

# Je Fabryjeva bolezen indikacija za transkatetrsko vstavitev aortne zaklopke? Prikaz primera uspešne kirurške zamenjave aortne zaklopke z neugodnim pooperativnim potekom

## Is Fabry disease an indication for a transcatheter aortic valve implantation? A case of successful surgical aortic valve replacement with an adverse postoperative course

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Fabryjeva bolezen, stenoza aortne zaklopke, zamenjava aortne zaklopke, večorganska odpoved

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**Izvleček**

**Namen:** Fabryjeva bolezen je izredno redka X-vezana lizosomska bolezen kopičenja, ki jo povzroča okvara encima  $\alpha$ -galaktozidaza A. Posledica te okvare je znotrajcelično kopičenje glikosfingolipidov. V srcu nakopičeni sfingolipidi in spremljajoča fibroza povzročajo hipertrofijo srčne mišice, motnje prevajanja, zadebelitev srčnih zaklopk in pospešeno nastajanje koronarne arterijske bolezni, kar bistveno pripomore k obolevnosti in smrtnosti teh bolnikov.

**Poročilo o primeru:** V prispevku prikazujemo primer 57-letnega bolnika s Fabryjevo boleznijo in hudo simptomatsko stenozo aortne zaklopke, pri katerem smo opravili uspešno kirurško zamenjavo aortne zaklopke brez nepričakovanih zapletov med operacijo, vendar s hudimi pooperativnimi zapleti z odpovedjo skoraj vseh organskih sistemov, sepso in smrtnim izidom.

**Zaključek:** Čeprav je bila bolnikova ocena kirurškega tveganja nizka

**Abstract**

**Purpose:** Fabry disease (FD) is an extremely rare X-linked lysosomal storage disorder caused by a deficiency of the enzyme  $\alpha$ -galactosidase A, which results in intracellular accumulation of glycosphingolipids. In the heart, accumulating sphingolipids and accompanying fibrosis promote hypertrophy, conduction disturbances, thickening of the valves, and accelerated coronary artery disease resulting in substantial morbidity and mortality.

**Case report:** Here, we present a case of a 57-year old male with FD, severe aortic valve stenosis, and permanent atrial fibrillation who underwent successful and uncomplicated surgical aortic valve replacement, but postoperatively developed severe complications of nearly all organ systems, which resulted in death.

**Conclusion:** Although the patient risk profile did not meet the criteria for transcatheter aortic valve implantation, this treatment option is

*in ni izpolnjeval formalnih kriterijev za transkatetrsko vstavitev aortne zaklopke, v prispevku razpravljamo o tej možnosti in jo celo predlagamo kot boljšo alternativo kirurgiji.*

*presented and discussed as a possible or even preferable alternative to surgery.*

Fabry disease (FD) is an extremely rare X-linked lysosomal storage disorder caused by a deficiency of the enzyme  $\alpha$ -galactosidase A, which results in intracellular accumulation of glycosphingolipids. The skin, cornea, kidney, peripheral nerves, and heart are especially affected by FD, leading to progressive failure of these organs (1). In the heart, accumulating sphingolipids and accompanying fibrosis cause thickening of the ventricular walls and hypertrophy, resulting in impaired diastolic and systolic function (2). Other cardiac manifestations include conduction disturbances, thickening of the valves, and accelerated coronary artery disease. Cardiovascular involvement substantially contributes to morbidity and mortality of these patients. Males (hemizygous) are more severely affected and present symptoms earlier than females (heterozygous) (3). The severity of the disease is highly variable with an average life expectancy of about 50 years in men and 70 years in women when left untreated (4). Recently, enzyme replacement therapy (ERT) was introduced as a therapeutic option based on evidence of reduced glycosphingolipid accumulation. However, although ERT is a promising therapeutic option, its clinical effectiveness in cardiac disease remains to be clarified (5).

Here, we report a case of a 57-year old male with FD receiving ERT with severe aortic valve stenosis and permanent atrial fibrillation who underwent successful and uncomplicated surgical aortic valve replacement, but postoperatively developed severe complications of nearly all organ systems, resulting in death.

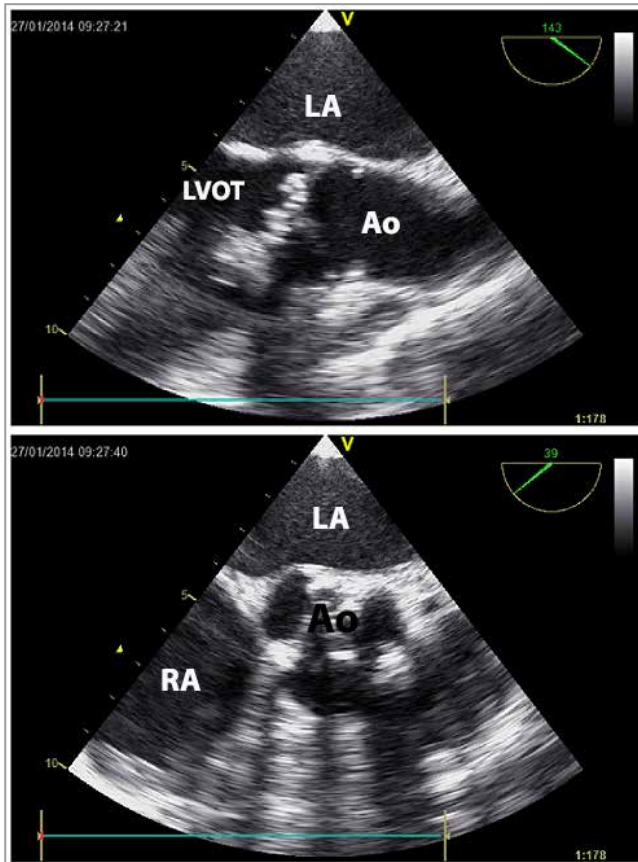
A 57-year-old male with severe symptomatic aortic valve stenosis was admitted for aortic valve replace-

ment. He was diagnosed with FD 12 years before and has received ERT for the last 11 years. Preoperative echocardiography showed a heavily calcified and stenotic aortic valve (mean/peak pressure gradients, 48 and 80 mmHg, respectively; valve area, 0.5 cm<sup>2</sup>), severe left ventricular (LV) hypertrophy (indexed LV mass, 185 g/m<sup>2</sup>), normal LV ejection fraction (53%), and enlarged atria (left atrial diameter, 5.3 cm; right atrial diameter, 4.6 cm) (Figure 1).

The patient was diagnosed with atrial fibrillation 2 years before and stage 4 chronic renal failure. Laboratory tests revealed elevated serum creatinine (354  $\mu$ mol/l), pro-BNP (B-type natriuretic peptide; 2683 pmol/l), and troponin I (0.76  $\mu$ g/l). Spirometry revealed moderate restrictive as well as obstructive lung function impairment. Surgical risk evaluation was low (EuroSCORE II, 2.24%).

A standard aortic valve replacement was performed through a full sternotomy with antegrade and retrograde cold blood cardioplegia for cardiac protection. A heavily calcified aortic valve was encountered. After careful decalcification, a Trifecta® stented pericardial biological valve was implanted (size, 21; St. Jude Medical, Inc., St. Paul, MN, USA). Radiofrequency ablation of the pulmonary veins, connecting lesions, and left atrial appendage was also performed. The left atrial appendage was then closed. Weaning from cardiopulmonary bypass was characterized by hemodynamic instability and rhythm disturbances.

In the intensive care unit, the patient stabilized over the next 24 h and was extubated one day after surgery. However, due to acute renal failure, renal replacement therapy was necessary. Recurrent



**Figure 1.** Transesophageal echocardiogram of the stenotic and heavily calcified aortic valve. LA, left atrium; RA, right atrium; Ao, aorta; LVOT, left ventricular outflow tract.

pleural effusions required bilateral chest drainage. Extensive right-sided pneumonia further complicated the postoperative course. The patient received antibiotic treatment under the supervision of an infectologist. However, his condition worsened and severe respiratory failure developed, requiring reintubation and mechanical ventilation. Furthermore, despite preventive administration of proton pump inhibitors, massive gastrointestinal bleeding occurred due to an acute diffuse erosive hemorrhagic gastritis, requiring blood transfusion. Additionally, signs of evolving paralytic ileus emerged. The kidneys showed no signs of recovery; thus, dialysis was continued. The pneumonia and respiratory function continued to worsen with evident clinical signs of sepsis with fever, leukocytosis, high C-reactive protein levels, and need for vasopressors. No patho-

gen was isolated from blood cultures or bronchial aspirate. LV function worsened and the LV ejection fraction was  $<20\%$ . Despite aggressive antibiotic and supportive treatment, the patient died due to sepsis and multiple organ failure on postoperative day 20.

Surgical aortic valve replacement is generally a safe procedure with low overall mortality and morbidity with a 10-year survival rate of about 70%, which is dependent on comorbidities and especially patient age (6). However, in a subset of patients with high or prohibitive surgical risk, transcatheter aortic valve implantation (TAVI) offers an excellent alternative treatment option. The current indications and recommendations for TAVI are specified in the current European (2012) and American (2014) guidelines (7,8). To sum up, TAVI can be performed in patients with severe aortic stenosis with no surgical option and as an alternative to high-risk surgery, when TAVI is favored by a multidisciplinary Heart Team. The surgical risk of these patients is usually evaluated using the EuroSCORE and STS (The Society of Thoracic Surgeons) scoring systems and classified as high when greater than 20% or 10%, respectively, or when the Heart Team considers that the patient has significant comorbidities or weakness/frailty not reflected in these scores (7,8). Current guidelines recommend TAVI only for inoperative or high-risk patients; however, there is also a strong worldwide trend of TAVI implementation for intermediate-risk patients (STS score 3%–8%) (9). Although the best results of TAVI are expected in lower-risk patients, there are two limitations that will determine wider approval: procedural safety and long-term durability of the valve itself.

In the presented case, the patient was considered low-risk (EuroSCORE II, 2.24%) and the Heart Team also classified him as low-risk and suitable for surgery. This decision was partly influenced by rare case reports in the literature describing successful open-heart surgery in patients with FD, although most were younger and/or female (10–12). Moreover, the patient was on enzyme therapy, in good

condition, and did not appear to be clinically feasible. However, preoperative levels of troponin, the presence of chronic renal failure, and spirometry results all indicated progressive multiple organ damage. Furthermore, being 57 years old, he had already reached the average life expectancy of male FD patients. Taking all this into account, we now believe that the progress of FD and consequently the surgical risk were underestimated. We also believe that in this group of patients, standard risk profile tests are not reliable, as they were not designed nor clinically tested in this group of patients.

In conclusion, although lacking experience in FD patients, we are now convinced that these patients should be evaluated with caution and on individual basis, and that the Heart Team should be required to include a specialist with superior knowledge in this field of medicine. Furthermore, in our opinion, especially in male patients aged >50 years with aortic stenosis, the threshold for TAVI should be low.

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