# Transcatheter Aortic Valve Implantation In A Patient With Systemic Senile Transthyretin Type Amyloidosis

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**ABSTRACT—** ***Trancatheter aortic valve implantation with CoreValve or Edwards-Sapien prosthesis is becoming the method of choice for treating severe, symptomatic aortic stenosis in surgical high risk patients. CoreValve implantation may worsen atrioventricular conduction with possible development of atrioventricular block. However, in patients with infiltrative cardiomyopathy, such as amyloidosis, conduction disturbances can be the result of the underlying disease alone.***

***88-yr old female patient with severe, symptomatic aortic stenosis, after was scheduled for transcatheter aortic valve implantation. The procedure itself was successfully performed however, after the procedure transient complete atrioventricular block developed and a temporary pacemaker electrode was inserted. One day after the procedure the atrioventricular block resolved into her basic heart rhythm which was chronic atrial fibrillation with slow ventricular response. Due to development of systemic signs of infection of unknown origin the temporary electrode was removed and implantation of permanent VVI-type pacemaker was indicated. While waiting for implantation the patient died of sudden cardiac death.***

***Results of autopsy showed a CoreValve in the proper aortic valve position without blocking the ostia of coronary arteries, mildly enlarged and moderately thickened left and right ventricles on macroscopic level. Histopathological examination showed that the patient had an underlying systemic senile amyloidosis of the transthyretin type with predominant involvement of the heart.***

***Our patient, who has undergone a transcatheter aortic valve implantation due to severe, symptomatic aortic stenosis, after two balloon valvuloplasties, was also suffering from systemic senile amyloidosis of transthyretin type. This was discovered only postmortem on autopsy.***

***Transcatheter aortic valve implantation may cause iatrogenic transient or permanent conduction disturbances with possible development of atrioventricular block and present the need for transient or permanent pacemaker implantation. However, her underlying infiltrative cardiomyopathy, could also lead to the same conduction system abnormalities. It is hard to conclude whether conduction disturbances in this case that lead to sudden cardiac death were entirely iatrogenic or entirely due to amyloidosis. In terms of complete atrioventricular block developing just after the procedure and ending in sudden cardiac death, conduction disturbances may have been due to her underlying infiltrative cardiomyopathy and exacerbated by the CoreValve implantation.***

**Key words—** TAVI, CoreValve, atrioventricular block, amyloidosis

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## 1. INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is becoming the method of choice for treating patients with severe, symptomatic aortic stenosis (AS) in high surgical risk patients (1). Several centers have reported favorable outcomes using either CoreValve (Medtronic, MN) or the Edwards-Sapien (Edwards Lifesciences, CA) prosthesis to treat AS (2-4).

CoreValve implantation worsens atrioventricular (AV) conduction in most patients. Therefore transient or permanent AV block is one of the most frequent complications of CoreValve TAVI requiring transient or permanent pacemaker

implantation (PPI) (5). Pre-procedural right-bundle-brunch-block (RBBB) is a strong predictor of AV block after CoreValve implantation (6). However, in patients with preexisting infiltrative cardiomyopathy like amyloidosis, conduction disturbances may also be the result of infiltration of cardiovascular structures by amyloid alone. The conduction system is commonly affected, leading to left-bundle-brunch-block (LBBB), sinoatrial block or even complete AV block (7).

## 2. CASE PRESENTATION

88-yr old female patient, with two previous procedures of balloon aortic valvuloplasty (BAV), was admitted to our institution for TAVI.

Initially the patient suffered from symptomatic calcified AS with aortic valve area (AVA) 0,6 $cm^2$ and maximal gradient of 60 mmHg on transthoracic echocardiography (TTE). She developed symptoms of dyspnea, angina pectoris, dizzines, but no fainting. Due to her poor general condition and several comorbidities she was rejected for conventional surgical aortic valve replacement and scheduled for BAV as bridging to TAVI. The patient also suffered from heart failure (NYHA III), chronic atrial fibrillation, arterial hypertension, diabetes mellitus type 2 and chronic kidney disease.

First BAV was performed successfully with 40 x 20 mm balloon which was inflated with 4 atmospheres for 8 seconds. The remaining transaortic valve gradient was 25 mmHg and there was no worsening of her mild aortic regurgitation. On control TTE an increase in AVA to 0.8 $cm^2$, a drop of gradient from 55 mmHg to 25 mmHg (measured invasively during BAV) and better left ventricular (LV) function was observed.

Five months later the patient became symptomatic again with dyspnea, angina pectoris and dizziness. Second BAV was performed, again with 40 x 20 mm balloon inflated with 4 atmospheres for 8 seconds. The procedure was again successful with remaining transaortic valve gradient of 20 mmHg.

During her second hospitalization for BAV we decided to perform further investigations to approach TAVI in the future.

Transesophageal echocardiography (TEE) after second BAV showed severe calcified AS (AVA 0.6 $cm^2$, maximal gradient 55 mmHg) with only mild aortic regurgitation, calcifications in the annulus of mitral valve with fibrotic leaflets and only moderate mitral regurgitation and normal tricuspid valve with mild to moderate tricuspid regurgitation. LV was of normal size with mild impairment of global systolic function (EF 50 %), mild concentric hypertrophy and mild diastolic dysfunction. Right ventricle was normal in size and function. Severe pulmonary hypertension was present at rest (mean systolic pressure in right ventricle of 46 mmHg + CVP). Annulus of aortic valve measured 2 cm.

Computer tomography angiography of thoracic and abdominal aorta, left subclavian and iliac arteries showed sections with atheromatous plaques but no significant stenoses or tortuosity.

ECG before implantation showed atrial fibrillation, with the ventricle rate of about 60/min and LBBB.

The patient was a TAVI candidate and was scheduled for CoreValve implantation. Before CoreValve implantation predilatation of aortic valve was performed with 40 x 22 mm balloon (inflation with 4 atmospheres). Implantation was successful with maximal gradient on CoreValve of 8 mmHg and mild aortic regurgitation (Fig. 1).

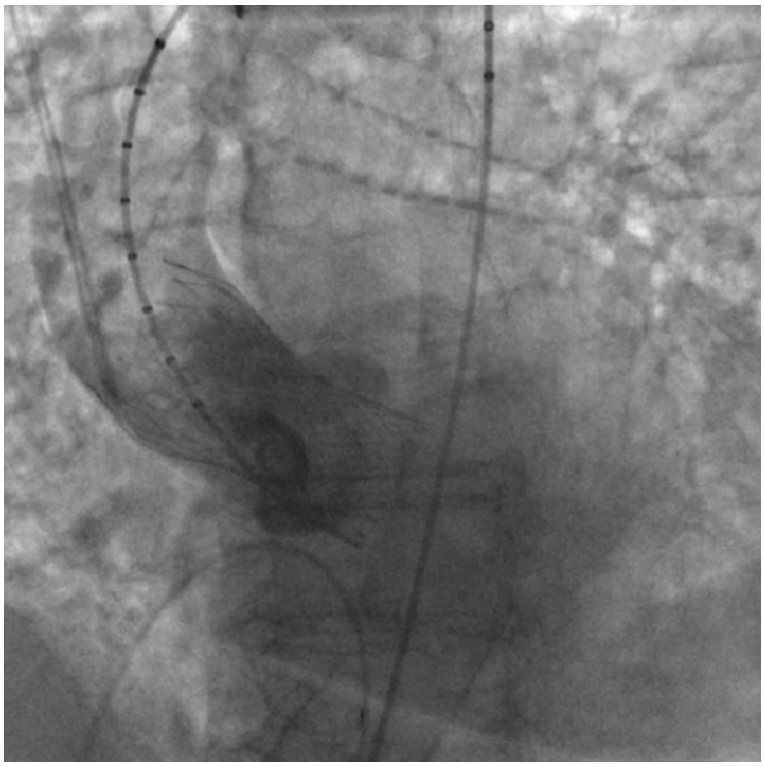

**Figure 1**. CoreValve bioprosthesis after implantation.

Control TTE showed a similar result as the index TTE: mild deterioration of global systolic function of LV with EF being about 50 %, poor systolic function of the right ventricle with both right chambers enlarged, normal function of implanted CoreValve with only mild paravalvular leak and other valves being the same as prior to TAVI in terms of function and morphology.

After the procedure the complete AV block developed and the patient received a temporary pacing. One day after TAVI the AV block resolved and she remained in her basic rhythm which was chronic atrial fibrillation with slow heart rate but sufficient for the temporary pacing electrode to be removed due to developing systemic infection of unknown origin. Dobutamine infusion was administered and the patient was monitored and scheduled for implantation of a VVI-type permanent pacemaker. While waiting for implantation the patient died of sudden cardiac death (SCD).

Autopsy was performed.

Autopsy showed that the patient was suffering from systemic senile amyloidosis of the transthyretin type with abundant amyloid deposits in the myocardium, aortic valve cusps and lungs.

**Macroscopic findings**:

The heart: there was fibrinous exudate on the pericardium. Small amount of pericardial effusion was present. Thickness of the left and right ventricles was 15 and 6 mm, respectively. Both ventricles were mildly enlarged, with flattened papillary muscles. Endocardium was intact. In the aortic valve position there was an artificial aortic valve (Fig. 2) with the native aortic valve cusps being very rigid and calcified. Pulmonal and tricuspid valve leaflets were normal, however mitral valve leaflets were thick and shrinkled. Myocardium was macroscopically normal on appearance. Coronary arteries had regional intimal thickening with several up to 50% stenoses. The implanted artificial valve did not block ostia of coronary arteries.

Other organs: macroscopically only changes consistent with the patient's age were found.

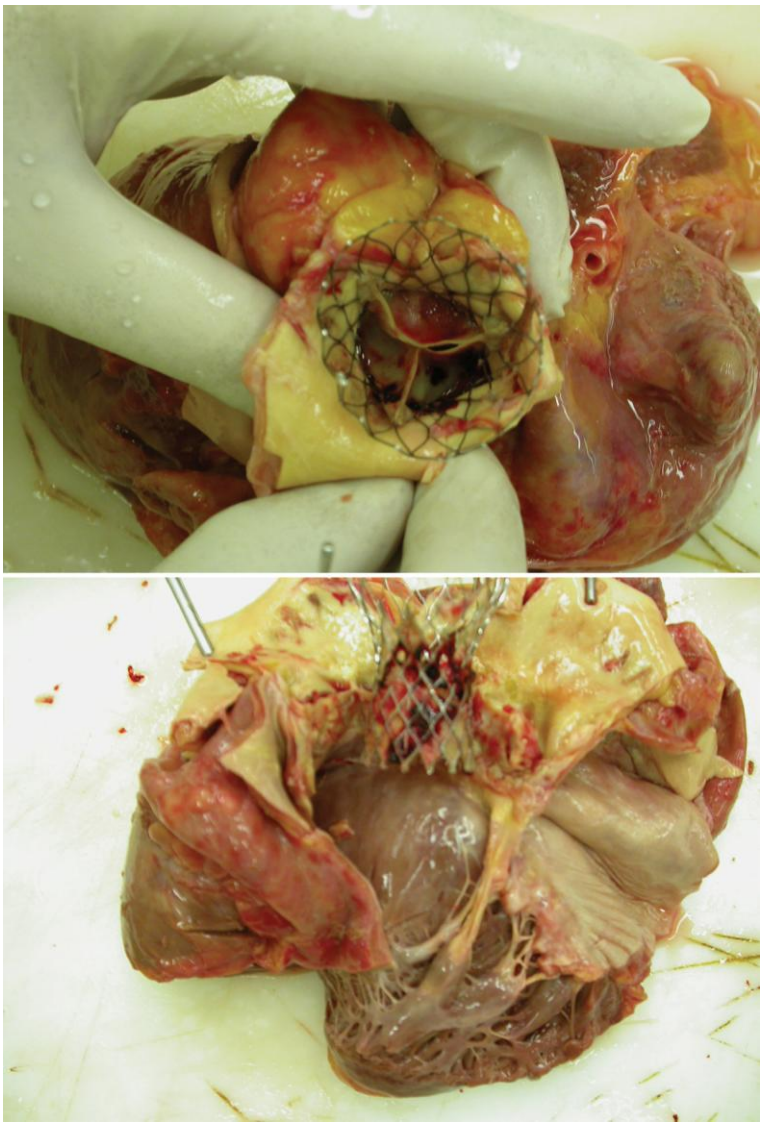

**Figure 2.** CoreValve in the position of native aortic valve. After day 10 the valve was fixed by granulation tissue and inflammatory reaction of the foreign-body type.

**Microscopic findings**:

The heart: abundant deposits of homogenous eosinophilic material (amyloid) were found in the interstitium and in the blood vessel walls of myocardium of the left and the right ventricle (Fig. 3). Staining with Kongo red showed positive reaction, with green birefringence under the polarized light. Immunohistochemistry showed positive reaction for transthyretin in the deposits (Fig. 4), and negative staining for amyloid A and light chains.

Native aortic valve: aortic valve cusps were thickened and calcified with focal osteoid formation and focal deposits of amyloid (Fig. 5). There was proliferation of granulation tissue in the annulus (a tissue response to artificial valve implantation).

CoreValve: chronic inflammatory reaction of the foreign-body type was found, but there was no amyloid deposition (Fig. 6).

The lungs: focal deposits of homogenous eosinophilic Kongo positive material (amyloid) were found in the interstitium and the blood vessel walls of the lungs.

Other organs: only changes consistent with the patient's age were found.

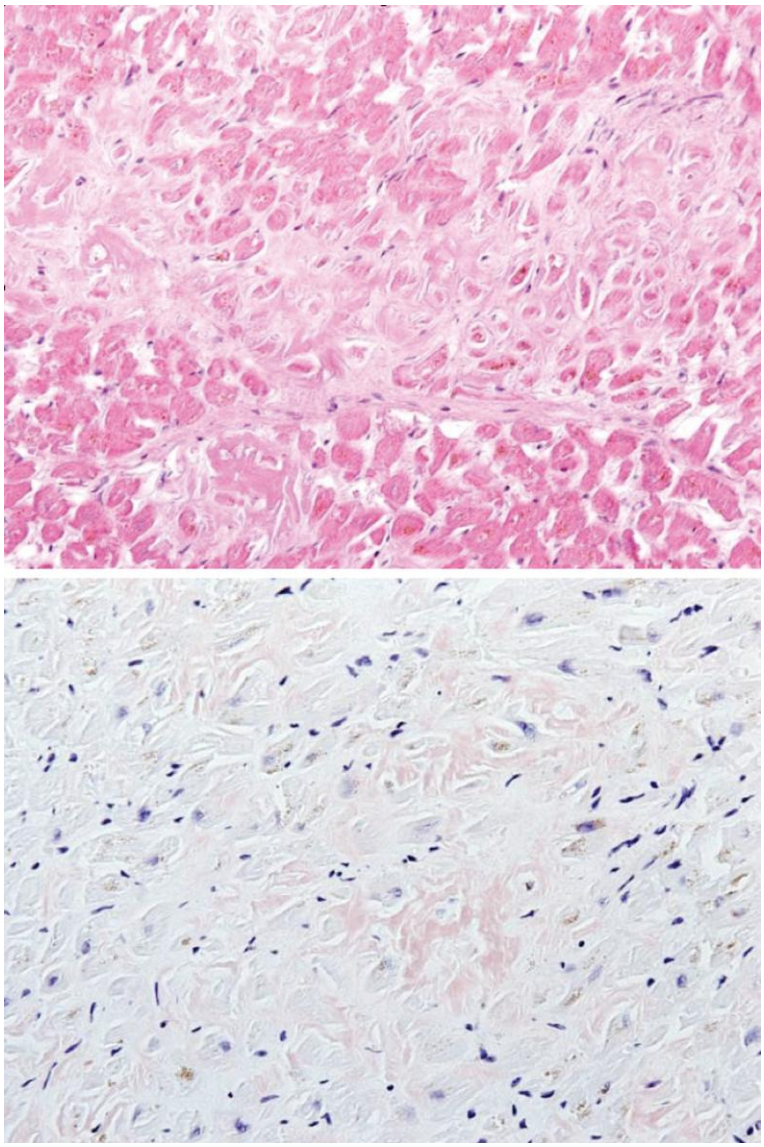

**Figure 3**. Interstitial amyloid deposits in the myocardium: upper HE, lower Kongo red staining.

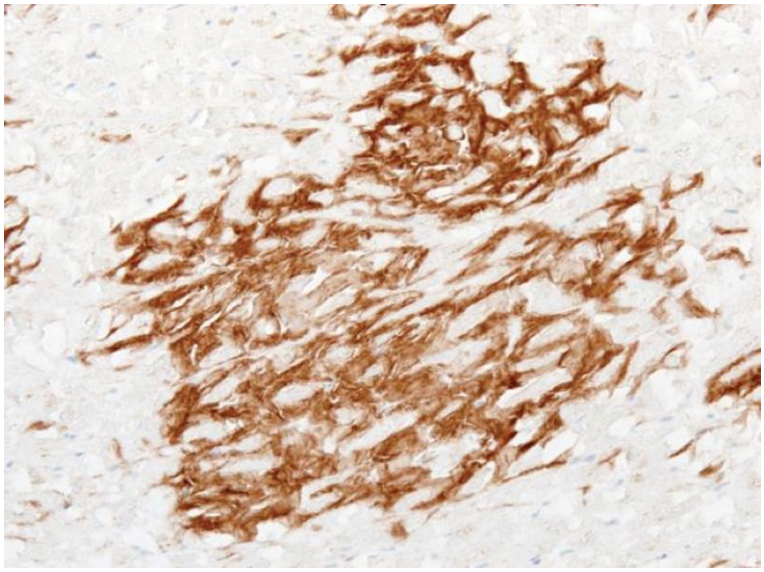

**Figure 4**. Positive immunohistochemical reaction for transthyretin in the myocardial amyloid deposits.

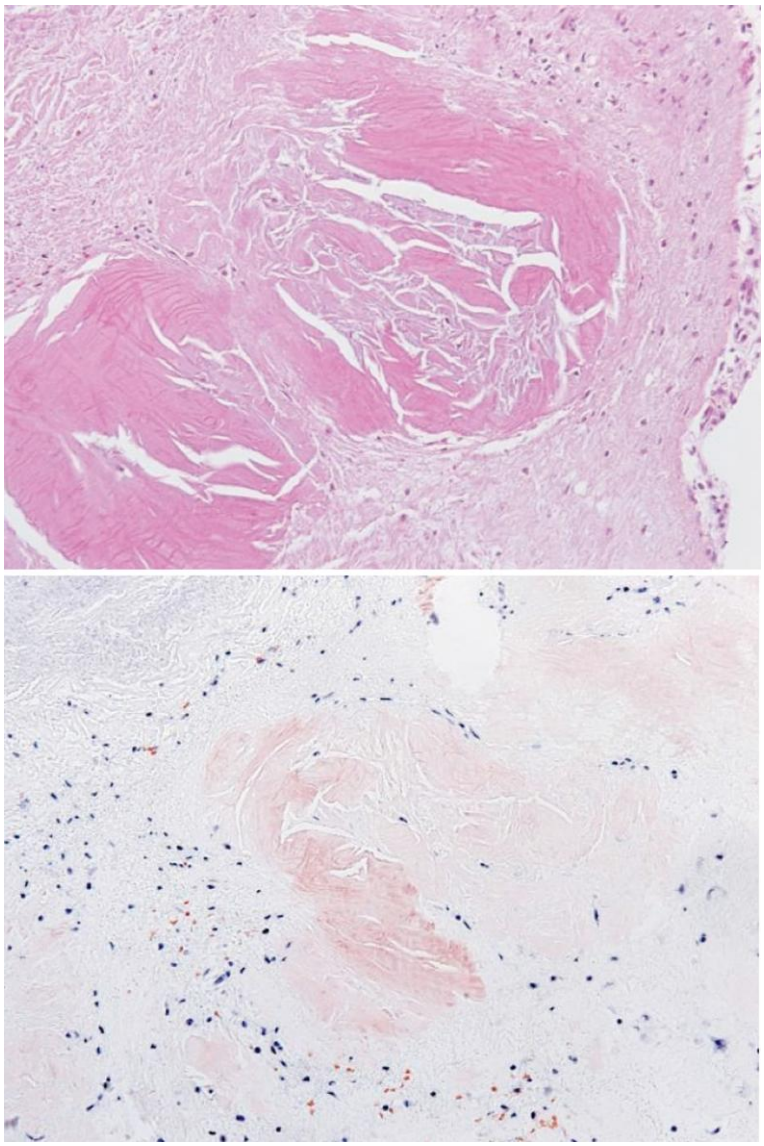

**Figure 5**. Abundant amyloid deposition in the native aortic valve, upper HE, lower Kongo red staining.

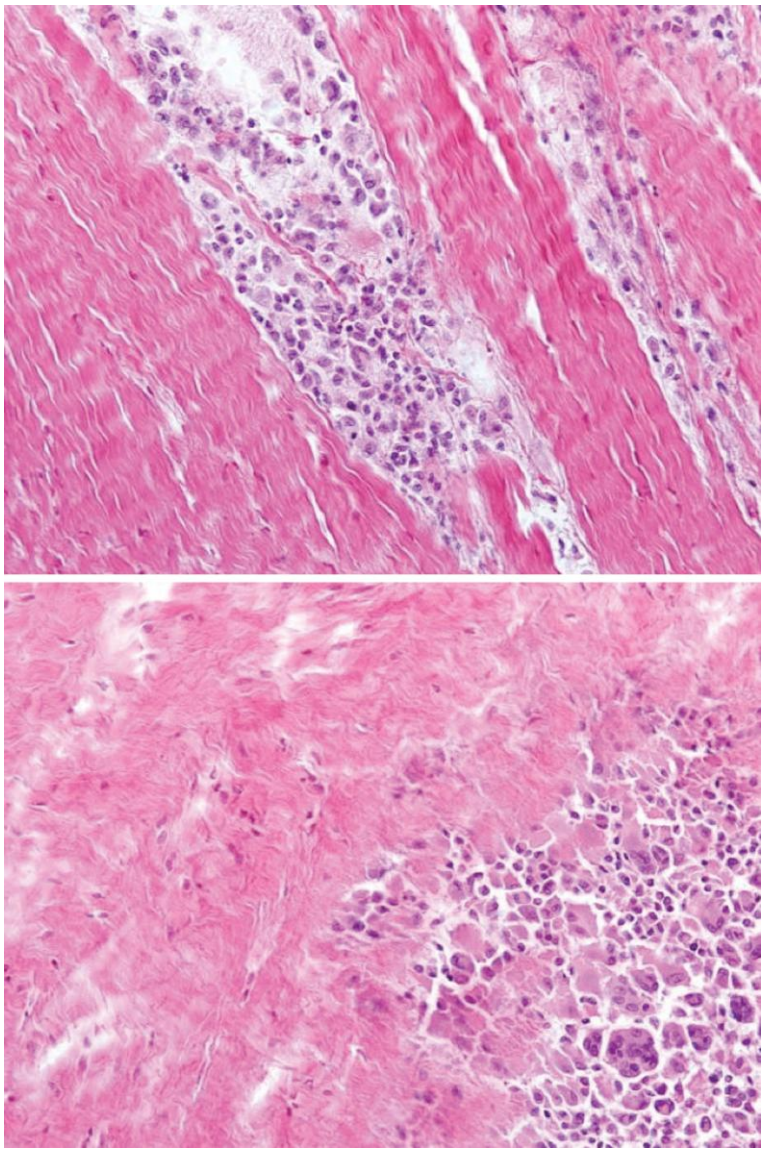

**Figure 6**. CoreValve: mononuclear cell infiltration with foreign-body type giant cells, no amyloid.

## 3. DISCUSSION

Transient or permanent AV conduction disturbances such as complete AV block with the need for transient or PPI represent an important clinical problem during and after TAVI. Baan JJ et al. have shown that between 29 and 65 % of patients after TAVI developed LBBB, complete AV block and/or presented with the need for PPI after CoreValve implantation (8) as was the case in our patient. The same is true for Edwards-Sapien valve only in smaller numbers (between 6 and 18 %) as Leon M et al. have shown (9).

Rutger-Jan Nuis et al. conducted an interesting study in which they tried to establish timing and potential mechanisms of new conduction abnormalities during the implantation of CoreValve in patients with AS. 65 patients with severe AS were treated with CoreValve implantation and 82 % developed peri-procedural conduction abnormalities. 91% of these developed during the procedure with the majority presenting before the actual valve implantation (56%). The best predictor of complete AV block after TAVI is RBBB (10). In case of CoreValve complete AV block is the case in 90% and 18% of patients with RBBB or without it respectively. However, the most common conduction abnormality was LBBB (83%) (11). Piazza N et al. have shown that the high frequency of new conduction abnormalities after CoreValve TAVI is due to close anatomical relationship between the aortic valvular complex and the conduction system (12) and Godino M et al. have shown that transapical TAVI may be associated with less new conduction abnormalities developing versus transfemoral TAVI, probably due to less manipulation in the left ventricular outflow tract (13).

New conduction abnormalities that develop after valve implantation are most likely due to the oedema or injury of the conduction system because of the valve implantation, but this needs to be confirmed by further studies.

Furthermore Bleiziffer et al. have shown that the balloon/annulus ratio also has impact on developing new conduction abnormalities with higher incidence in the group of higher ballon/annulus ratios. From this study we can conclude that the ideal balloon/annulus ratio would be 1.0 (14).

While waiting for PPI our patient died due to SCD. At autopsy an underlying infiltrative cardiomyopathy caused by systemic senile amyloidosis of the transthyretin type with predominant involvement of the heart was discovered.

Nonhereditary form of systemic senile amyloidosis associated with wild-type transthyretin is more frequent in elderly men and impacts predominantly the heart. On the other hand hereditary transthyretin-related amyloidosis is the most frequent form of familial systemic amyloidosis which can present as wide spectrum of clinical settings from predominantly neurologic involvement to strictly cardiac presentation. Clinical consequence of extracellular deposits of amyloid protein is restrictive infiltrative cardiomyopathy. With the progression of the disease not only disturbances in myocardial function are observed (mainly diastolic dysfunction, also systolic to some extent) but rather also conduction abnormalities since amyloid does not only infiltrate myocardium (causing thickening of the myocardium) but also the conduction system. Involvement of the conduction system often leads to the development of conduction abnormalities such as LBBB or even complete AV block. It has been suggested to consider the possibility of a hereditary transthyretin-related amyloidosis in all patients who present with unexplained increase in LV wall thickness on echocardiography (7).

Using data from the above mentioned studies we can speculate that the conduction system of our patient could have been to some degree already diseased before TAVI due to amyloid infiltration, but the condition was clinically silent. Transient complete AV block developed after the CoreValve implantation most likely due to the effect of the nitinol frame on the conduction system with the transient need for pacemaker implantation. This could have been the combination of oedema or injury due to CoreValve implantation to the most likely already previously diseased, but clinically silent, with amyloid infiltrated, conduction system.

Further studies will have to be conducted for the speculations in the case of our patient to be confirmed.

## 4. CONCLUSIONS

Our patient, who has undergone TAVI due to severe, symptomatic aortic stenosis, after two BAV procedures, was also suffering from senile, systemic amyloidosis of the transthyretin type, which was only found out postmortem at autopsy.

TAVI alone can cause iatrogenic transient or permanent conduction disturbances with possible development of AV block and the need for transient or permanent pacemaker device implantation. However, patient's underlying infiltrative cardiomyopathy, could also have lead to the same conduction system abnormalities.

It is hard to conclude whether conduction abnormalities in the case of our patient that lead finally to SCD were entirely iatrogenic or entirely due to amyloidosis. In terms of complete AV block developing just after the procedure and ending in SCD, we can speculate that conduction abnormalities resulting in SCD of our patient were most likely due to her underlying disease and exacerbated by the CoreValve implantation.

This case indicates that before implanting advanced and expensive devices in the elderly population we should screen patients for possible underlying diseases that can lead to fatal outcomes to either avoid implantation or plan the PPI just after the procedure.

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