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Aortic Valve Surgery and Reduced Ventricular Function

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1. Introduction

Aortic valve disease is a fatal disease with but a single cure. Removal of the mechanical obstruction in aortic stenosis (surgery or TAVI) and replacement of an incompetent valve (so far only surgery) are the only treatment options.
While aortic valve replacement in patients with isolated valve disease and normal pump-function of the heart has become a routine procedure and is performed with excellent results all over the world, it can be a rather challenging procedure in severely ill patients with heart failure and comorbidities. Patients with low ejection fraction are one of the most challenging patient groups in cardiac surgery.
According to the guidelines for the management of patients with valvular heart disease as recommended by all major heart associations including the European Society of Cardiology, American College of Cardiology, American Heart a ventricular function reduced to below 50% ejection fraction is considered a class I, level of evidence B and C indication respectively for aortic valve surgery. (ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease, Bonow et al., 2006) Despite this fact there is a high number of patients presenting with severely reduced ventricular function for aortic valve surgery.
In aortic insufficiency 70% have a function reduced to below 50% and around 10% present with a significantly reduced function of less than 30% EF. In case of aortic stenosis the numbers are a less dramatic but still more than 40 % of patients referred for valve surgery have an ejection fraction below 50%.
This is due to the fact that aortic valve disease can go unnoticed for a very long time resulting in heart failure at time of presentation. Another fact is that at least some patients are treated conservatively for a too long period of time until their EF deteriorates.
Apart from that, due to the demographic development there is an increasing number of patients with aortic valve disease and advanced age resulting in a high number of elderly patients with more comorbidities and reduced ejection fraction.

2. Impaired ventricular function

In the scientific literature there are various definitions with different thresholds describing impaired ventricular function in patients undergoing aortic valve surgery. Ali and co-workers
define reduced left ventricular ejection fraction as <60%, which is in fact an unusual cut off level. (Ali et al., 2006)
Sharony et al. included patients with an ejection fraction < 40% in their study on aortic valve replacement in patients with impaired ventricular function. (Sharony et al., 2003) Mihaljevic T. et al. used a more complex system including 5 subgroups according to cardiac pump-function. Impairment of LV function was graded qualitatively as follows: EF 50% or greater, none; EF 40% to 49%, mild EF 35-39% moderate; EF 26%-34% moderately severe, and EF 25% or less, severe. They demonstrated the prognostic value of this grading system in previous studies. (Mihaljevic T. et al., 2008) For the sake of clearness of this book chapter we include scientific studies with a cut off level of less than 40% and cite the exact values as described in the respective publications.

3. Pathogenesis

Indications for aortic valve replacement are either aortic stenosis, or aortic insufficiency or combined lesions. It is important to distinguish between the indications for aortic valve due to the fact that aortic insufficiency is a risk factor in itself for worse outcome following surgery beyond the impact of reduced left ventricular function. (Chaliki et al., 2002; Sionis et al., 2010)
34% of all the patients with valve pathologies referred to cardiac surgery are patients with aortic stenosis but only 10% are admitted with aortic insufficiency. (Vahanian et al. 2007 ESC, VHD Guidelines, 2007) Around 10% of the patients with aortic stenosis have combined lesions, but stenosis is the clinically predominant pathology in these cases and therefore these lesions are included into the statistics of aortic stenosis.

3.1 Aortic regurgitation (AR)
The literature regarding aortic valve replacement in patients with aortic insufficiency and impaired ejection fraction is extremely limited with very few patients studied. Aortic insufficiency as compared to aortic stenosis turns out to be a significant predictor of both mortality and morbidity after aortic valve replacement. Chaliki et al. investigated 450 patients with aortic insufficiency. Only about 10% (n=43) of those patients had a severely impaired left ventricular function (<35%). A major finding of the study is that these patients constitute a high risk group even after successful surgery. The operative mortality rate in this group was excessive with 14% as compared to patients with moderately impaired and normal ejection fraction, with 6.7% and 3.7% mortality rates respectively. This difference becomes even more pronounced in the long term follow-up: At 10 years after surgery only 41% of the patients with low ejection fraction survived as opposed to 56% and 70% in patients with moderately impaired EF and normal EF respectively. Of note, aortic valve replacement for aortic insufficiency does not lead to any significant improvement in pump-function regardless of the preoperative ejection fraction. (Chaliki et al. 2002) (table 1)
In view of the high risk of AVR in patients with heart failure, surgery should ideally be performed before such a severe decrease in EF occurs. However, patients do remain asymptomatic for a long time even if the ejection fraction is already reduced. The decision to recommend operative intervention to asymptomatic patients with chronic, severe aortic regurgitation is very difficult because aortic valve replacement continues to entail immediate risk, and biologic and mechanical valves still have problems resulting in significant mortality and morbidity. (Scognamiglio, et al., 2005) On the other hand for patients who
have AR and already have severe LV dysfunction, an important issue to consider is whether AVR represents too high a risk and conservative treatment is preferable.

Table 1. Comparison of pre- and postoperative echocardiographic values (Chaliki et al. 2002)

Natural history studies have focused mainly on asymptomatic patients with normal function. In a recent study patients were stratified according to their ejection fraction and it was demonstrated that those with markedly lower EF had a higher rate of congestive heart failure than patients who had moderately reduced or normal EF before AVR.

The outcome of conservatively treated patients with even mild LV dysfunction is poor. Indeed, patients with either EF 55% or LV systolic dimension 25 mm/m², even if asymptomatic at presentation, have excessive long-term mortality rates if treated conservatively. Although patients with severe LV dysfunction could not be analyzed specifically, the uniform risk increase with decreasing EF under conservative treatment suggests that such patients are at very high risk if not operated on and that an aggressive approach is justified.

Sionis et al. even evaluated if it is beneficial to offer these patients cardiac transplantation instead of performing aortic valve replacement. But they conclude from their data of only 27 patients that while the mortality of patients with aortic valve insufficiency and impaired ventricular function undergoing aortic valve replacement is high, it is not excessively high justifying listing for transplantation. Additionally a lot of these patients do not develop heart failure and therefore still benefit from AVR. (Sionis et al., 2010)

Conversely, although patients with a markedly low EF and severe AR are at high risk, their medium-term outcome is not uniformly ominous. The usual operative mortality rate reported for AVR ranges from 1% to 7%. Chaliki et al. show excessive operative mortality rates among patients with markedly low EF, but it is not overwhelming. A majority of patients remain free of heart failure 10 years after AVR. Therefore, a notable period of event-free survival can be achieved in most patients after correction of AR despite their very low preoperative EF. The functional status of most patients improves after surgery, irrespective of preoperative EF. Thus, a markedly low EF (<35%) is not, in our judgment, a contraindication to AVR. (Chaliki 2002)

In light of the fact that patients with aortic insufficiency and reduced ejection fraction do not benefit from aortic valve replacement regarding pump function it would be necessary to re-evaluate the guidelines for aortic valve replacement in those patients, since currently AVR in asymptomatic patients is only recommended when EF declines down to <50% or end-
diastolic diameter increases >70 mm or end-systolic diameter increases > 50mm (or >25 mm/m² body surface area)

However it is difficult to schedule patients with aortic insufficiency and normal EF for surgery because often these patients remain asymptomatic until the pump-function is markedly reduced. When EF is significantly impaired the outcome of surgery is worse but on the other hand the mortality rate of asymptomatic AR patients is rather low and surgery does not improve quality of life. So it remains a matter of debate if the time point of surgery has to be delayed in a later stage if the surgical outcome becomes worse or if surgery should be performed as soon as possible even in asymptomatic patients as long as left ventricular function is still normal.

Scognamiglio et al. showed that patients with AR and reduced LVEF can benefit from an unloading therapy with Nifedipine, so that the need for surgery can be delayed by prolonging the asymptomatic period while preserving LVEF (Scognamiglio 2005).

From the data from the literature we conclude that patients with AI and impaired EF should be considered at high risk, carefully evaluated and if suitable scheduled for surgical intervention as soon as possible.

### 3.2 Aortic stenosis (AS)

In developed countries, aortic stenosis is the most prevalent of all valvular heart diseases. It is primarily a manifestation in patients with advanced age. The disorder is becoming more frequent as the average age of the population is increasing. Symptomatic severe AS is a lethal disease if left untreated. (Figure 1, Figure 2, Carabello, 2009)

Aortic valvular abnormalities are quite frequent in old patients. In the Cardiovascular Health Study, in which 5201 men and women older than 65 years were examined, 26% of
study participants had aortic sclerosis (a thickening of the valve or calcification without significant obstruction). A slight predominance of the disorder was noted in men. 2% of all patients had frank aortic stenosis.

A clear increase in prevalence of sclerosis was seen with age: 20% in patients aged 65–75 years, 35% in those aged 75–85 years, and 48% in patients older than 85 years. For the same age-groups, 1.3%, 2.4%, and 4% had frank aortic stenosis.

The only effective therapy is the mechanical relief of the obstruction. (Carabello, 2009) with operative replacement of the valve or transcatheter aortic valve implantation (TAVI) as treatment options. Therefore it is one of the clearest decisions for a doctor to recommend valve replacement for aortic stenosis. Balloon valvuloplasty plays an important role in the pediatric population but a very limited role in adults because its efficacy is low while complication rates are high (>10%).
In asymptomatic patients with aortic stenosis survival is comparable to an aged matched population (figure 3). Therefore there is no point in treating asymptomatic patients. As soon as those patients develop symptoms, survival is markedly reduced (Grossi et al. 2008). However one of the problems are asymptomatic patients with severe stenosis and reduced ejection fraction at time of surgery. It is recommended to perform aortic valve replacement in patients with asymptomatic severe aortic stenosis and an ejection fraction <50 (class of recommendation I) however the level of evidence is only C. (Vahanian 2007 ESC Guidelines) According to the paper by Hannan E. and colleagues, as soon as the aortic valve is replaced in these patients risk adjusted survival returns to level that is not statistically different to the survival of people from the general population who are age and sex matched to this group. As with aortic regurgitation reduced ejection fraction emerges as one of the most significant risk factors of early and late mortality (Figure 4, Hannan et al. 2009). Michaljevic and coworkers showed that among other risk factors like older age, greater degree of aortic stenosis, greater LV mass index, smaller standardized prosthesis-patient size, in addition LV dysfunction and advanced symptoms influence the long term survival of patients undergoing aortic valve replacement (Figure 5, Mihaljevic et al. 2008).
Fig. 4. Hannan and coworkers investigated the survival after aortic valve replacement with concomitant CABG according to cardiac risk factors. The Dashed line is the survival of age- and sex-matched population. Solid and dash-dotted lines represent survival for aortic valve replacement patients with and without concomitant coronary artery bypass grafting, respectively. (Hannan et al. 2009)

Fig. 5. Long term (> 1 year) survival of patients undergoing AVR with and without ventricular dysfunction (EF<40%) (Mihaljevic et al. 2008)
Since AS is a disease of elderly patients the outcome depends on comorbidities and concomitant surgical procedures (CABG). Onset of dyspnoea and other symptoms of heart failure presage the worst outlook for the patient with aortic stenosis. Whereas concentric hypertrophy helps to maintain systolic performance, increased wall thickness impairs diastolic function. The percentage of patients with low ejection fraction in the surgical population of AS ranges from 10-15%.

As in aortic insufficiency, valve replacement for stenosis has become a routine procedure and again patients with reduced ejection fraction represent a challenge for the cardiac surgeon. Low ejection fraction has been identified as a significant risk factor for both reduced early and late mortality after AVR.

### 3.2.1 Low gradient low flow aortic stenosis

Low gradient low flow AS is defined as aortic stenosis with an effective aortic area <1cm², LVEF <40% and a mean transaortic pressure gradient of < 30 mmHg. Assessment is usually performed by dobutamine stress testing. This is necessary to confirm that the reduced effective orifice area is in fact severe rather than an effect of low flow on a mild or moderately stenosed valve (2) Contractile reserve on dobutamine stress testing is defined by an increase in the systolic velocity integral or stroke volume by at least 20% during dobutamine infusion. Aortic valve replacement is recommended by the AHA for patients with low gradient low flow aortic stenosis with contractile reserve (Class1: level of evidence C) (Monin, et al. 2003)

Especially patients without contractile reserve represent a high risk group (figure 6). Monin and colleagues showed that patients with contractile reserve have better prognosis than those without contractile reserve. Both groups of patients have much better life expectancies when the diseased valve is replaced in comparison to medical treatment only. (figure 6)

![Patient Survival](image_url)

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Fig. 6. Monin et al. showed that patients without contractile reserve (group II) perform worse than those with contractile reserve (group I). Nevertheless for both groups valve replacement has much better results than medical treatment alone.
A more recent paper by Clavel et al. used a slightly different definition with an aortic valve area of <1.2 cm² and <40% ejection fraction however a mean gradient of <40 mmHg. (Clavel, et al. 2008) This multicenter study showed that patients with low flow low gradient AS are a high risk population with an operative mortality of 18% and 3-year survival rates of only 57%.

In a best evidence topic of Subramanian et al. performed a meta analysis of the current literature on severe aortic stenosis but poor left ventricular function with no contractile reserve. To discuss whether it is ever worth contemplating aortic valve replacement in this setting. Out of the 251 papers screened for this analysis 14 presented the best evidence to answer this question.

The conclusion of the study was that patients with severe aortic stenosis and a contractile reserve of <20% improvement in stroke volume on dobutamine stress testing have a very poor prognosis of only 10-20% at two years. Heart transplant would offer the best chance of survival to those eligible but for those not eligible, a surgical option should not be discounted for selected patients. The American Heart Association guidelines state that prognosis is very poor for either medical or surgical treatment, but the European Society of Cardiology guidelines state that surgery can be performed in these patients but should take into account the clinical condition of the patient. The operative mortality is around 30% and the French Multicentre study on low gradient aortic stenosis has shown that if the patient survives there is likely to be an improvement in symptoms and ejection fraction. Thus, absence of contractile reserve on stress testing does not exclude myocardial recovery after surgery, although it is a strong predictor for operative mortality. (Subramanian et al; 2008)

4. Strategies for improved outcome

As stated above poor left ventricular function is a negative prognostic factor after aortic valve Replacement regardless the type of the aortic valve disease. Therefore it is important to find objective prognostic variables to identify patients who benefit the most from a surgical intervention and to exclude patients with an excessively high operative risk. Several studies have reported various approaches to improve postoperative outcome in theses patients.

4.1 B-Type natriuretic peptide as a predictor of heart failure following aortic valve surgery

Biomarkers, especially pro-BNP have been associated with heart failure and poor ventricular function. Pro-BNP might be an objective prognostic variable for outcome after surgical aortic valve replacement. (Nozohoor et al. 2009)

NT pro-BNP levels have been to be elevated in patients with aortic valve stenosis. And has already been suggested to monitor the progression of the disease non-invasively as well as to time surgery for aortic stenosis optimally. Further more pro-BNP correlates with endsystolic wallstress in patients with aortic stenosis. At our department it has become standard of care to administer a 24 hour infusion course of levosimendan 3 days prior to surgery in patients with low EF and high proBNP levels, in order to precondition patients for surgery (data not yet published). In our experience pro-BNP decrease more than 50% on average due to this treatment.
Järvelä et al. investigated the impact of levosimendan in aortic valve surgery. A total of 24 patients were included in this study, 12 per arm however only with a moderate reduction in pump-function (treatment group 48%, control 54%). Levosimendan was started at induction of anaesthesia and continued over 24 hours. While induction of anesthesia led to reduction of EF in both groups, ejection fraction slowly recovered almost to preoperative levels in the control group. In contrast to that the ejection fraction of patients receiving levosimendan even improved in comparison to the preoperative levels. (Figure 7). (Järvelä et al. 2008)
Eventhough the preoperative ejection fraction was only moderately reduced. The application of levosimendan led to an improvement of EF. This seems rather promising especially when having in mind, that patients with severely reduced EF don not improve in ventricular function after aortic valve replacement without any concomitant treatment.

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Fig. 7. Effects of levosimendan on cardiac performance and recovery in aortic valve surgery (Järvelä et al. 2008)

4.2 Statins
Statins have become a blockbuster drug primarily for artherosclerotic diseases, but they have pleotropic effects. This triggered the interest on potential beneficial effects of these drugs for other indications like aortic aneurysms and calcific valvular heart disease. Considerations regarding statin-therapy for valvular heart diseases are on the one hand slower progression of calcification in patients with aortic stenosis and on the other hand there are studies showing that statin therapy improves the outcome after aortic valve replacement.
Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid lowering studies have had conflicting results. There are studies suggesting statin-therapy for every patient with aortic stenosis and on the other hand there are studies showing that statin therapy improves the outcome after aortic valve replacement. (Fedoruk et al. 2008) However Rossebo et al. showed that statin-therapy did not reduce the composite outcome of combined aortic-valve events and ischemic events in AS patients. Statin-therapy resulted in reduced incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (Rossebo et al. 2008) Nevertheless the overall outcome of patients with statin-therapy in this study was superior to those without statin-therapy, this might be due to the fact that a high percentage of AS patient have concomitant ischemic cardiovascular diseases. Therefore we would suggest statin-therapy as standard of care for every patient with aortic stenosis.
4.3 Prosthesis patient mismatch
Prosthesis patient mismatch (PPM) occurs when the effective orifice area (EOA) of a prosthetic valve is too small relative to the patient’s body size. It is graded as moderate if the ratio of effective orifice area (EOA) in cm square to body surface area in m square is <0.85 cm²/m² and severe if it is <0.65 cm²/m². PPM has been a controversial topic ever since valves have been implanted. (Mascherbauer, 2008; Yap CH 2007)

Urso et al. concluded in their best evidence topic that there is no strong evidence that moderate patient-prosthesis mismatch (PPM) (indexed IEOA0.85 and >0.65 cm²/m²) is an independent risk factor for 30-day or mid-term overall mortality for adult patients undergoing AVR. An exception could be represented by patients with poor ejection fraction, a condition that can make moderate mismatch a predictor of overall mortality after AVR. On the other hand, severe mismatch is a predictor of overall 30-day or mid-term mortality for patients undergoing AVR independently from the presence of poor ejection fraction. In conclusion, our review suggests that the condition of severe PPM should be always avoided, while the presence of moderate mismatch could be tolerated in patients with normal ejection fraction without any impact on overall survival. (Urso 2009)

Ruel an colleagues concluded that prosthesis–patient mismatch at an indexed effective orifice area of 0.85 cm²/m² or less after aortic valve replacement primarily affects patients with impaired preoperative left ventricular function and results in decreased survival, lower freedom from heart failure, and incomplete left ventricular mass regression. Patients with impaired left ventricular function represent a critical population in whom prosthesis–patient mismatch should be avoided at the time of aortic valve replacement. (Ruel 2005)

There are various ways for reduction of PPM including aortic root enlargement, use of a supra-annular or high performance prosthesis, and the use of a stentless bioprosthesis, aortic homograft, or pulmonary autograft. (Hashimoto 2006)

4.4 The awake patient in cardiac surgeons
Since heart valve surgery in high-risk patients is associated with considerable morbidity and mortality epidural anaesthesia without mechanical ventilation has been proposed to reduce invasiveness. Bottio et al. showed that heart valve surgery utilising cardiopulmonary bypass is feasible and can be safe using epidural anaesthesia. By maintaining autonomic ventilation, a low mid-term morbidity and mortality was observed in patients in whom there was an unacceptable operative risk. (Bottio 2007)

Nevertheless we feel that this is only a niche for cardiac surgical adventurers and only an important step in as far that proof of concept has been demonstrated, however not a method we would recommend to any of our patients.

4.5 Future perspectives
4.5.1 Transcatheter aortic valve implantation (TAVI)
A substantial number of AS patients have reduced ejection fraction and severe coexisting conditions that preclude surgery. Recently transcatheter aortic-valve implantation (TAVI) has emerged as less invasive and safer alternative for those patients. TAVI can be performed either by a retrograde approach, in which a catheter is inserted through the common femoral artery, or by an antegrade, transapical approach, in which a catheter is inserted through the apex of the left ventricle with the use of an anterolateral thoracotomy. (Lazar, 2010) Initially single-center, nonrandomized trials have shown the feasibility of TAVI in patients who are not suitable candidates for surgical replacement of the aortic valve. (Himbert et al. 2009, Webb et al. 2009)
Fig. 8. Implantation of an Aortic Quick Connect Bioprosthetic valve (Edwards Lifesciences)
In 2011 Leon and his coauthors report the results of the placement of Aortic Transcatheter Valves (PARTNER) trial, a prospective, randomized, multicenter trial to determine the optimal method of treating patients with critical aortic stenosis who are considered not to be suitable candidates for surgery. This revealed promising results showed a 20% reduction in mortality in comparison to medical treatment alone in patients with significant aortic stenosis not suitable for surgery. Furthermore the trial revealed that TAVI can achieve similar results as surgery in high risk patients. (Leon 2011)

4.5.2 Sutureless aortic valve bio prostheses

Another step towards reduction of operative time and thus lowering the burden of surgical intervention for the patient is the invention of sutureless aortic bioprosthesis. Currently there are 3 different valve types on the market: Perceval (Sorin), Enable (ATS, Medical) and Aortic Quick Connect (Edwards Lifesciences). They require only three stitches at the nadirs of the annulus to navigate the valve into the right plane prior to deployment of the nitinol stent. Initial clinical experience with these valves was satisfactory revealing promising results. In case of the Perceval valve the study investigators were able to implant a well-functioning sutureless stent-mounted valve in the aortic position in less than 20 minutes of aortic crossclamping. This was associated with excellent early clinical and hemodynamic outcome in high-risk patients. (Flameng et al. 2011). The sutureless valve implantation technique is also feasible and safe with the ATS 3f Enable Bioprosthesis. Valve implantation resulted in excellent hemodynamics and significant clinical improvement. Overall, these data confirm the safety and clinical utility of the Enable(®) Bioprosthesis for aortic valve replacement. (Martens et al., 2011) Data for the most recent sutureless valve to appear on the market, the Aortic Quick Connect, are also excellent. (Kocher et al., 2011)

The quick implantation procedure shortens the operative time, in particular the cross clamp time. Which has been shown to be a variable for poor outcome after aortic valve replacement.

5. Conclusion

Aortic-valve replacement or transcatheter aortic valve implantation are the most effective treatments to alleviate symptoms and improve survival in patients with critical aortic stenosis. Aortic valve disease especially stenosis is on the rise as it is primarily a disease of the elderly. Patients with decreased EF are clearly a high risk population, demonstrating both increased morbidity and mortality after aortic valve surgery. However in this chapter we could show that the cardiovascular medical community has so far responded to this challenge by devising new strategies to cope with the problem of an ever sicker patient population. A substantial number of these patients with coexisting conditions that used to preclude surgery are nowadays treated by less invasive approaches like TAVI. Furthermore there is progress on many fronts: Serum markers like BNP will help to time the intervention, levosimendan is already employed to precondition the patients prior to surgical interventions. New technologies like sutureless valves and TAVI significantly reduced the burden of the intervention. Apart from these new inventions one of the most important strategies to improve the outcome of patients undergoing aortic valve replacement with and without impaired left ventricular function is meticulous surgical performance.
Patients with an aortic valve pathology and a severely reduced ejection fraction constitute a significant challenge. However, in light of the recent inventions, innovations, new technologies and strategies for this patient cohort we are positive that the scientist and medical professionals in the field of cardiovascular medicine will be able to tackle this problem.

6. References


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Kocher A et al. 2011 Technical consideration regarding the implantation of a novel sutureless valve, 2011 ISMIC meeting


The aortic valve is located at the center of the heart. It is the core of cardiac anatomy and aortic valve surgery has led the field of cardiac surgery. This book describes all aspects of aortic valve surgery and it will help clarify daily questions regarding the clinical practice in aortic valve surgery, as well as induce inspiration and new insights into this field.

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