surgical point of view, it may therefore be advocated to reimplant the coronary arteries using large buttons, since any subsequent proliferative membrane formation will take longer time to develop and to cover the ostia.

Conclusion

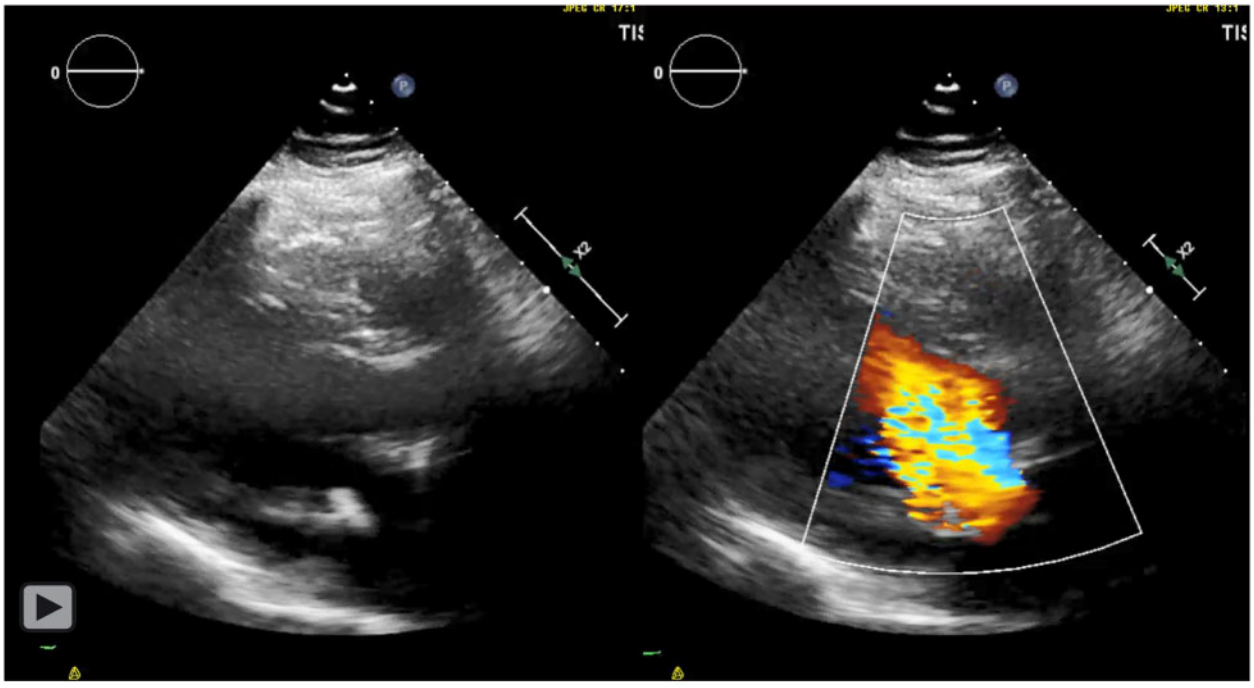
Full root freestyle implantation with reimplantation of the coronary arteries may be complicated by bilateral ostial stenosis caused by pseudointimal membranes covering the coronary ostia. Mechanical disruption of the membranes during coronary angiography may cause pathological dissection of these and thus occlusion and ischaemia. Caution is therefore warranted for patients with reimplanted coronary ostia, who present with symptoms of cardiac ischaemia. These patients do not necessarily have risk factors of coronary artery disease and the complication may occur years after surgery. Further research is warranted to elucidate the pathophysiological mechanism causing bilateral coronary ostial stenosis in patients with FB, and whether this phenomenon may occur in other cases of coronary reimplantations.



Video 1 Preoperative coronary angiography video from 2017 showing 90% ostial stenosis of left main coronary artery.



Video 2 Preoperative coronary angiography video from 2017 showing 90% ostial stenosis of right main coronary artery.



Video 3 Transthoracic echocardiography 3 months postoperatively 2017, showing parasternal long-axis view of the freestyle in aortic position, with and without colour Doppler.

Lead author biography

Kirstine Bekke studied medicine at the University of Copenhagen, Denmark. She graduated in January 2020. Her main interests are cardiothoracic surgery and research. During her studies, she has worked as a research assistant in the Department of Cardiothoracic Surgery, Rigshospitalet, University of Copenhagen, Denmark. During her studies, she also completed two clinical stays abroad respectively at Universitätsklinikum Münster, Germany and Mbulu Hospital, Tanzania.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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