Surgical solutions for complex aortic root pathology

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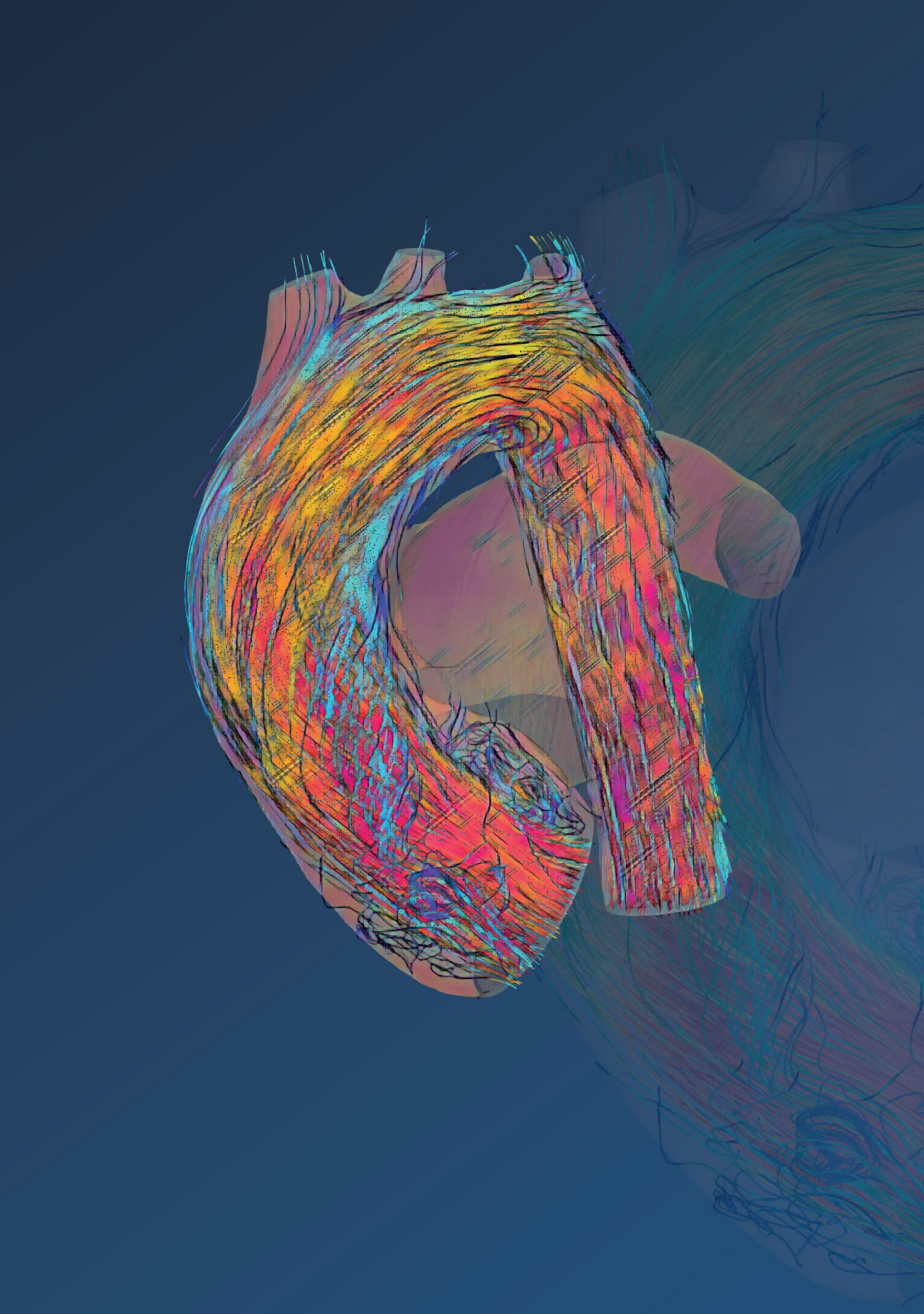

SUMMARY AND FUTURE PERSPECTIVES

CHAPTER 9

This thesis addresses long-term clinical outcomes after biological aortic root replacement focusing on stentless prostheses. Stentless prostheses have the advantage of a large effective orifice area, providing optimal hemodynamics. Which type of prosthesis is ideal for which patient, however, depends on several factors, such as age and comorbidities. In this thesis, outcomes after aortic root replacement with the use the pulmonary autograft and the Freestyle stentless bioprosthesis are presented. The data presented in this thesis can be used to guide prosthesis choice.

In ***Chapter 1,*** the spectrum of aortic valve and root pathology is introduced, and surgical treatments are described. The development, anatomy, morphology and dynamics of the aortic valve and root are discussed in detail. The complex relationship between the different parts which form the aortic valve apparatus is illustrated. Proper function of the valve relies on each of these parts are functioning optimally. Diastolic stress on the valve leaflets in a normal aortic root is shared with the aortic root wall. This may implicate increased valvular stress on prostheses that do not replace the complete root, or composite prostheses consisting of a (stented) valve prosthesis inside a vascular tube graft. The etiology and natural history of aortic valve disease in children and adults are discussed, as well as the several treatment options currently available.

Aortic valve disease in young children is mostly congenital. Severe congenital aortic stenosis can be accompanied by left ventricular outflow tract obstruction (LVOTO) due to underdevelopment of the outflow tract and myocardial hypertrophy. Often, these patients have other cardiac anomalies. The amount of hypoplasia of the left ventricle determines whether a biventricular correction is possible, or if there is need for a univentricular palliation. In case biventricular correction is feasible, the LVOTO needs to be relieved and the underdeveloped aortic valve and root need to be replaced. As prosthetic valves have fixed sizes, they are incapable of growing with the child. In these patients, the patients' own pulmonary valve can be used to replace the aortic valve, as this is capable of somatic growth. Furthermore, the LVOTO can be relieved by incising the interventricular septum. Outcomes after this so-called 'Ross-Konno' procedure in 48 patients are discussed in ***Chapter 2.***

The median age of the study population was 12.8 months, with 46% of patients under 1 year of age. The vast majority of patients (92%) had undergone 1 or more previous cardiac interventions. The high risk of the Ross-Konno procedure

was demonstrated by an early mortality rate of 12.5%. A poor LV function, as an expression of severity of hypoplasia, was an independent risk factor for early mortality. Median follow-up time of the patient cohort was 4.3 years (range, 0 to 20 years). Reoperation for autograft failure was necessary in 5 patients at a median age of 14 years after the Ross-Konno procedure, mostly for autograft dilatation and concurrent regurgitation. Freedom from all-cause reoperation at 10- and 15 years was 55% and 33%, respectively. Most reoperations were necessary for degeneration or size mismatch of the right-sided conduit.

The results described in Chapter 2 show that the Ross-Konno procedure is a durable solution for multilevel LVOTO in a highly complex patient population. The high early mortality rates in patients with impaired left ventricular function, however, emphasize the importance of patient selection. Reoperation for autograft failure may occur late after the Ross-Konno procedure.

In young patients with aortic valve disease without underdevelopment of the left ventricle, surgery can often be postponed to later in life, for example by dilating a stenotic valve using balloon valvuloplasty. Furthermore, congenital aortic valve disease may first present itself during (young) adulthood. In these patients, the pulmonary autograft can be used to replace the aortic valve, without the need for left ventricular outflow tract augmentation, i.e. the Ross procedure. As shown in Chapter 2, autograft dilatation may necessitate reintervention on the pulmonary autograft in time. In ***Chapter 3*** outcomes after both the Ross, and the Ross-Konno procedure are reported, focusing on autograft function during long-term follow-up, analyzed using a competing risks model.

Data on 154 patients who underwent the Ross (n=105) and Ross-Konno (n=49) procedure was analyzed. There were 8 (5%) early deaths, 6 of whom underwent the Ross-Konno procedure, and 10 (7%) late deaths. Survival rates at 15 years were 86% in the total cohort and 91% in the isolated Ross subgroup. Cumulative incidences of all cause reoperation at 15 and 20 years were 35.2% and 45.3%, respectively. Twenty-six patients needed autograft reoperation, 20 due to dilatation. Cumulative incidences of autograft reoperation at 15 and 20 years were 20.1% and 31.1%, respectively.

The data presented in Chapter 3 shows that the Ross procedure can be performed safely in young patients with low number of valve related events. Autograft

function remains stable in the first decade after surgery, but autograft dilatation in the second decade necessitates reintervention.

As shown in Chapters 2 and 3, dilatation of the pulmonary autograft may necessitate reintervention during (long-term) follow-up. In ***Chapter 4*** a surgical technique in which the autograft is reinforced in order to prevent late dilatation of the autograft wall is presented. After harvesting, the pulmonary autograft is reimplanted in a vascular tube graft, scalloping all three sinus walls. This technique makes autograft regurgitation due to dilatation of the sinus walls impossible, potentially lengthening the durability of the pulmonary autograft. This technique, however, is only possible in fully grown patients, as it deprives the capability of growth of the autograft with somatic growth of the patient.

Several stentless bioprostheses are currently available to replace the aortic valve and root. The Freestyle stentless bioprosthesis has been available since 1992. In ***Chapter 5*** long-term outcomes after the use of this prosthesis are described. Furthermore, a competing risks regression model was constructed to provide predictive data on the expected clinical trajectory after aortic valve and root replacement using this prosthesis

Data on 604 patients operated on between 1993 and 2014 were collected both retrospectively and prospectively. This chapter shows that the Freestyle prosthesis can be used safely to replace the aortic valve and root, demonstrated by the decline in early mortality rates over the years, with no early mortality in elective, isolated root replacement surgery during the last 5 years of the study period. Competing risks regression identified patients' age, renal function, and implantation technique of the bioprosthesis as significant risk factors for death (age, renal function) and the development of structural valve deterioration (age, implantation technique). Full root replacement and increasing age were protective for structural valve deterioration. The cumulative incidences of structural valve deterioration at 15 years ranged from 36% in patients with maximum risk factors (young, poor renal function, subcoronary implanted prostheses) to 4% in patients >70 years of age with a good renal function who underwent full-root replacement.

Chapter 5 shows that the Freestyle prosthesis is a valuable option in patients with an indication for aortic root replacement. The predictive data presented in this chapter can be used to fully inform patients on the expected (individualized)

clinical trajectory after implantation of this prosthesis, aiding the shared decision making process of prosthetic valve choice.

The previous chapter showed good performance of the Freestyle prosthesis in a wide variety of patients. In ***Chapter 6,*** the use of this prosthesis in the specific setting of extensive (prosthetic) aortic valve infective endocarditis is addressed. Severe infective endocarditis of the aortic valve often extends into perivalvular structures, such as the aortic-mitral continuity and the roof of the left atrium, and to a lesser extent the membranous septum towards the right atrium, and the pulmonary valve. The cornerstone of treatment in infective endocarditis is the radical resection of all infected tissues. This necessitates, often complex, reconstruction of all resected structures. The pliable suture ring of the Freestyle prosthesis facilitates optimal implantation of the prosthesis in the reconstructed 'annulus'.

Fifty-four consecutive patients were analyzed, 29 of whom had prosthetic valve endocarditis and 13 had septic emboli prior to surgery. The early mortality rate was 11%, and estimated 5 year survival was 70%. There was no survival difference between native and prosthetic valve endocarditis. One patient underwent reoperation for recurrent endocarditis at 2.3 years after index surgery. Prosthesis function was good after a median follow-up time of 3.5 years.

Infective endocarditis of the aortic valve, extending into perivalvular structures is a life threatening condition requiring aggressive surgical debridement of all infected tissues and subsequent reconstruction. Chapter 5 shows that the Freestyle prosthesis is a valuable option in this specific setting. Although early mortality rates are high, demonstrating the severity of this disease, surgery is the only curative treatment available for these patients. Low incidences of recurrent endocarditis were seen in the studied patient population.

Their remains controversy about the preferred type of prosthesis to replace the aortic valve and root. Both biological and mechanical prostheses have their advantages. In short, bioprosthesis degenerate in time, but mechanical prostheses require anticoagulant treatment with all of its accompanying risks. In ***Chapter 7,*** outcomes after the use of both type of prostheses are presented. To make both patient groups comparable, the two groups were matched using propensity score matching.

Data on 117 patients who received a mechanical valved conduit were compared to 260 patients who received a Freestyle stentless bioprosthesis. Propensity score matching resulted in 103 matched pairs. Median age after matching was 65 years in both groups. A trend towards less valve related complications (thromboembolic- and bleeding events, reintervention, and valve related death combined) in the bioprosthetic group before matching was confirmed by a significant difference after matching. Furthermore, overall mortality in the patient group receiving a bioprosthesis was significantly lower compared to the patients who received a mechanical conduit. This difference was mainly ascribed to more sudden, unexplained deaths, which are likely to be due to fatal (cerebral) bleeding events due to anticoagulation treatment. Although the difference in incidence of reintervention on the prosthesis was not significantly different in this cohort, more reinterventions in the bioprosthetic group are to be expected with longer follow-up.

Chapter 7 shows that both mechanical and bioprosthetic aortic root replacement are feasible options. In the mid-term, bioprosthetic aortic root replacement is associated with less valve-related complications.

As previously mentioned, bioprostheses are subject to structural degeneration in time, often necessitating reintervention. With an increased use of bioprostheses, also in younger patients, it can be expected that reinterventions will be necessary more often in the coming years. In Chapter 8, an extensive overview of the risks associated with reinterventions after previous aortic valve or root replacement using the Freestyle bioprosthesis is presented.

A series of 75 patients after previous aortic valve or root replacement using a stentless bioprosthesis were analyzed. Median age was 62 years, and most patients needed reintervention due to structural degeneration of their prosthesis. Redo root replacement was the most common intervention (51 patients), followed by surgical AVR (16 patients) and transcatheter AVR (8 patients). The early mortality rate was 9.3%, and lowest in redo root replacement. After a learning curve, mortality in elective reoperations for SVD had zero mortality. Transcatheter reinterventions carry the risk of (often fatal) coronary obstruction. Chapter 8 shows that patient' characteristics, rather than the type of reintervention, contribute most to the risk of early death. Considerations in redo surgery, as well as in transcatheter valve-in-valve interventions are extensively discussed in Chapter 8.

Reinterventions after stentless aortic valve or root replacement carry an acceptable risk in the current era. Periprocedural risks are mostly determined by patient' characteristics. Transcatheter reinterventions require careful consideration of anatomic factors to minimize the risk of coronary obstruction.

FUTURE PERSPECTIVES

To date, no perfect prosthesis exists to replace a diseased aortic valve and root. All currently available prostheses have their advantages, but also their shortcomings. However, there are several developments to improve valve prostheses.

Mechanical prostheses

For mechanical prosthesis, the burden of anticoagulant treatment is the main disadvantage. Current developments are aimed to lower this burden by lowering the target International Normalized Ratio (INR). Current guidelines advice an INR of 3.0 – 3.5 for most modern mechanical prostheses [1]. Changes in valve design (e.g. smoother hinges) or improved endothelization of the valve leaflets might lower the target INR, lowering the risk of thromboembolic and bleeding complications [2,3]. However, it has to be awaited whether the anticoagulant burden accompanying mechanical prostheses can be lowered enough to increase their use in valvular heart disease.

Biological prostheses

For biological prostheses, new treatment methods are being developed to treat the valve tissue, aimed at decreasing the immunologic response and preventing calcification. Furthermore, structural alterations are made to better facilitate possible future valve-in-valve therapies by creating an expansion zone in the prosthesis, enabling larger sized transcatheter prostheses [4]. This could minimize the burden of reintervention after bioprosthetic valve failure.

Tissue engineering

In theory, tissue engineered heart valves (TEHV) are the ideal valve prosthesis. The goal of tissue engineering, is providing a living, competent valve, capable of continuous remodeling. Ideally, the valve should be capable of growth, expanding their use in young children. A three-dimensional scaffold is needed to

accommodate repopulation with the patients' own cells. The use of decellularized aortic and pulmonary homografts is currently being explored in the ARISE [5] and ESPOIR [6] trials, respectively, with promising early results.

Alternatives to existing valves, scaffolds can be created by molding or suturing biomaterials to a stent, electrospinning, 3D bioprinting, or a combination of these techniques [7]. Regardless of the technique used, scaffolds need to be, amongst others, biodegradable, non-immuno- and thrombogenic, capable of repopulation and mechanically robust [7]. Although the possibilities of THEV are exciting, many challenges have to be overcome before they can be routinely used clinically in the treatment of diseased heart valves.

Patient involvement

As mentioned, the ideal valve prosthesis still does not exist. Therefore, involving patients in the decision on type of prosthesis is of paramount importance. Different patients have different lifestyles and lifegoals, influencing this decision. In order to choose a certain type of prosthesis, patients should be fully informed on the available options, and the accompanying advantages and disadvantages. Wishes and expectations of the patient should be taken into account, and final prosthesis selection should be a shared decision between the patient and surgeon. The data presented in this thesis aid this shared-decision making process.

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