Screening, complications and outcome of aortic valve implantation
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Chapter 4

Thromboembolic events after transcatheter aortic valve implantation

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ABSTRACT

BACKGROUND
Thromboembolic events are a major complication after transcatheter aortic valve implantation (TAVI). The occurrence of thromboembolic events within a week after TAVI in half of the cases suggests a procedure related cause.

AIMS
To report the course and outcome of thromboembolic events, and to elucidate the origin of thrombi, after TAVI.

METHODS
We report the course and outcome of three patients with aortic valve stenosis treated by TAVI, complicated by a thromboembolic event. All cases were followed by mechanical thrombectomy, which created an opportunity to perform histopathologic analysis of the retrieved material.

RESULTS
We found thrombectomy material originating from the aortic valve and outflow tract. In addition, analysis of the timing of thrombus formation revealed thrombi formed during as well as soon after the TAVI procedure.

CONCLUSION
Analysis of thrombectomy material provides insight in the pathophysiologic mechanism of cerebral infarcts during TAVI. Procedure related manipulation; in combination with the use of thrombogenic material plays an important role in the development of ischemic stroke after TAVI.
INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has evolved towards the standard treatment for patients with severe aortic valve stenosis at high risk for surgical valve replacement. The occurrence of a thromboembolic event is a feared major complication. Both clinical apparent strokes and, more frequently occurring, silent cerebral infarcts have been reported in association with TAVI. According to a weighted meta-analysis, 30-day stroke incidence was 3.2% for major stroke and 4.0% for combined major and minor stroke(1). The occurrence in half of these events within one week suggests a procedure related origin. Manipulation of the aortic valve and vessel wall may induce embolization during, or shortly after TAVI. In addition, the prosthesis implantation itself may induce platelet aggregation, activating of coagulation pathways, ultimately leading to thromboembolic events. To elucidate the origin of the thrombus, causing stroke after TAVI, we report the histopathologic analysis of thrombectomy material in three cases of thromboembolic complications after aortic valve implantation.

CASES

Patient A, a 72 year old, extremely obese woman (BMI 52.7 kg/m2). A transfemoral TAVI was performed under conscious sedation with propophol. Heparin was administered before sheath-insertion, to achieve an activated clotting time of 250-300 seconds according to institutional protocol. A 29mm Medtronic CoreValve was implanted (Medtronic, Minneapolis, Minnesota, USA). Due to complicated deployment with suboptimal positioning of the prosthesis, a second CoreValve was implanted successfully. Following TAVI, the patient’s consciousness declined. A Computed Tomography Angiography (CTA) scan of the brain demonstrated a basilar artery occlusion. According to hospitals protocol, intravenous thrombolysis was contraindicated by the TAVI procedure. Thrombectomy was performed 6 hours after TAVI. Recanalization was successful, however without clinical improvement. Brainstem reflexes remained absent, and the patient deceased one day after TAVI. Brain autopsy revealed extensive ischemic-reperfusion damage. Basilar artery cross-sectional analysis showed no atherosclerotic changes of the vessel wall, indicating the embolic nature of the thrombectomy material. Cardiac autopsy showed two CoreValves in the aortic valve position. Removal of the prostheses exposed mural thrombus at the site of impression in the left ventricular outflow tract (Figure-I image A to C). Histologic analysis, revealed thrombus composed of a layered pattern of erythrocytes and fibrin and to a lesser extent platelet aggregates and neutrophilic granulocytes. There were no signs of lytic changes or karyorrhexis, indicating it was
fresh thrombus of less than one day old (Figure-I image D). Further staining showed fragments of elastic arterial wall, originating from the aortic wall. The material derived from underneath the prostheses was of similar histologic appearance. These results suggest embolization to the basilar artery originating from fresh mural thrombus and aorta wall from underneath the prostheses, during or directly after TAVI.

**Patient B**, an 87 year old woman with atrial fibrillation and pacemaker implantation in her medical history. Her preoperative medication included coumarin derivatives, which were discontinued 3 days preprocedurally and carbasalate calcium daily 100 mg. A transaortic TAVI was performed successfully with a 26mm Edwards SAPIEN 3 prosthesis (Edwards Lifesciences, Irvine, California, USA). Per-procedural heparin was administered to achieve activated clotting time >300s. Coumarine was restarted one day post-TAVI. Postprocedural echocardiography revealed paravalvular regurgitation. Hence, eight days post-TAVI, postdilatation was performed under local anesthesia. During postdilatation, a right-sided hemiparesis and aphasia were noted. A CT-scan of the brain confirmed an ischemic stroke, with a dense media sign and occlusion of the left Middle Cerebral Artery at CTA (Figure-II image A). Two hours after symptom onset, thrombectomy resulted in complete recanalization (Figure-II image B and C). The patient was discharged with moderate hemiparesis and mild expressive aphasia. Histologic analysis of the thrombectomy material revealed a composition dominated by platelets and fibrin and to a lesser extent erythrocytes admixed with large numbers of granulocytes. Cellular components showed lytic changes indicating that the thrombus was between 1 and 5 days old. A salient feature was the presence of numerous Neutrophil Extracellular Traps (NETs), which have been described mostly in lytic thrombi (Figure-II image D). These findings suggest that manipulation during postdilatation caused dislodgement of an existing thrombus to the Middle Cerebral Artery.

**Patient C**, an 83-year old woman. A transfemoral TAVI with a 26mm CoreValve was performed under local anesthesia. Directly after the successful implantation, a drooping mouth was noted. Neurological examination revealed progressive left sided hemiparesis. On the CT-scan a dense media sign was seen and CTA showed an occlusion of the right Middle Cerebral Artery (Figure-III image A). Thrombectomy within four hours resulted in complete recanalization. (Figure-III image B and C). The patient was discharged without any neurological disability. Histological staining of the material derived at thrombectomy showed a fresh thrombus with a layered pattern of mainly platelets and fibrin, mixed with areas of erythrocytes and to a lesser extent, granulocytes and few NET structures. A striking feature was
the elastin rich fragment of arterial wall, suggesting that manipulation of the fragile aortic wall, caused dislodgement of this particle from the aorta (Figure-III image D).

**DISCUSSION**

The occurrence of a thromboembolic event is a major complication of TAVI procedures with immediate and long-term implications. The difference in outcome of our patients might be partly explained by the different locations of the thrombus. However, also a fast performance of the thrombectomy seems essential. Recently a large randomized controlled trial (MR CLEAN), proved the clinical benefits of endovascular treatment in patients with an ischemic stroke caused by a proximal occlusion of the anterior circulation, performed within 6 hours after symptom onset (2). The procedure of patient A was performed under sedation while the other procedures (postdilatation and TAVI) were performed under local anesthesia only. The use of propophol conceivably delayed recognition of stroke symptoms, with a significant time delay in the start of thrombectomy. A procedure under local anesthesia, allows immediate recognition of changes in neurological function. This potentially shortens the time between the onset of symptoms and reperfusion by thrombectomy. Considering the high risk of stroke related to TAVI procedures, we advocate that in-hospital cerebral thrombectomy service should be available when performing TAVI.

Previous reports focused on material, captured by embolic protection devices during the TAVI procedure (3). However, thus far, no reports are available on the embolic material eventually inducing stroke during or after TAVI. In our series the thrombectomy created an opportunity to analyze the retrieved materials providing pathophysiological insights. New thrombus may form and both new and pre-existing thrombus may dislodge due to manipulation as confirmed by our series. In cases A and C we found particles of the aortic wall, suggesting that procedural manipulation of a fragile wall plays a role in the occurrence of cerebral infarction. The more rigorous manipulation in a valve-in-valve procedure (A) or postdilatation (B) could trigger embolization. In addition, the usage of foreign material including the implantation of a prosthetic valve could be thrombogenic itself since histopathology showed a thrombus formed during (A) or after the TAVI procedure (B).
CONCLUSION

Analysis of thrombectomy material provides insight in the pathophysiology of stroke in TAVI patients. The presented cases illustrate that procedure-related manipulation; in combination with the use of thrombogenic material plays an important role in the development of ischemic stroke after TAVI. Moreover, this report describes the importance of adequate and rapid reaction on signs of thromboembolic events for improving clinical outcome. The cases demonstrate both the advantage of performing TAVI in an awake patient as well as the availability of thrombectomy service on site.

REFERENCES

Figure I Patient A

**Image A:** Post mortem angiography: two CoreValves in aortic position, patent coronary arteries; stent in the LAD.

**Image B:** Autopsy Patient A: view of the opened thoracic aorta and its branches; malposition of the first implanted CoreValve, no thrombi in carotid arteries (subclavian arteries not visible in this picture). Ao = Ascending aorta; H = Heart; *= Carotid artery bifurcation.

**Image C:** Autopsy Patient A: detail of the opened left ventricle outflow tract and proximal aorta showing fresh mural thrombus underneath the removed bioprostheses. Ao = Ascending aorta; M = Left ventricle myocardium; FC = fibrous continuity between non-coronary cusp of aortic valve and anterior leaflet of the mitral valve; Arrow: Thrombus.

**Image D:** Haematoxylin and Eosin (H&E) stain of thrombectomy material from the basilar artery Patient A, showing red fresh thrombus with layered appearance.
Figure II Patient B
Image A: CT-angiography contrast filling defect distal M1 segment of the left Middle Cerebral Artery (MCA) (arrow).
Image B: Digital subtraction angiography (DSA) prior to mechanical thrombectomy confirming the filling defect.
Image C: DSA after mechanical thrombectomy; complete recanalization.
Image D: H&E stain of thrombectomy-derived tissue: neutrophils, platelets and erythrocytes without signs of ingrowth of smooth muscle cells, numerous Neutrophil Extracellular Traps (NETs).
Figure-III Patient C
Image A: CT-angiography contrast filling defect in the M1 segment of the right MCA (arrow).
Image B: DSA prior to mechanical thrombectomy confirming the filling defect.
Image C: DSA after mechanical thrombectomy Complete recanalization.
Image D: Elastica van Gieson stain of thrombectomy-derived tissue: platelets and fibrin, erythrocytes, granulocytes, focal NET structures and elastin rich fragments of arterial wall suggesting aortic origin.