Hemodynamic concepts in aortic valve replacement

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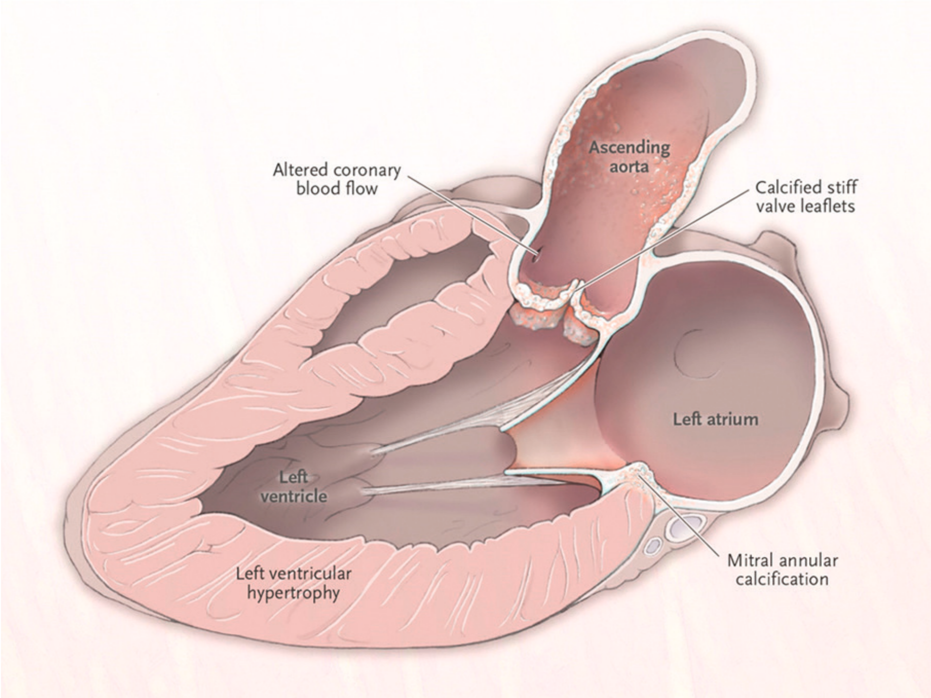
INTRODUCTION AND GENERAL OUTLINE OF THE THESIS

NORMAL AND ABNORMAL FUNCTION OF THE AORTIC VALVE

The aortic valve forms the gate between the heart and systemic circulation. It needs to open and close properly to prevent hemodynamic obstruction and guarantee unidirectional blood flow: from the left ventricle to the aorta. Valve motion is driven by pressure differences between these compartments during the cardiac cycle. The opening and closing properties rely on functional and anatomical aspects such as valve leaflet morphology, mobility and coaptation.

Aortic stenosis (AS) refers to a state in which the valve's opening property is diminished. AS is one of the most prevalent valvular heart diseases in adults in the Western world [1] and is present in around 2.8% of people aged 75 years and older [2]. It is a progressive condition predominantly of degenerative nature and mechanistically related to atherosclerosis [1-3]. The pathophysiological process is mainly driven by calcification, along with fibrosis and inflammation. Pediatric valvular heart disease is very different and falls outside the scope of this thesis. Risk factors for AS in adults include age, dyslipidemia, diabetes mellitus, hypertension and smoking, among others. Bicuspid aortic valve, a congenital abnormality in which one commissure is either absent or underdeveloped, is an important risk factor and is present in about 1-2% [1,2] of patients with AS. In contrast to degenerative or senile AS, bicuspid AS develops much earlier in life. In AS, obstruction at the level of the valve could lead to insufficient cardiac output and pressure overload of the left ventricle (LV) resulting in adverse remodeling and heart failure *(Figure 1)*. In contrast, aortic regurgitation or insufficiency emerges when the valve closes inadequately allowing blood to leak back to the heart [4]. Aortic regurgitation (AR) shares certain risk factors with AS such as bicuspid aortic valve. In developing countries, rheumatic disease is the main cause of AR. In sporadic instances, aortic dissections or endocarditis result in acute regurgitation which requires urgent intervention. AR mainly leads to volume overload which negatively impact LV function and inherently increase the risk of mortality and morbidity. The primary focus of this thesis is hemodynamic obstruction, i.e., stenosis, rather than regurgitation.

Figure 1. Sequelae of severe aortic stenosis.



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AORTIC VALVE REPLACEMENT

The indications for intervention on the aortic valve are based on hemodynamic severity of aortic valve disease, symptoms and LV function [5,6]. The main idea is to intervene on the valve before other components of the heart are irreversibly damaged. After the onset of severe aortic valve disease, the prognosis rapidly deteriorates if no intervention is performed [7]. Potential interventions can be divided into surgical and transcatheter aortic valve replacement (SAVR and TAVR, respectively). The first SAVR procedure was described by Hufnagel *et al.* in 1954 [8]. Since then, the surgical techniques, perioperative management, and the prosthetic heart valves have drastically improved. For the latter, a distinction is made between mechanical and biological valves with porcine or bovine pericardial leaflets. Surgical biological valves can be further subdivided into stented, stentless and sutureless bioprostheses. Homografts or pulmonary autografts, used in the Ross procedure, are additional options but these are rarely used in acquired aortic valve disease in older adults [9]. SAVR can be performed through a full sternotomy or by using less invasive access routes, like upper hemi-sternotomy, right anterior or axillary thoracotomy (so-called mini-AVR). An even less invasive interventional alternative to SAVR, without the use of extra corporeal circulation techniques is transcatheter TAVR which was first described by Cribier *et al.* in 2002 [10]. While this treatment was initially proposed for high-risk individuals, it is currently offered to patients across the entire range of surgical risk [5,6]. In contemporary practice, way more TAVR than SAVR procedures are annually performed [11]. The choice for specific interventions and prosthetic valves for individual patients is based on patient characteristics, prosthetic valve durability and, importantly, patient preference [5,6].

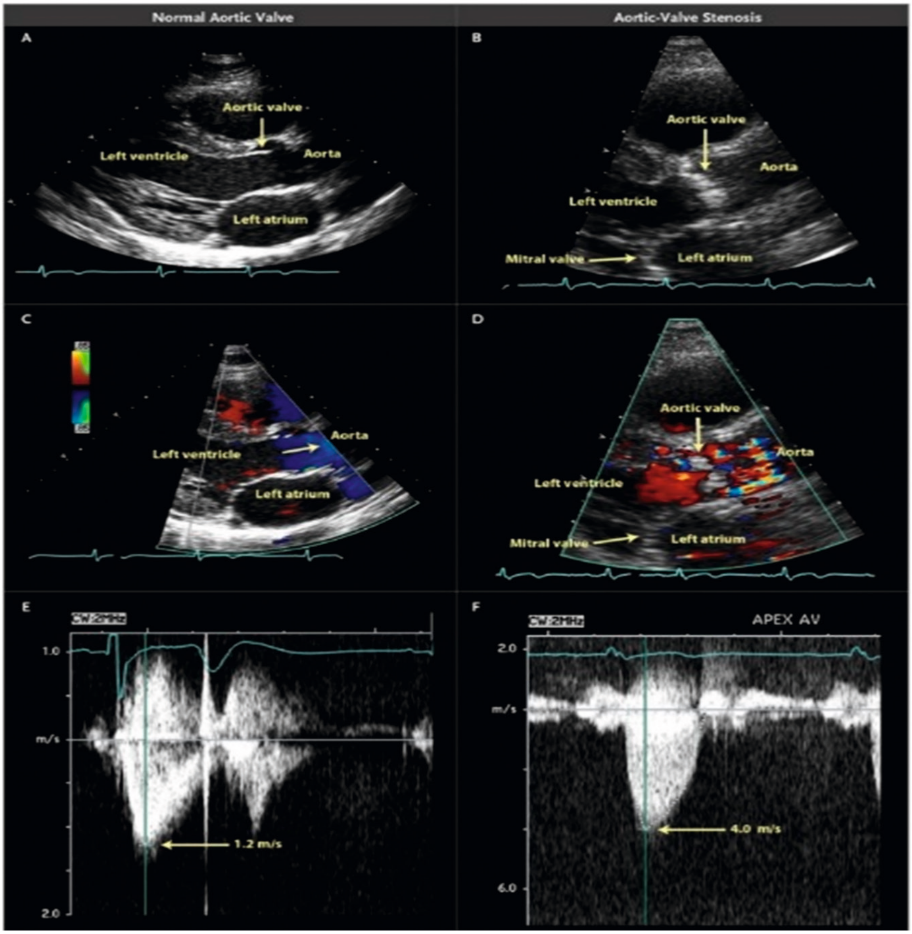
THE ROLE OF ECHOCARDIOGRAPHY IN AORTIC VALVE REPLACEMENT

Echocardiography plays a central role in the assessment of the performance of the aortic valve. It guides the indication for intervention on the native aortic valve as well as the evaluation of prosthetic heart valves, both after implantation and during follow-up. This imaging tool, based on ultrasound, could provide quantitative information such as the opening area of the valve as well as qualitative insights like leaflet mobility and the presence of paravalvular leak in a quick examination. Before the era of echocardiography, valvular performance was assessed via cardiac catheterization [12]. Pioneers like Liv Hatle, Catherine Otto, and Jae Oh demonstrated that non-invasive estimation of hemodynamic parameters like the pressure gradient and the aortic valve area corresponded well to invasive catheterization measurements [13-16]. To note, it is good to realize that current hemodynamic measurements are based on complex fluid dynamics fundamentals [17]. Several pragmatic assumptions are made to simplify the clinical assessments [18]. For example, the behavior of fluids like blood is expressed by the Navier-Stokes equation which forms the base of the Bernoulli equation, and in clinical practice, the simplified Bernoulli equation is used to determine the transvalvular gradient.

Preoperative assessment

In preoperative care, the severity of AS is categorized as mild, moderate or severe using three primary echocardiographic parameters: the peak aortic jet velocity, the mean pressure gradient, and the aortic valve area [19]. To measure these parameters, blood velocity during the cardiac cycle needs to be recorded at the level of the aortic valve and in the left ventricular outflow tract (LVOT), of which geometric measurements like the LVOT diameter are also required *(Figure 2)*. In addition, various physiological and geometrical assumptions are made for pragmatic reasons. Next to these primary parameters, many other exist [19], however, current international guidelines lack any recommendations for AVR based on them [5,6]. In asymptomatic patients, the indication for intervention relies solely on echocardiography which underscores its pivotal role even more. The natural history of asymptomatic AS is not benign [20,21], and asymptomatic patients with “very severe” stenosis seem to benefit from early intervention [22,23]. In a reasonable amount of patients, the primary echocardiographic parameters are discordant [24]. The diagnosis of AS is challenging when the mean pressure gradient and aortic valve area depict different levels of disease severity. Even in case of preserved left ventricular ejection fraction, flow alterations are thought to play a crucial role in explaining this discrepancy. Hence, a classification based on flow-gradient patterns was proposed to improve the diagnosis of true severe AS [25]. Many uncertainties remain regarding the accuracy of this diagnostic classification, and the characteristics, prognosis, and optimal interventional strategy for these flow-gradient groups [24-26].

Figure 2. Echocardiographic evaluation of a normal and stenotic aortic valve.



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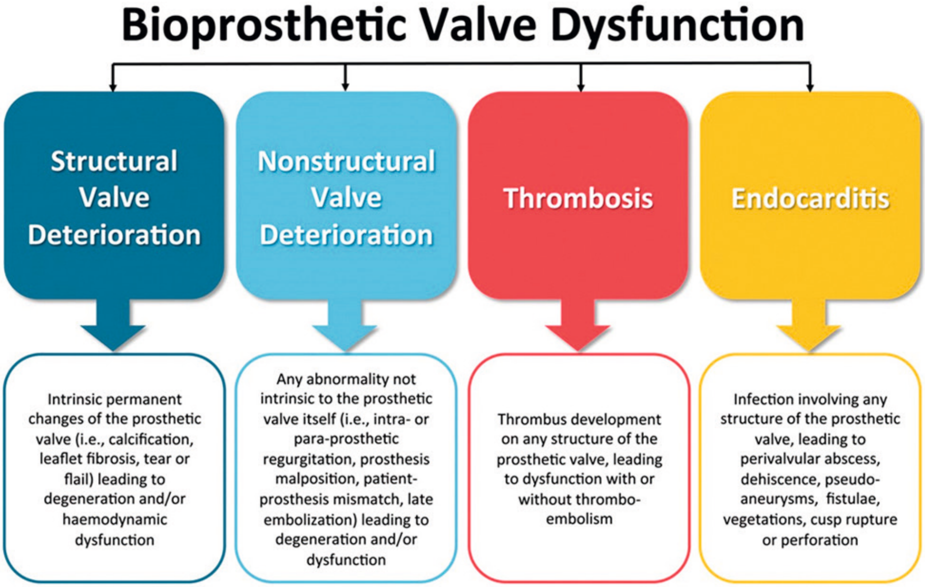
Perioperative management

In perioperative care, echocardiography is used to assess the technical success of prosthetic valve implantation and motion of the leaflets. Especially, the presence of paravalvular leak is carefully evaluated since it is associated with worse outcomes [27]. Specific interventional strategies or surgical approaches could affect hemodynamic outcomes such as paravalvular leak or the effective orifice area after implantation, for example through the prosthetic valve type or the suturing technique.

Postoperative assessment

In postoperative care, quantitative echocardiographic measurements are performed to investigate whether the prosthetic valve is sufficient for the patient's hemodynamic requirements. Because prosthetic valves are placed inside the aortic annulus / root, and most prostheses contain a sewing ring and struts, they could hinder the blood flow and generate some hemodynamic obstruction themselves [28,29]. If there is considerable hemodynamic obstruction after an intervention, this is called prosthesis-patient mismatch (PPM). This problem is currently defined by echocardiographic thresholds for the effective orifice area indexed to body surface area (BSA) [30]. PPM after AVR seems to be associated with increased mortality in most studies [31-33], however, the current definitions have been challenged for the appropriateness of the cut-offs and the validity of BSA indexation [34,35]. Up to now, no other echocardiographic parameters have been considered for the definition of PPM. Bioprosthetic valve dysfunction due to PPM or paravalvular leak are categorized as non-structural valve deterioration [30,36] *(Figure 3)*. The performance of prosthetic valves could also be hampered as a result of endocarditis, valve thrombosis, or structural valve deterioration (SVD). The latter is defined as irreversible damage to intrinsic components of the prosthesis such as the leaflets or the struts, and is caused by mechanical wear and immunological processes [30,36]. Durability remains a major, if not the most important, concern for biological heart valves. To detect prosthetic degeneration early, preferably at times that redo surgery or valve-in-valve reintervention could still be performed, new echocardiographic definitions have been proposed for hemodynamic SVD [30,36,37]. These definitions have been developed based on theory and their accuracy and clinical utility have yet to be explored.

Figure 3. Sources of bioprosthetic valve dysfunction.



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CHALLENGES IN ECHOCARDIOGRAPHIC IMAGING

Echocardiographic parameters are proxies for valvular performance, the underlying construct that we aim to measure, but they are also affected by physiological elements like LV function, vascular function and biological variability as well as non-physiological sources such as measurement error. These factors complicate the interpretation of valvular performance. Examples of challenging situations comprise assessment in patients with irregular contraction patterns or altered flow states. This thesis is in part devoted to distinguishing valvular performance from other disturbing sources to improve the interpretation of echocardiography and aid clinical decision-making by cardiologists and cardio-thoracic surgeons concerning the native and bioprosthetic aortic valve. The main challenges regarding hemodynamic concepts in aortic valve replacement that are addressed in this thesis are summarized in Table 1.

Table 1. The main challenges addressed in this thesis regarding hemodynamic concepts in aortic valve replacement.

Aortic Valve Replacement	Main challenge addressed in this thesis
Preoperative assessment	• The diagnosis of severe aortic stenosis in asymptomatic patients • The diagnosis of severe aortic stenosis in low-flow patients
Perioperative management	• The surgical strategy to optimize hemodynamic performance • The research methods to determine optimal surgical strategies
Postoperative assessment	• The prognostic value of prosthesis-patient mismatch and other parameters for residual hemodynamic obstruction • The diagnosis of hemodynamic structural valve deterioration

GENERAL OUTLINE OF THE THESIS

The overall aim of this thesis is to improve the evaluation of the native and bioprosthetic valve by cardiologists and cardio-thoracic surgeons to optimize clinical management. This thesis is delineated in chronological order starting at the onset of native aortic valve disease via the implantation of the tissue valve to end with bioprosthetic valve degeneration. While the primary focus lies on the clinical content, special attention is paid to the application of various epidemiological methods for measurement error, causality, predictive analytics, missing data, and longitudinal data analysis.

Part I is dedicated to hemodynamic performance of the native aortic valve, specifically aortic stenosis. In **Chapter 2**, the impact of measurement error in the echocardiographic assessment of AS severity is investigated in context of current thresholds for intervention in international guidelines [5,6]. In **Chapter 3 and 4**, the accuracy and clinical utility of the flow-gradient classification of severe AS are explored. The main pitfall of this classification is echocardiographic estimation of stroke volume; hence, experts have stressed that corroboration with other methods is essential [24-26]. In **Chapter 3**, the robustness of the flow-gradient classification is analyzed by studying reclassification due to different echocardiographic stroke volume measurements and measurement error. In **Chapter 4**, the impact of BSA on the classification of paradoxical low-flow severe AS is investigated. In the definition of this classification, BSA is used twice to index both stroke volume and aortic valve area [25], therefore it might disproportionally affect the probability to be classified as paradoxical low-flow stenosis. **Chapter 5** describes the differences in echocardiographic assessment of the native and bioprosthetic valve between a central core laboratory and clinical centers.

Part II focusses on the role of interventional strategies and surgical approaches regarding hemodynamic performance of bioprosthetic valves. In **Chapter 6**, outcomes after minimally invasive procedures such as right anterior thoracotomy and hemisternotomy are compared to conventional sternotomy. In **Chapter 7**, the effect of suturing techniques with pledgets is contrasted with techniques without pledgets in a cohort study. **Chapter 8** is a systematic review and meta-analysis on the same topic summarizing all available evidence. **Chapter 9** describes a step-by-step surgical tutorial of the implantation of a stentless aortic bioprosthesis. In **Chapter 10**, perioperative care differences of SAVR between North America and Europa are described to examine the generalizability of region-specific study results. These continents have separate guidelines [5,6] but the extent of practical differences is unknown. **Chapter 11** zooms in on methodological practice of studies on the optimal interventional strategy. The quality of reporting and conduct regarding confounding adjustment is investigated in observational studies not only on aortic valve procedures but on cardiothoracic interventions in general.

Part III addresses echocardiographic concepts in the postoperative phase. In **Chapter 12**, it is studied whether different postoperative echocardiographic parameters and the current thresholds for PPM [30] add prognostic value to a preoperative risk score for the prediction of all-cause mortality 5 years after SAVR. In **Chapter 13**, the reproducibility of the results of the previous study is examined in pooled data of three randomized controlled trials. Furthermore, the added prognostic value for cardiovascular mortality is also specifically targeted. Thereafter, the focus is shifted to the assessment of durability of bioprosthetic valves. In **Chapter 14**, the consistency of current definitions for hemodynamic SVD [30,36,37] is investigated.

This thesis ends with a summary of the main findings including a general discussion and outline of future perspectives on hemodynamic performance of the native and bioprosthetic aortic valve which is detailed in **Chapter 15.** A summary in Dutch is provided in **Chapter 16**.

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