Transcatheter Aortic Valve Replacement (TAVR) in Low Flow-Low Gradient Severe Aortic Stenosis without Cardiac Reserve.

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Highlights:
With accumulating positive evidence in favor of transcatheter aortic valve replacement (TAVR) over a surgical approach, it has replaced surgical AVR to become the mainstay of treatment for severe symptomatic aortic stenosis in patients with prohibitive and high surgical risk. There is significant surgical mortality and morbidity associated with surgical aortic valve replacement in patients with low flow-low gradient (LFLG) true severe aortic valve stenosis (AS) and severely reduced left ventricular ejection fraction (rEF) without contractile reserve (CR). CR is measured following use of dobutamine in an attempt to increase cardiac output by more than 20% while differentiating severe from pseudostenosis in some cases. The value of transcatheter aortic valve replacement (TAVR) over a surgical approach for these patients with rEF LFLG true severe AS and no CR is uncertain. We present a patient with LFLG severe AS and low left ventricular EF without contractile reserve who underwent TAVR and experienced significant improvement in their clinical status without complications.

Keywords:
low flow low gradient, aortic stenosis, Transcatheter aortic valve replacement, TAVR, contractility reserve

Citation:

Introduction
Aortic stenosis (AS) is commonly diagnosed following physical examination or echocardiography revealing signs of stenosis, with a majority of patients being asymptomatic at presentation. Transthoracic echocardiography has become the test of choice in diagnosis and evaluation of aortic stenosis compared to routine use of invasive hemodynamic measurement [1]. The severity of aortic stenosis is estimated using a combination of echocardiographic parameters such as transaortic mean pressure gradient, flow rate (determined by stroke volume), peak aortic velocity and calculated valve area using the Gorlin equation. Severe aortic stenosis patients have an aortic velocity of ≥ 4m/s, mean transvalvular pressure gradient ≥ 40mmHg and valve area ≤ 1.0cm2. The transaortic gradient varies depending on severity of stenosis and flow rate which in turn depends upon the stroke volume and ejection time. Low flow, low gradient (LFLG) severe AS is currently defined as a valve area ≤ 1.0 cm2 with an aortic velocity < 4.0 m/s or mean transvalvular pressure gradient < 40mmHg in patients and is seen with either normal (nEF) or reduced ejection fraction (rEF) [2].

Among patients with LFLG AS and rEF (EF < 50%), there exists a patient subset with no flow reserve/cardiac reserve (CR). CR is defined as an increase in stroke volume ≥ 20% above baseline following dobutamine challenge (Figure 1). Aortic valve replacement (AVR) is the first line of treatment in patients with true severe valvular AS. Patients with LFLG AS have a poor outcome even with AVR, and outcomes are worse in patients without cardiac reserve [3]. Transcatheter aortic valve replacement (TAVR) is used in patients with severe AS at high to prohibitive surgical risk. TAVR has not been studied well in this patient population and we present a patient with LFLG severe AS without CR treated successfully with TAVR.

Case description
An eighty-seven year old Caucasian male with prior history of chronic kidney disease, non-obstructive coronary artery disease, and atrial fibrillation on anticoagulation presented to the hospital with a wrist fracture following a fall. Further enquiry revealed that the patient had an episode of syncope that precipitated the fall. He also complained of an inability to walk more than 15 feet

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The patient was assessed to be in the NYHA Class II symptom category in comparison to class III/IV symptoms at initial presentation. A repeat echocardiogram revealed improvement in ejection fraction to 25% within 30 days of the procedure with an increase in stroke volume (Figure 2). He continued to follow up as outpatient demonstrating an augmented functional capacity and required no further hospitalizations at 10 months.

**Discussion**

To our knowledge, this is the first case where an elderly man with LGLF severe aortic stenosis, severely reduced EF (15%) and no flow reserve has been shown to have significant, sustained subjective and objective improvement following successful TAVR. Since its emergence, TAVR has changed the landscape of structural interventional cardiology in treating aortic stenosis. TAVR has advanced from its initial limitations, and addressed its many pitfalls over the years with newer generation valves, evidence for improved outcomes and growing expertise [4].

Severe symptomatic aortic stenosis is the most frequently encountered valvular heart disease among the elderly and has a poor outcome if left untreated [5]. TAVR is a well-proven, effective and reproducible therapy for aortic valve stenosis in patients with multiple comorbidities, organ dysfunction, functional frailty, advanced age and a high surgical risk [6]. Those symptomatic from AS generally experience substantial improvement in symptoms and an increased survival, irrespective of the presence of left ventricular dysfunction following AVR [7]. Patients with likely severe AS and a low transvalvular pressure gradient due to significant LV failure have considerable operative risk. These patients may potentially benefit from TAVR.

In patients with LV systolic dysfunction and severe AS with mean gradient < 40mmHg, a dobutamine challenge supports selecting those who would benefit from AVR [8]. The dobutamine challenge aids in distinguishing true aortic stenosis from pseudo aortic stenosis. In the latter, primary contractile dysfunction causes decreased valvular opening, which in turn contributes to limited valve mobility and apparent stenosis [2]. Dobutamine effectively increases flow across the aortic valve, reduces the transaortic gradient and peak velocity, thus leading to a higher calculated aortic valve area in most cases with pseudostenosis [9]. This has significant clinical implications as only those with true severe AS will likely benefit from AVR. Discerning the underlying etiology in patients with no flow reserve remains challenging.

The American Heart Association/American College of Cardiology 2014 valvular guidelines recommend a class IIa indication for surgical AVR in patients with LGLF AS with consideration for TAVR among those at high risk for surgery. Tribouilloy et al showed a survival benefit with surgical aortic valve replacement compared to medical therapy for aortic valve stenosis in patients with no flow reserve.

Due to the patient’s underlying comorbidities, high frailty index and high surgical risk involved, he underwent trans-catheter aortic valve replacement using a 29mm Edwards Sapien 3 bio prosthetic valve. He also received a biventricular implantable pacemaker/defibrillator following persistent complete heart block after the valve replacement. His post-operative course was prolonged but the patient recovered well and was eventually discharged to a rehabilitation facility. He responded very positively to the rehabilitation regimen and on follow-up was able to walk up to 150 feet without difficulty or limiting shortness of breath. A remarkable improvement in overall symptoms was noted, and the patient was assessed to be in the NYHA Class II symptom category in comparison to class III/IV symptoms at initial presentation. A repeat echocardiogram revealed improvement in ejection fraction to 25% within 30 days of the procedure with an increase in stroke volume (Figure 2). He continued to follow up as outpatient demonstrating an augmented functional capacity and required no further hospitalizations at 10 months.

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to medical therapy at 5-year follow-up in patients with LFLG AS without CR despite an operative mortality rate of 22% [10]. In a European Multicenter study, Monin et al similarly reported that absence of CR was a powerful independent predictor of overall mortality in patients with LFLG AS and reported a higher operative mortality (32%) among those treated surgically despite an overall benefit over medical treatment [11]. In a French study, Quere et al showed that despite the higher operative mortality with surgical AVR (SAVR) among with patients with LFLG severe AS with rEF and no CR, those who survived the procedure experienced significant improvement in EF [12]. In conclusion lack of CR does predict high post-operative mortality, but among those who survive, a significant improvement in EF, symptoms and long-term survival may be seen.

The large scale randomized PARTNER trials excluded patients with severe left ventricular dysfunction but there is growing data favoring TAVR when it comes to LFLG severe AS with rEF compared to SAVR [13-15]. Passeri et al showed effectiveness of transfemoral TAVR in improving survival among patients with mild-moderate LV dysfunction (EF >20%) and inoperable AS compared to standard medical therapy [16]. In a meta-analysis of 7,673 patients with severe AS who underwent TAVR, patients with a low stroke volume index (< 35ml/m2), low gradient and low EF (< 30%) had significant higher mortality at follow up. But the overall low peri-procedural risk and high procedural success, makes TAVR a very vital option in patients with LFLG severe AS with rEF [17]. The patient described here was an elderly, frail, poorly functional due to underlying LFLG severe AS with rEF and was considered at a very high risk for SAVR (Euro score II mortality risk was 14.56%). After a careful assessment of the risks and benefits of TAVR, the patients underwent successful TAVR without complication and showed sustained functional (dyspnea, exercise tolerance) and objective (including EF and stroke volume, walking distance) improvement during follow-up. The role of a multidisciplinary team/ heart team consisting of a cardiovascular surgeon, an interventional cardiologist, structural heart disease and imaging experts cannot be underestimated and is key in the management of complex cardiovascular diseases. A heart team approach is also currently mandated by regulatory and reimbursement agencies such as the US FDA and Centers for Medicare and Medicaid Services [18].

Patients with LFLGs severe AS with rEF without CR are under-represented in studies but remain among the highest risk patients with evidence for possibly symptomatic and survival benefit with SAVR or TAVR. A large prospectively conducted multi-center study is warranted in this patient population to assess the benefit of TAVR compared to SAVR or medical therapy, but until then a careful and thorough assessment of individual cases must be performed by the Heart team with consideration for TAVR in those at high operable risk.

Declarations of Interest
The authors have no interest to disclose

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References
9. Grayburn P, Eichhorn E. Dobutamine Challenge for Low-Gradient Aortic Stenosis. Circulation. 2002;106(7):763-765. DOI: 10.1161/01.01.01.0000025707.19008.0E.