Left Ventricular Efficiency for Pure and Mixed Aortic Valvular Disease

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A Thesis
in
The Department
of
Mechanical, Industrial & Aerospace Engineering

Presented in Partial Fulfillment of the Requirements
For the Degree of
Master of Applied Science (Mechanical Engineering) at
Concordia University
Montréal, Québec, Canada

August 2025

Concordia University
School of Graduate Studies

This is to certify that the thesis prepared

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Entitled: Left Ventricular Efficiency for Pure and Mixed Aortic Valvular Disease

and submitted in partial fulfillment of the requirements for the degree of

Master of Applied Science (Mechanical Engineering)

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Abstract

Left Ventricular Efficiency for Pure and Mixed Aortic Valvular Disease

Mahdis Asaadi

Aortic stenosis (AS) and aortic regurgitation (AR) are common across all age groups, yet their co-occurrence in mixed aortic valve disease (MAVD) remains poorly understood, particularly in terms of its impact on left ventricular (LV) performance and clinical assessment. Although patients with congenital aortic valve disease may remain asymptomatic, the risk of irreversible myocardial fibrosis, increased LV wall stress, and sudden death in untreated cases underscores the need for earlier intervention. While treatment guidelines exist for mild and severe cases, the optimal approach for moderate aortic valve disease (modAS, modAR) remains unclear. To address this, we developed a novel noninvasive parameter, LV efficiency, using a mathematical model to evaluate LV performance. The model was first validated *in silico* and in vivo using synthetic patient data ($N = 520$) and 25 pediatric patients (9 healthy, 8 modAS, 8 modAR). We then extended the model to MAVD by simulating 46,200 unique combinations of AS and AR severity, stroke volume (50–80 mL), heart rate (60–90 bpm), and systolic pressure (120–140 mmHg). LV efficiency showed a strong nonlinear power-law relationship with stroke work ($R^2 = 0.813$), with healthy subjects maintaining efficiency above 90% (synthetic: 90.74%, in vivo: 92.22%). ModAS cases showed moderate reduction (synthetic: 78.15%, in vivo: 76.29%, $p < 0.05$), while modAR had the lowest values (synthetic: 57.86%, in vivo: 65.81%, $p < 0.05$). Severe MAVD dropped below 20%, and moderate MAVD spanned 60–35%, overlapping with simulated severe AS. These results suggest that LV efficiency may offer a robust tool for monitoring disease severity and guiding intervention, even at the moderate stage. By capturing the combined hemodynamic burden of AS and AR, this parameter has the potential to support earlier risk stratification, optimize clinical decision-making, and improve outcomes across the spectrum of aortic valve disease.

To my parents.

To my sister and the rest of my family.

For any mechanical system to function correctly, it must adhere to certain fundamental laws, including thermodynamic principles. The human body is no exception.

Acknowledgement

I would like to express my sincere gratitude to my collaborators on this work: *Dr. Abdelghani Djebbari, Dr. Wadi Mawad, Dr. Zahra Keshavarz-Motamed, and Dr. Nagib Dahdah.*

Dr. Zahra Keshavarz-Motamed, whose foundational work on lumped parameter modeling is the cornerstone of this research. Her contributions not only laid the groundwork for this study, but also allowed us to build upon her pioneering work to explore a prevalent, yet understudied, pathology.

Dr.Wadi Mawad and Dr. Nagib Dahdah, for their clinical insights and for providing the pediatric clinical data that allowed us to validate our work beyond in silico simulations.

The most sincere thank you goes to my supervisors, Dr. Lyes Kadem and Dr. Ebenezer Ekow Essel. I am very grateful to Professor Essel for his continuous guidance and encouragement throughout the many projects and evolving directions this research has taken. I am especially thankful to Professor Kadem, whose invaluable mentorship has shaped my academic and professional journey since our first meeting during my undergraduate studies. As a mentor, professor, and advisor, his continuous support has been essential in shaping both the kind of research I aspire to pursue and the researcher I strive to become.

I owe my deepest gratitude to my parents, whose profound academic and professional journeys continue to inspire me and whom I strive to emulate in every way. Their unyielding dedication to learning and continuous growth has been a constant source of motivation, and it is because of them that I have the courage and determination to pursue my own path. They have instilled in me the greatest gift of all: an unquenching thirst for education and curiosity, and for that I am eternally grateful.

Table of Contents

List of Figures

List of Tables

Glossary

Aortic Regurgitation (AR) Leakage of blood backward through the aortic valve into the left ventricle during diastole.

Aortic Stenosis (AS) Narrowing of the aortic valve, restricting blood flow from the left ventricle to the aorta.

Aortic Valve Area (AVA) The size of the opening of the aortic valve; a measure of AS severity.

Aortic Valve Replacement (AVR) Surgical Replacement of the aortic valve.

Atrioventricular (AV) Coupling The functional relationship and coordination between the atria and ventricles, particularly in terms of their contraction and relaxation.

Cardiac Computed Tomography (CT) An imaging technique that uses X-rays to create cross-sectional images of the heart; useful for assessing valve calcification (calcium scoring).

Diastolic Function The ability of the heart to relax and fill with blood during diastole. Assessed by parameters like E/A ratio and e' velocities.

Dobutamine Stress Echocardiography (DSE) An echocardiographic test performed while administering dobutamine to increase heart rate and contractility, used to assess valve severity under stress and differentiate true-severe from pseudo-severe AS.

Doppler Echocardiography A type of echocardiography that measures the speed and direction of blood flow.

Echocardiography A non-invasive imaging technique using sound waves to create images of the heart.

Global Longitudinal Strain (GLS) A measure of the overall shortening of the left ventricle along its long axis during systole; reduced GLS can indicate subclinical LV dysfunction.

Left Atrium (LA) The upper left chamber of the heart that receives oxygenated blood from the lungs.

Left Ventricle (LV) The lower left chamber of the heart that pumps oxygenated blood to the body.

Left Ventricular Ejection Fraction (LVEF) The percentage of blood pumped out of the left ventricle with each beat; a measure of systolic function.

Left Ventricular End-Diastolic Volume (LVEDV) The volume of blood in the left ventricle at the end of diastole (relaxation).

Left Ventricular End-Systolic Volume (LVESV) The volume of blood in the left ventricle at the end of systole (contraction).

Left Ventricular Mass Index (LVMI) A measure of the size of the left ventricle, adjusted for body size; increased LVMI indicates hypertrophy.

Left Ventricular Outflow Tract (LVOT) The area below the aortic valve through which blood exits the left ventricle.

Left Ventricular Stroke Work (LVSW) Efficiency A proposed non-invasive parameter to evaluate LV performance, particularly in pediatric patients with moderate aortic valve disease.

Lumped Parameter Model (LPM) A simplified mathematical model that represents complex physiological systems as a network of interconnected components (e.g., resistances, compliances, inertances).

Mean Pressure Gradient (MG) The average pressure difference across the aortic valve during systole; a measure of AS severity.

Mixed Aortic Valve Disease (MAVD) The presence of both significant aortic stenosis and aortic regurgitation. Also referred to as mixed AS/AR.

NT-proBNP / BNP Hormones released by the heart in response to increased pressure or volume overload; elevated levels can indicate heart failure or significant cardiac stress.

Peak Aortic Jet Velocity (Vmax) The highest speed of blood flow through the aortic valve; a measure of AS severity.

Pressure Half-Time (PHT) The time it takes for the pressure gradient across a valve to decrease by half; used to assess AR severity.

Relative Wall Thickness (RWT) A measure of the thickness of the LV wall relative to its size; increased RWT indicates concentric remodeling.

Right Ventricle (RV) The lower right chamber of the heart that pumps deoxygenated blood to the lungs.

Strain Analysis An echocardiographic technique that measures the deformation of the heart muscle, providing insights into myocardial function. Global Longitudinal Strain (GLS) is a common measure.

Stroke Volume (SV) The volume of blood ejected from the left ventricle with each beat.

Transcatheter Aortic Valve Replacement (TAVR) A minimally invasive procedure to replace the aortic valve.

Transvalvular Flow Rate (TFR) The volume of blood flowing across a heart valve per unit time.

Vena Contracta (VC) The narrowest part of the regurgitant jet; a measure of AR severity.

1 | Introduction

1.1 Introduction into Aortic Valvular Disease

1.1.1 Cardiac Cycle

The heart's function as a biological pump can be understood through thermodynamic and mechanical principles that describe energy transfer and pressure–volume relationships. This framework enables a more quantitative understanding of cardiac performance and pathophysiology, particularly when applied to the dynamics of the left ventricle and aortic valve which are the two structures central to this thesis.

In an average adult, the heart beats between 60 and 80 times a minute [1]. In the space between one heartbeat and another, a series of pressure and volumetric changes occur, called a cardiac cycle. These changes in pressure and volume result in the movement of blood, not only through the different chambers of the heart, but throughout the body as a whole [2]. This process involves coordinated sequence of rhythmic contractions and relaxations of the four chambers of the heart, ensuring efficient blood circulation. Understanding this cycle is fundamental to recognizing the cardiovascular pathologies discussed in this thesis, as well as the intuition behind some of the thermodynamic principles that have been adapted from the mechanical domain to the anatomical and medical contexts.

An image of the heart, along with its chambers, is shown in Figure 1.1. The heart is divided into two halves through the middle, and each half is further divided into two chambers called the ventricle and the atrium [2].

The *left ventricle* is responsible for ejecting blood through the *aortic valve* into the aorta and, subsequently, into the rest of the body. This work focuses entirely on the *left ventricle* and the *aortic*

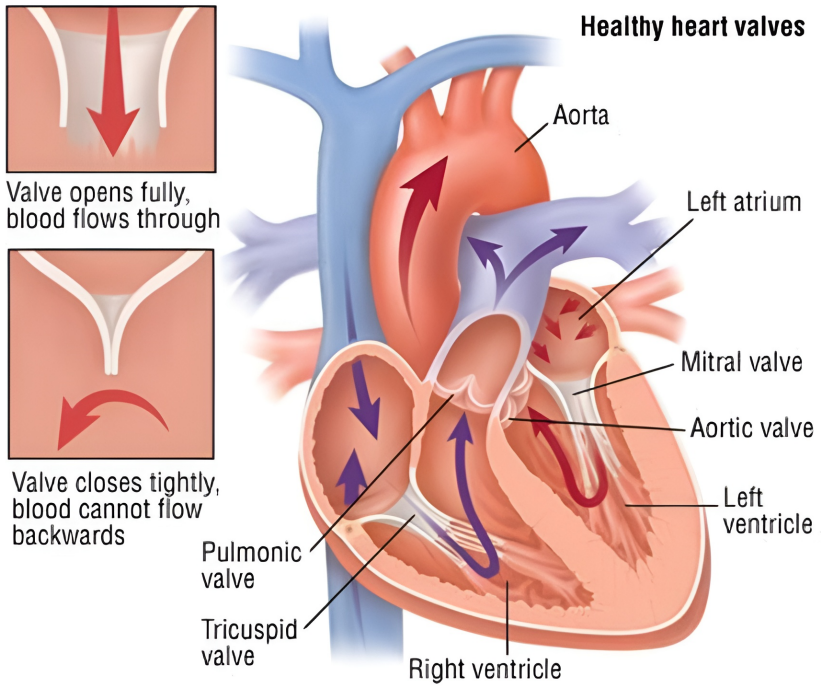
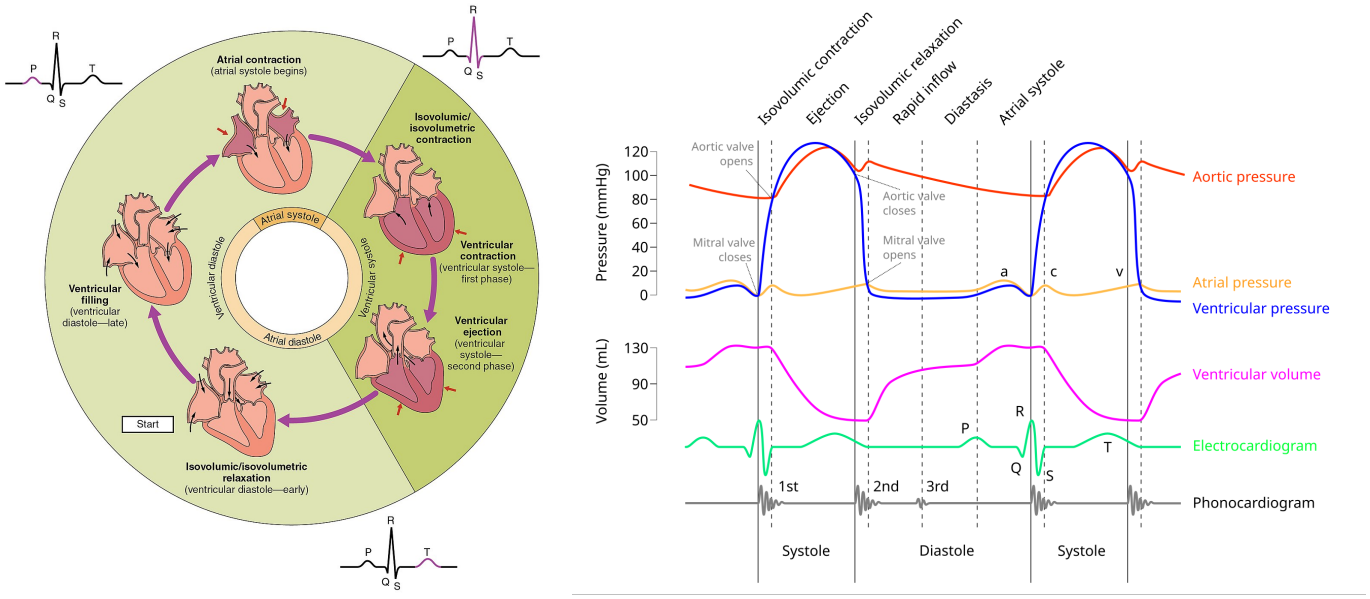


Figure 1.1: Heart and valve anatomy. Reproduced from the Canadian Cardiovascular Society's 2022 Heart Valve Disease Report [3].

valve, as any disruption or malfunction of these two structures can have significant adverse effects on overall health.

The cardiac cycle begins with *atrial systole*, where the atria contract to push blood into the ventricles. This phase is followed by *ventricular systole*, during which the ventricles contract to send blood into the pulmonary artery and aorta. Finally, *diastole*, involves the relaxation of the heart muscle, allowing the chambers to refill with blood. This continuous cycle ensures that deoxygenated blood is sent to the lungs for oxygenation and oxygenated blood is delivered to the rest of the body. The resulting changes in pressure and volume are illustrated in Figure 1.2, known as the Wiggers diagram or venous pressure tracings. Figure 1.2 also demonstrates the isovolumetric nature of these cardiac contractions and relaxations. In particular, the left ventricular and aortic pressure curves shown here will be a point of discussion throughout this study.



(a) Cardiac Cycle **(b)** Wiggers Diagram

Figure 1.2: Cardiac cycle and Wiggers diagram. Reproduced from Wikipedia contributors [4, 5] under the Creative Commons Attribution-ShareAlike License (CC BY-SA 3.0).

1.1.2 Aortic Valve Disease (AVD)

As can be seen in Figure 1.1, *heart valves* play a crucial role in ensuring unidirectional movement of blood through the different chambers of the heart.

As mentioned previously, the *aortic valve*, located between the left ventricle and the aorta, regulates the unidirectional flow of blood from the left ventricle into the aorta, thus ensuring that oxygenated blood is distributed efficiently throughout the body. This unidirectional flow is essential to maintain consistent circulation [6, 7]. Any dysfunction in aortic valve performance can severely affect cardiac function and disrupt proper delivery of oxygenated blood to body tissues, leading to various complications. The aortic valve is therefore central to this study, which examines its role in the cardiac cycle and the effects of its dysfunction on overall cardiac performance [6, 7].

Aortic Valve Disease (AVD) is the umbrella term that encompasses various conditions that affect the aortic valve, the primary subtypes being Aortic Stenosis (AS) and Aortic Regurgitation (AR), which are defined and explained below. Furthermore, AVD comprises more than 60% of all forms of

valvular disease [8] and affects more than 24 million people per year [9]. Given its high prevalence and significant impact on cardiovascular health, studying AVD is crucial to improving diagnosis, treatment, and patient outcomes.

1.2 Aortic Stenosis - Definition, Causes & Treatment

1.2.1 Pathophysiology

Affecting more than 9 million people worldwide, AS is one of the most prevalent valvular heart diseases in developed countries and ranks second highest valvular disease in the western world [9, 10], with its prevalence expected to at least double by 2050 [11]. It is characterized by the narrowing of the aortic valve opening, which restricts blood flow from the left ventricle into the aorta [12]. This condition is primarily caused by the progressive calcification and stiffening of the aortic valve over time. However, congenital heart defects, such as a bicuspid aortic valve, or rheumatic fever in childhood, also increase the risk of developing AS [13, 14]. If left untreated, symptomatic AS results in severe health complications and significantly higher mortality, with death rates often exceeding those of many cancers [12].

Following the Bernoulli principle of fluid mechanics, when fluid flows through a constricted passage, its velocity increases, while its pressure decreases [15]. In the context of AS, as blood flows through the stenotic aortic valve, and the restricted orifice, the velocity escalates from a low speed in the left ventricular outflow tract (LVOT) to a significantly higher speed at the vena contracta (VC) — the point where the flow streamlines converge, resulting in the narrowest cross-sectional area and highest velocity (maximal kinetic energy) but with the least pressure just beyond the valve [16–18].

This progressive stiffening and narrowing of the valves forces the heart, particularly the left ventricle, to work harder to maintain adequate blood flow. In other words, AS imposes a chronic *pressure overload* on the left ventricle, as it must generate higher pressures to overcome the obstruction and maintain adequate blood flow. This causes the heart to compensate by thickening the ventricular walls through a process known as left ventricular hypertrophy (LVH). This structural adaptation helps

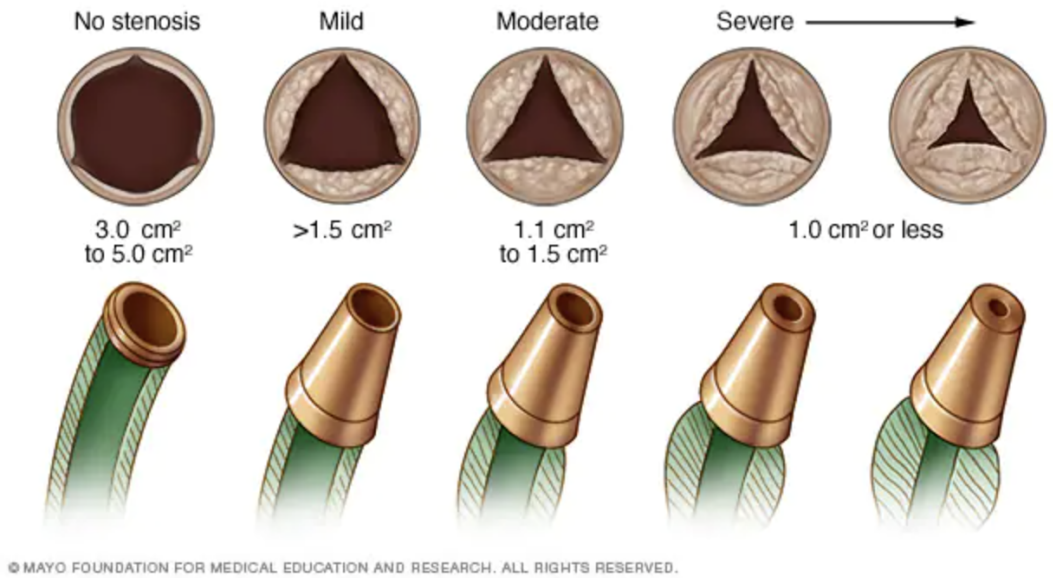


Figure 1.3: Visualization of nozzle-like phenomena in aortic stenosis severity and fluid flow. Reproduced from [19].

maintain cardiac output by compensating for narrowing of the aortic valve and aims to preserve the ejection fraction (EF), which is the percentage of blood ejected from the left ventricle with each contraction, despite the growing obstruction [20].

The schematics behind LVH will be further explored in a later section 1.5. Figure 1.3 shows the varying orifice sizes associated with different severity levels of aortic stenosis, ranging from non-stenosis to severe cases where the effective orifice area is 1.0 cm^2 or less. The narrowing of the aortic valve orifice results in a nozzle-like behavior of blood flow.

Over time, the left ventricle compensates for the increased workload by undergoing *concentric hypertrophy*, a form of LVH characterized by thickening of the ventricular walls. Although compensatory changes initially help maintain cardiac output, they eventually become maladaptive, ultimately leading to inadequate cardiac output, heart failure, and, if left untreated, death [13, 20]. A visual example of AS, along with the physiological changes that occur in the left ventricle, namely the narrowing of the anatomical aortic valve area (AVA) and LV hypertrophy is shown in Figure 1.4.

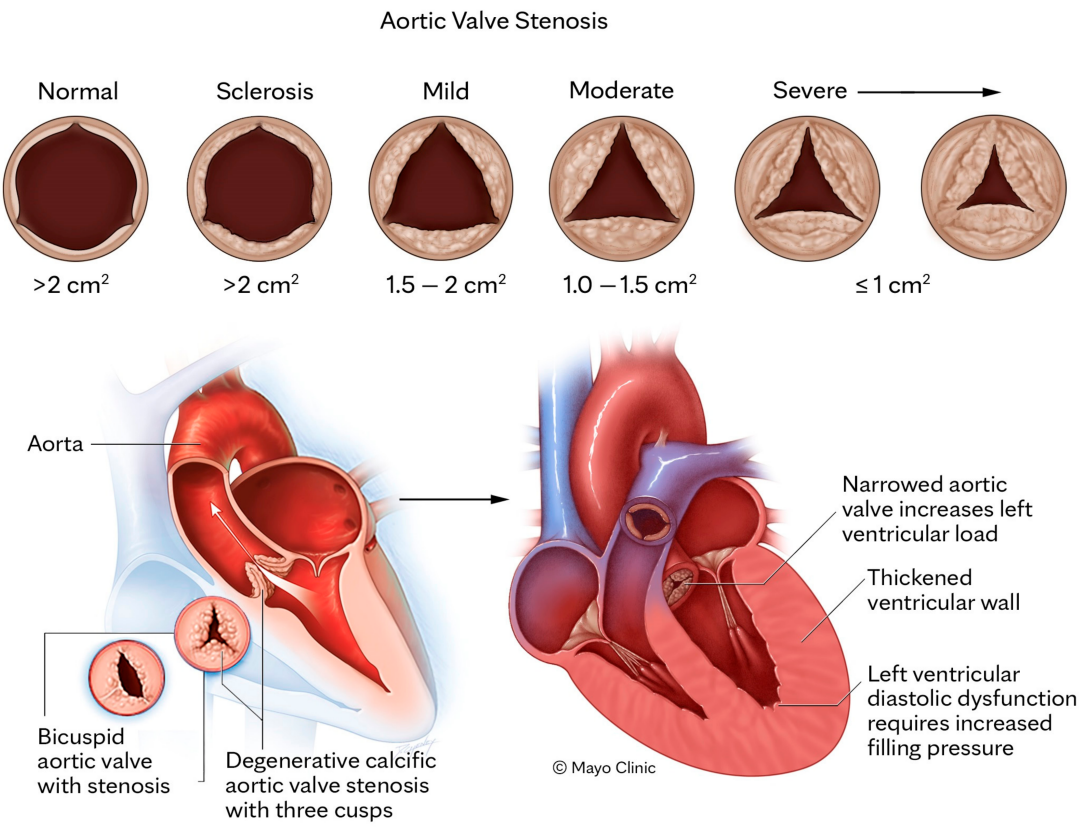


Figure 1.4: Stages of aortic valve stenosis and associated left ventricular hypertrophy. Adapted from Scalia *et al.* [21] under the terms of the Creative Commons Attribution License (CC BY 4.0).

As mentioned previously, aortic stenosis (AS) leads to increased stiffness of the valve leaflets [16, 19], which impairs the valve's ability to fully open during systole, the phase of the cardiac cycle when the heart contracts and pumps blood into the aorta. Consequently, the cross-sectional area of the aortic valve area (AVA) narrows significantly, restricting blood flow. It is important to distinguish between the Geometric Orifice Area (GOA), which is the anatomical valve opening, and the Effective Orifice Area (EOA), which represents the functional opening available for blood flow, or the jet area in the vena contracta. EOA is a term that will be used often during this work and is always less than or equal to the GOA [16, 18]. Figure 1.5 illustrates the relationship between the EOA, GOA, and the pressure differentials involved. The difference between the GOA and the effective orifice area EOA can be quantified using the contraction coefficient (C_c) [18]. The EOA is used to quantify the progression of the severity of AS, and a reduction in EOA correlates with an increased stenosis severity. Figure 1.6 presents a simplified schematic of how blood velocity and flow streamlines evolve

through a stenotic valve, illustrating the effects of flow acceleration, jet contraction, and pressure recovery downstream.

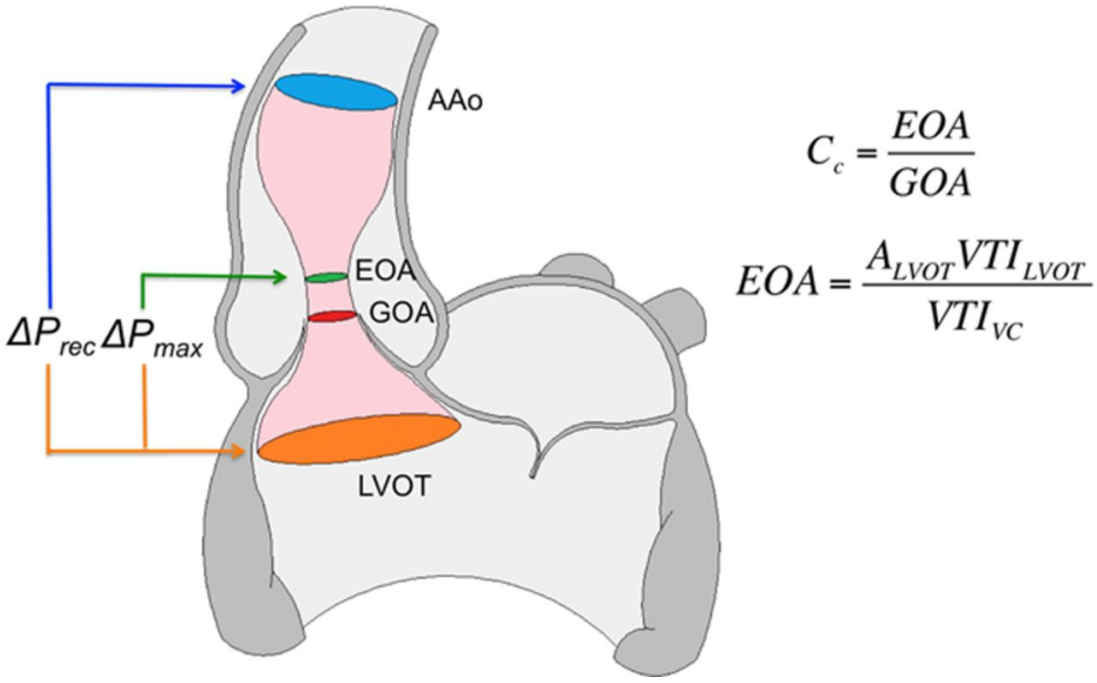


Figure 1.5: Schematic of flow through the a stenotic aortic valve. *AAo* in the figure depicts the ascending aorta. Reproduced from Garcia *et al.* [16] under fair dealing for educational and research purposes.

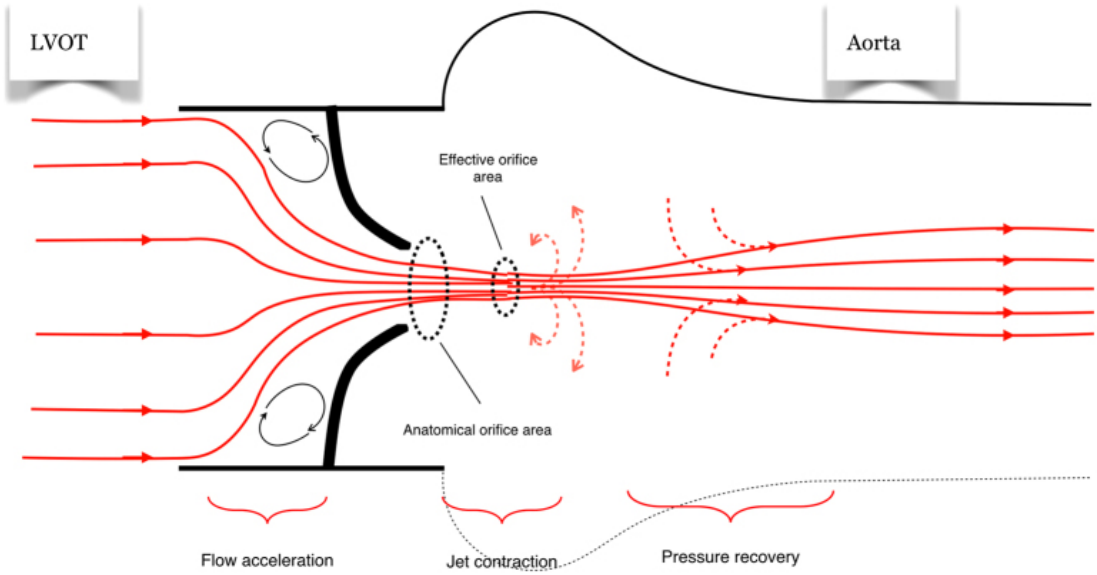


Figure 1.6: Hemodynamics through a stenotic valve. Reproduced from Ring *et al.* [22] under the terms of the Creative Commons Attribution License (CC BY 4.0).

1.2.2 Treatment

AS severity is categorized based on valve anatomy, patient symptoms, hemodynamic parameters, and the adaptive response of the left ventricle (LV) [23]. According to the 2020 ACC/AHA guidelines, AS progresses through distinct stages: Stage A (patients at risk), Stage B (progressive AS), Stage C (severe asymptomatic AS), and Stage D (symptomatic AS). Stage D is further divided into D1 (high-gradient AS), D2 (low-flow, low-gradient AS with reduced ejection fraction), and D3 (low-flow, low-gradient AS with preserved ejection fraction), acknowledging the complexity of cases with discordant hemodynamic findings [11, 23]. A summary of the American Heart Association (AHA) break down is provided in the Appendix in table A.3.

The classification of aortic stenosis (AS) is primarily based on three key echocardiographic measurements: AVA, aortic peak jet velocity, and mean transvalvular pressure gradient. These parameters are used to categorize the disease as mild, moderate, or severe, which in turn guides the timing and type of intervention. A summary of these thresholds is presented in Table 1.1. Current guidelines recommend intervention for patients with symptomatic or rapidly progressive severe AS, as well as for asymptomatic individuals with a reduced left ventricular ejection fraction (LVEF) below 50% [11, 24]. Treatment typically involves Aortic Valve Replacement (AVR), either through Surgical Aortic Valve Replacement (SAVR) or Transcatheter Aortic Valve Implantation (TAVI). These interventions are particularly in symptomatic patients, those with rapidly progressing severe AS, or asymptomatic patients with significantly reduced LVEF. A comprehensive overview of the clinical assessment and intervention workflow is shown in the Appendix under B.1.

Challenges in Existing Treatment Protocols

However, recent studies have shown growing concern that irreparable myocardial damage has already occurred by the time symptoms appear or LV function begins to decline [11, 24]. A 2023 study by Stassen et al. went on to further highlight that moderate AS has also been associated with a considerable risk of adverse cardiovascular events, including death, making AS not just "a disease of the aortic valve but also of the ventricle" [11]. This further highlights the motivation and need

behind this work which is to have a more holistic set of parameters that simultaneously account for both valvular function and left ventricular response, capturing not only flow-related variables through echocardiography, but also for the mechanical burden placed on the left ventricle. While biomarkers have been explored as early indicators of myocardial stress, a topic further discussed in Section 1.4, the aim here is to propose a more comprehensive approach, grounded in both physiological and mechanical principles, that can be applied across all forms of AVD, including concomitant presentations.

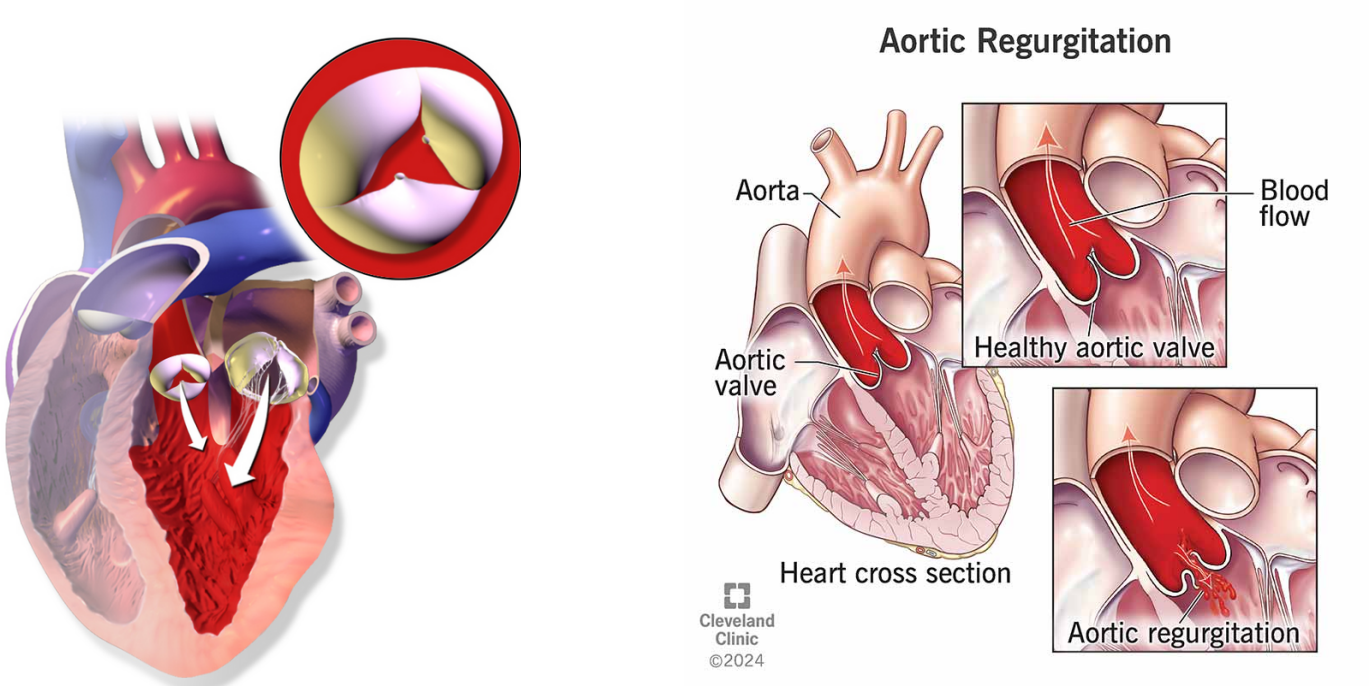
Table 1.1: Classification of the Severity of AS in Adults

Description	**Mild**	**Moderate**	**Severe**
Aortic Stenosis			
Jet velocity (m/s)	<3.0	3.0-4.0	>4.0
Mean gradient (mmHg)	<25	25-40	>40
Valve Area (cm^2)	>1.5	1.0-1.5	<1.0
Indexed Valve Area (cm^2/m^2)			<0.6

1.3 Aortic Regurgitation (AR)

Aortic regurgitation (AR), another subcategory of AVD, occurs when the aortic valve fails to close properly, allowing blood to flow backward into the left ventricle from the aorta. This results in chronic *volume overload*, as the left ventricle must accommodate both normal blood incoming from the left atrium and regurgitant blood from the aorta. Over time, this increased volume load leads to *eccentric left ventricular hypertrophy*, a compensatory enlargement of the left ventricle characterized by chamber dilation and wall thinning. AR is the third most frequently occurring valvular disease, with lifetime prevalence estimates of 13% in men and 8.5% in women [25]. Structural deterioration of the aortic valve is the leading cause of chronic aortic regurgitation, with the condition advancing more aggressively in those with a bicuspid valve [25]. Advanced AR poses serious health risks, with three-quarters of affected individuals either undergoing valve replacement surgery or dying within a decade of diagnosis [25]. Symptoms include fatigue, shortness of breath, and palpitations, and if left untreated, chronic AR can lead to heart failure. Figure A and Figure B 1.7 illustrate the dual load of blood from the left atrium and the regurgitant flow. Table 1.2 summarizes the threshold values used

to classify AR severity. As with AS, the indications for valve replacement are typically the onset of clinical symptoms of congestive heart failure or a decline in left ventricular (LV) function [26].



[A] [B]

Figure 1.7: Aortic Regurgitation [A] Depiction of the volume overload from the left atrium and aorta. Adapted from BruceBlaus via Wikimedia Commons [27]. [B] Closer look at the regurgitant flow. Adapted from Cleveland Clinic © Cleveland Clinic. Used under fair use for educational purposes [28].

Table 1.2: Classification of the Severity of AR in Adults

Description	**Mild**	**Moderate**	**Severe**
Aortic Regurgitation			
Regurgitant Volume (ml/beat)	<30	30-59	≥60
Regurgitant Fraction (%)	<30	30-49	≥50
Regurgitant Orifice Area (cm^2)	<0.10	0.10-0.29	≥0.30

1.4 Role of Biomarkers in Aortic Valve Disease

As mentioned previously, the optimal timing for intervention in severe aortic stenosis (AS) is well established. However, recent studies have shown a growing number of moderate AS cases associated with adverse outcomes or increasing exercise intolerance [11, 26]. The compensatory left ventricular

hypertrophy that occurs in aortic valve disease (AVD) often helps maintain cardiac output, which explains why many patients with AS, including those with severe disease, can remain asymptomatic at rest. Despite this lack of symptoms, AS, even at a moderate stage, poses a significant clinical risk, as heart failure symptoms can manifest during physical activity [24].

Given the limitations of symptom-based assessment, biomarkers have gained traction as complementary tools for AVD severity progression and risk assessment, reflecting a broader shift toward earlier intervention strategies [26]. These biomarkers are used to risk stratify asymptomatic patients with severe AS, identify a subgroup of patients with moderate AS who show rapid progression of AS or have an increased risk of cardiovascular events [11]. When combined with imaging indicators of left ventricular remodeling, they can help detect patients who exhibit a more maladaptive response to pressure overload and those who could benefit from closer clinical surveillance or even earlier intervention/AVR [11].

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker/peptide that is secreted in response to increased myocardial wall stress, while High-sensitivity troponin T (hs-TnT) may provide predictive information in subjects with AS such as the likelihood of future AS surgery [24, 29]. As guidelines have approved NT-proBNP as a biomarker to be used as a prognostic marker for AS [24] and as developing a holistic prognostic parameter is the ultimate goal of this work, NT-proBNP was used as a reference to validate our proposed model. This validation is detailed in our publication, entitled, *On Left Ventricle Stroke Work Efficiency in Children with Moderate Aortic Valve Regurgitation or Moderate Aortic Valve Stenosis*, included in Section 3 [30].

1.5 Left Ventricular Hypertrophy in Aortic Valve Disease: A Need for Advanced Modeling

Cardiac hypertrophy is a fundamental adaptation to chronic pressure or volume overload. Traditionally, it has been described as a feedback mechanism in which concentric hypertrophy develops in

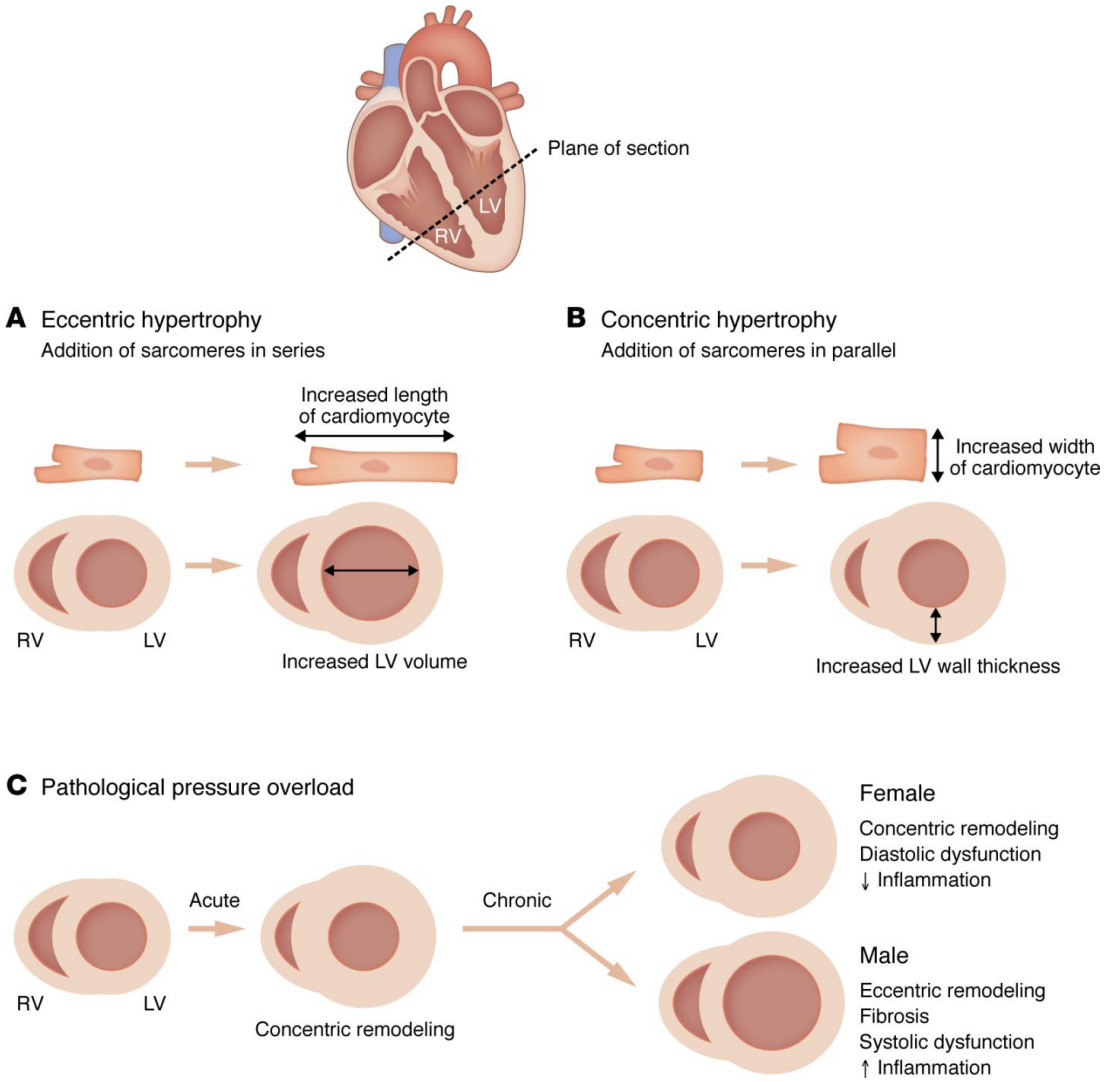


Figure 1.8: Illustration of concentric and eccentric hypertrophy, showing ventricular remodeling in response to pressure and volume overload. Adapted from Figure 3 in Martin and Leinwand, 2024 [33]. © The Journal of Clinical Investigation. Used under fair use for educational purposes.

response to pressure overload, thickening the ventricular walls to normalize wall stress, while eccentric hypertrophy occurs in volume overload, leading to chamber dilation to maintain adequate stroke volume [31, 32]. However, this process is not always precisely regulated: hypertrophy may be insufficient, failing to offset mechanical stress, or excessive, exceeding what is necessary for compensation [20].

As shown in Figure 1.8, concentric hypertrophy, characterized by thickening of the ventricular wall, develops as a compensatory response to pressure overload (e.g., in aortic stenosis), while eccentric

hypertrophy, marked by chamber dilation, results from volume overload (e.g., in aortic regurgitation) [33]. Although these adaptations aim to maintain cardiac output, cases in which both pressure and volume overload coexist require a more nuanced understanding of ventricular remodeling.

Despite significant advances in mechanical modeling, many existing approaches primarily focus on isolated pressure or volume overload conditions. However, when multiple loading conditions coexist, ventricular remodeling follows more complex patterns that cannot always be categorized as purely concentric or eccentric hypertrophy. To better capture these interactions, models must be refined to account for the combined effects of pressure and volume overload, particularly in conditions where traditional classifications break down. A more comprehensive lumped parameter modeling approach provides a structured framework to quantify these dynamics, as well as their collective impact on ventricular adaptation.

One such condition that exemplifies this challenge is mixed aortic valve disease (MAVD), where the heart must simultaneously adapt to pressure and volume overload. Although traditional classifications distinguish between concentric and eccentric hypertrophy, MAVD presents a unique remodeling pattern that cannot be fully described by either category alone [34]. Understanding the interplay between these competing forces is crucial for accurately modeling ventricular remodeling in MAVD, which will be explored in the following section.

1.6 Mixed Aortic Valvular Disease (MAVD)

AS and AR are generally considered distinct conditions, each imposing a single predominant hemodynamic load: pressure overload in AS and volume overload in AR. However, in Mixed Aortic Valve Disease (MAVD), both stenotic and regurgitant dysfunctions coexist, forcing the left ventricle to adapt to simultaneous pressure and volume overload. This dual burden leads to a unique pattern of ventricular remodeling that does not fit neatly into traditional classifications of concentric or eccentric hypertrophy [35].

Unlike isolated AS or AR, where the heart follows a relatively predictable compensatory pathway,

MAVD presents competing mechanical stimuli that influence ventricular adaptation in complex ways. The left ventricle in MAVD typically undergoes severe hypertrophy with mild chamber dilation, resulting in altered pressure-volume dynamics. As shown in Figure 1.9, left ventricular dilation in MAVD is less pronounced than in isolated AR, while systolic pressure is elevated, similar to AS [35]. Additionally, the combination of hypertrophy and reduced compliance leads to increased diastolic filling pressure, further complicating ventricular function.

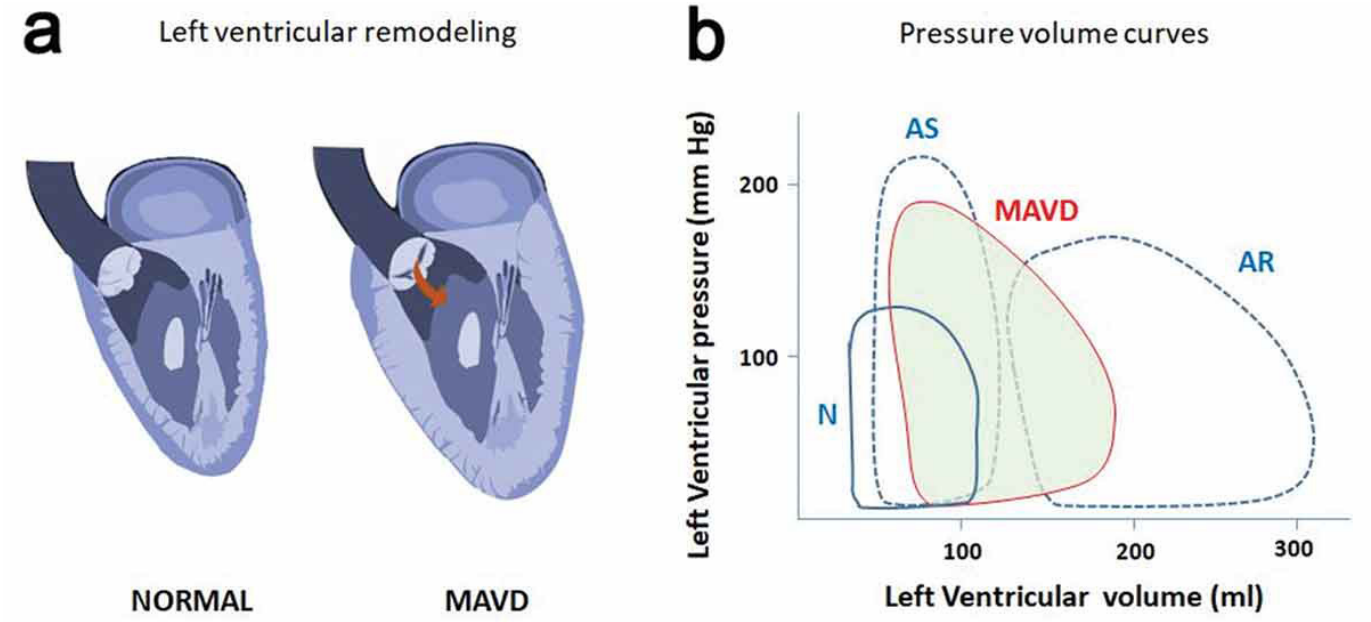


Figure 1.9: **(a)** Left ventricular remodeling in Mixed Aortic Valve Disease (MAVD), showing hypertrophy with mild dilatation due to combined pressure and volume overload. **(b)** Pressure–volume curves comparing normal (N), aortic stenosis (AS), aortic regurgitation (AR), and MAVD. MAVD exhibits elevated systolic pressure (like AS) and moderate dilatation (less than AR), reflecting combined loading. Adapted from Unger and Clavel (2020) [35]. Licensed under CC BY-NC-ND 4.0.

Despite its clinical significance, MAVD remains underexplored, with much of the existing literature focusing primarily on isolated AS or AR rather than the complex interplay between pressure and volume overload in MAVD. This condition presents a distinct hemodynamic profile that challenges conventional diagnostic and therapeutic strategies. As a result, there is an urgent need to establish dedicated MAVD-specific guidelines to ensure accurate diagnosis and optimal patient management. The following chapter will review the current state of MAVD research, highlighting key knowledge gaps, diagnostic challenges, and emerging treatment strategies that reinforce the need for a more customized clinical approach.

2 | Literature Review

2.1 Mixed Aortic Valvular Disease: Prevalence, Research Gaps, and Diagnostic Pitfalls

2.1.1 Prevalence of Mixed Aortic Valvular Disease (MAVD)

MAVD, characterized by the simultaneous presence of aortic stenosis (AS) and aortic regurgitation (AR), is among the most frequently encountered forms of multiple valve disease [10, 36].

A nationwide study in Sweden identified MAVD as the most common presentation of multiple valve pathology [35–38]. Among individuals diagnosed with AS, approximately 75% also exhibited some degree of AR, while 17.9% of those with primary AR also present with AS [39]. These findings underscore the frequent coexistence of AS and AR, further highlighting the fact they rarely occur in isolation. Additionally, in a 2020 study, Unger et al. [35] noticed that of 306 patients with *severe* AS, 24% also had moderate or severe concomitant AR, which led to an increased risk of adverse cardiovascular events.

2.1.2 Diagnosis Pitfalls

Despite its high prevalence, MAVD remains under-recognized in both research and clinical practice. Significant knowledge gaps remain regarding its natural history, severity assessment, optimal timing for intervention, patient outcomes, and the overall impact of the associated cardiac damage [35, 36, 38–44]. Most existing studies on valvular heart disease focus on isolated AS or AR, with little attention given to patients presenting with both lesions [45, 46]. As a result, current clinical guidelines primarily assess disease severity based on the dominant lesion, an approach that oversimplifies the complex interactions between stenotic and regurgitant valve dysfunction [39]. A key contributor to

these diagnostic challenges is the limited reliability of echocardiographic assessments in the context of dual valve pathology.

Limitations of Echocardiography in Mixed Aortic Valve Disease

Echocardiography is a mandatory step in defining the severity of AVD which requires the combined measurements of AVA, peak aortic jet velocity, and/or a mean pressure gradient [44].

In isolated AS, severity is commonly assessed using AVA, peak velocity, and mean gradient. However, a 2023 study by Stassen et al. demonstrated inconsistencies between the commonly used parameters, namely between the AVA and the pressure gradient, to assess AS severity [11]. This is due to factors such as low-flow states or inconsistent measurement conditions, leading to diagnostic uncertainty [11]. In isolated AR, echocardiographic evaluation relies on parameters such as LV dilation, pressure half-time, vena contracta width, effective regurgitant orifice area, and regurgitant volume. These markers, however, are sensitive to loading conditions and ventricular compliance, and may not reliably capture the severity of regurgitation across all patient profiles [34, 36]. Additional studies have shown that the high transvalvular flow associated with AR may overestimate the severity of the AS component when using peak velocity and mean gradient [36, 43].

Furthermore in both cases, measurement errors are frequent and can lead to inconsistent assessment and severity misclassification [11, 44].

In MAVD, the limitations observed using Doppler echocardiography and other imaging modalities in isolated cases of AVD are further confounded by the unique hemodynamics of MAVD [34–36, 43].

Standard parameters for AR severity, such as LV dilation, pressure half-time, vena contracta width, effective regurgitant orifice area, and regurgitant volume, may be misleading or inaccurate due to the presence of AS and resulting LV hypertrophy [34–36, 43]. Furthermore, these discrepancies can lead to conflicting diagnoses depending on the parameter used [11, 44]. This issue is further amplified in MAVD, where the combined effects of stenosis and regurgitation disrupt standard evaluation

guidelines.

Many widely used echocardiographic techniques for assessing AS and AR were validated in patients with single valve disease and may not accurately reflect the severity of mixed pathology [10]. As a result, MAVD is often under-diagnosed or misclassified, leading to inappropriate treatment strategies. Although advanced imaging modalities may offer better diagnostic precision, their application in MAVD remains limited and requires further investigation.

To address these challenges, further research is needed to investigate the complex pathophysiological mechanisms underlying MAVD to determine the optimal time to intervene, especially in asymptomatic patients [36, 43].

2.1.3 Pathophysiology and Unique Hemodynamic-Structural Considerations of Mixed Aortic Valvular Disease

What distinguishes MAVD from isolated AS or AR is the combined pressure and volume overload imposed on the LV. Unlike single-valve disease, where compensatory remodeling follows a more predictable trajectory, MAVD leads to distinct structural and functional changes in both the LV and left atrium. Patients with moderate MAVD show significant alterations in cardiac morphology that exceed those observed in isolated valve disease [47]. Additionally, the phenotypic characteristics of MAVD differ from isolated AS or AR given that these patients display only mild LV dilation [34]. These features may have an important role in accelerating the development of symptoms and worsening the manifestations of MAVD [34]. This suggests that even moderate forms of MAVD may require closer monitoring and early intervention [36].

Aortic stenosis creates a pressure overload that exacerbates concentric hypertrophy of the LV, leading to reduced LV compliance. This results in a disproportionate increase in LV diastolic pressure with even small increases in volume during diastole. In contrast, aortic regurgitation leads to volume overload, causing LV dilation and eccentric hypertrophy. The combination of these two mechanisms results in a unique pattern of LV remodeling that significantly alters disease progression [10]. In cases

of significant AR, the increase in elevated diastolic pressure forces the LV to fill at a steeper portion of the pressure–volume curve, potentially causing symptoms to manifest earlier than in patients without concomitant AR [10]. As the ventricle dilates to accommodate the increased stroke volume, wall tension rises, worsening dilation and reducing coronary perfusion, which can contribute to earlier symptom onset [10].

However, AS limits the degree of LV dilation in response to the volume overload, and the progression of AS tends to be slower compared to pure AR [36]. The severity of AS plays a dominant role in clinical outcomes [10], suggesting that even mild AR may worsen the clinical stage of valve disease, necessitating stricter monitoring in patients with moderate MAVD, similar to those with isolated severe AS. In diagnostic terms, the increased stroke volume in MAVD can produce a higher transvalvular gradient, potentially overestimating the severity of AS. Nonetheless, measurements such as peak aortic jet velocity and mean gradient remain useful for assessing AS severity and prognostic impact [10]. Importantly, a simplified Bernoulli formula should be avoided due to the high left ventricular outflow tract velocities present in these patients [36].

The combination of modest LV dilation and significant LV wall thickening in MAVD results in larger indexed LV mass compared to patients with isolated AR or isolated AS, underscoring the intricate impact of this combined pathology [36].

2.1.4 Outcomes in patients with Mixed Aortic Valvular Disease

Retrospective studies and emerging evidence highlight that even moderate MAVD, defined as moderate AS with moderate AR, is associated with significant cardiovascular morbidity, with adverse outcomes occurring at rates comparable to or worse than those observed in isolated severe AS or AR [47]. Without dedicated studies, the full impact of MAVD on long-term patient outcomes remains unclear [45, 46].

Recent studies indicate that patients with moderate MAVD experience higher rates of adverse cardiovascular events, rapid symptom progression, and increased post-aortic valve replacement complications [46, 48, 49]. Preoperative LV hypertrophy has become an important predictor of postoperative outcomes, reinforcing the need for improved risk stratification [50]. The combined pressure and volume overload in MAVD places the LV under critical suboptimal loading conditions, accelerating myocardial remodeling and functional decline [46].

2.2 Importance of Correct Diagnosis and Optimal Timing of Intervention

A fundamental challenge in MAVD management is the difficulty in accurately assessing the severity of the disease, and consequently determining the optimal timing of intervention. Current guidelines focus primarily on severe AS or AR, leaving a critical gap in the treatment of moderate MAVD [10].

This gap in clinical guidelines stems from the historical focus on single-valve disease, with current recommendations predominantly assessing severity based on the dominant lesion. As a result, MAVD remains poorly characterized, and treatment strategies often rely on an oversimplified approach, determining intervention timing based on whether AS or AR appears more severe [49, 51]. However, emerging evidence suggests that MAVD imposes a unique and complex hemodynamic burden on the left ventricle, distinct from isolated AS or AR. The combined pressure overload of AS and the volume overload of AR creates a suboptimal loading condition, leading to structural and functional changes that significantly alter the progression of the disease [46].

To address this critical gap, it is essential to refine diagnostic tools and develop novel parameters that better characterize the combined hemodynamic burden imposed by MAVD. This study seeks to contribute to the fundamental understanding of MAVD-induced LV overload by introducing a novel parameter left ventricular efficiency (η_{LV}), which integrates both pressure and volume overload effects as a non-invasive metric for disease progression.

2.3 Moderate MAVD is Comparable to Severe AS in Clinical Outcomes

Recent evidence suggests that moderate MAVD may have a prognostic impact similar to that of severe AS. Studies show that patients with moderate MAVD experience clinical outcomes comparable to patients with severe AS, particularly in terms of mortality and adverse cardiovascular events [46, 52]. Furthermore, post-AVR outcomes indicate that the risk of complications remains high in MAVD patients, with persistent LV dysfunction despite valve replacement [46].

These findings highlight the need for reevaluating current classification systems and considering moderate MAVD as a distinct entity requiring earlier intervention. The integration of novel biomarkers such as NT-proBNP and advanced imaging techniques could improve risk assessment and guide clinical decision-making [42].

2.4 New Treatment Strategies

The therapeutic management of Mixed Aortic Valve Disease (MAVD) is complex, with no definitive guidelines currently available [36, 40]. In clinical practice, management is typically based on guidelines for the predominant valve lesion, although this approach may be too reductionist [36, 40, 43]. In cases where the severity is balanced AS and AR are balanced in severity, (e.g., in cases of moderate AS and moderate AR) intervention decisions should not rely solely on traditional hemodynamic indices and should instead rely on symptoms and objective left ventricular (LV) consequences, such as dilation or dysfunction [36]. As mentioned previously, a hemodynamically severe or moderate MAVD (even if composed of two moderate lesions) should be managed with the same urgency as isolated severe disease [36]. In other words, recent literature have emphasized that a hemodynamically severe MAVD (even if composed of individually moderate lesions) should invariably be considered as hemodynamically severe, and managed according to guidelines for isolated severe lesions [35, 36, 40]. Consequently, new paradigms are increasingly focused on refining disease classification using a combination of advanced imaging, functional testing and emerging diagnostic markers, as well as earlier intervention.

2.4.1 Aortic Valve Replacement

Although aortic valve replacement (AVR) (either surgical (SAVR) or transcatheter (TAVR)) is the established interventional treatment for severe aortic valve disease, the novelty revolves primarily around the strategies for *when* and and *how* to apply these existing treatments in the complex context of MAVD.

Observational data have shown that asymptomatic patients with MAVD, including those with *moderate* lesions, have adverse outcomes comparable to those seen in isolated severe AS [35].

Early intervention in MAVD without comorbidities is suggested as a feasible alternative based on some studies, given that AVR dramatically improves survival independent of symptoms [34, 35]. However, a substantial risk of death may remain even after AVR, emphasizing the potential role of early intervention [34, 35].

Several studies report a significantly higher risk of mortality among untreated MAVD patients, and AVR has been shown to reduce all-cause mortality even in the absence of classical indicators such as small aortic valve area or overt symptoms [34, 35]. Notably, patients with moderate AS and reduced LV ejection fraction (LVEF) who underwent SAVR had better outcomes than those managed conservatively, suggesting that earlier intervention may benefit select subgroups [36]. These findings point toward a potential paradigm shift in timing, moving away from a strictly symptom-driven model. Ongoing trials focused on moderate AS, including PROGRESS, EXPAND TAVR II, and TAVR UNLOAD, may help establish more precise thresholds for early AVR in the MAVD population [44].

Given the diagnostic ambiguity introduced by the hemodynamic interaction between AS and AR, a more nuanced assessment strategy is essential. Standard echocardiographic parameters, such as peak velocity, mean gradient, and aortic valve area (AVA), may be misleading when dual lesions are present. To overcome these limitations, the use of multimodality imaging is increasingly emphasized. Cardiac computed tomography (CT) offers a valuable tool for quantifying aortic valve calcification

and confirming AS severity, particularly in low-gradient or discordant cases. Cardiac magnetic resonance (CMR) plays a complementary role by enabling precise quantification of AR severity, measuring LV volumes and function, and detecting myocardial fibrosis through late gadolinium enhancement (LGE), which carries prognostic significance. Stress echocardiography can also be employed to unmask symptoms or identify flow reserve, particularly in patients with ambiguous findings at rest. Emerging techniques such as 4D flow CMR hold promise for visualizing complex flow dynamics in MAVD and may be incorporated into future diagnostic algorithms.

In addition to structural imaging, novel functional parameters are being explored to better stratify risk and guide treatment. Left ventricular global longitudinal strain (GLS), for instance, has been associated with adverse outcomes in MAVD and may detect subclinical dysfunction earlier than traditional measures. Similarly, left atrial (LA) and LV atrioventricular coupling has been shown to be impaired in patients with moderate MAVD at levels comparable to severe isolated AS or AR. These alterations in chamber interaction could help identify patients who may benefit from earlier intervention despite only moderate anatomical disease. Cardiac damage staging frameworks, incorporating LV function, mitral valve or LA enlargement, pulmonary hypertension or tricuspid regurgitation, and right ventricular dysfunction, have also demonstrated prognostic value and may aid in determining the timing of intervention. Biomarkers such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) reflect LV wall stress and correlate with adverse outcomes in moderate MAVD, suggesting they may serve as useful adjuncts in decision-making.

Patient-specific computational modeling has also been proposed as a future tool for MAVD management. Techniques such as lumped-parameter modeling or Lattice Boltzmann methods can simulate complex hemodynamics and LV workload, especially in patients with additional conditions such as coarctation of the aorta [38]. Artificial intelligence (AI) and machine learning approaches may offer the ability to integrate data from imaging, biomarkers, and clinical parameters to improve phenotyping, predict progression, and support personalized treatment decisions [43].

A further innovation in MAVD management is the stepwise transcatheter approach. Traditionally, patients with multivalvular disease have undergone combined surgical correction of all lesions. However, in older or higher-risk surgical patients, a staged approach using transcatheter techniques is emerging. This involves treating the most hemodynamically severe lesion first, typically with TAVR, and then reassessing the residual lesion(s) to determine whether additional interventions are warranted. This approach allows for dynamic re-evaluation of valvular function and ventricular response, potentially improving outcomes while reducing procedural risk.

Finally, while no medical therapy has been shown to halt the progression of severe AS, early-phase research into therapies targeting lipoprotein(a), PCSK9 inhibitors, and RNA-based strategies is ongoing. These agents may eventually play a role in slowing or preventing the progression of mild-to-moderate AS, although their specific application to MAVD remains speculative at this stage. Additionally, non-invasive ultrasound-based methods for softening calcified valves represent a potentially disruptive future technology that will require further validation.

In summary, while the foundational treatment for MAVD remains AVR, new strategies are evolving to improve timing, risk stratification, and patient selection. These include the integration of multimodal imaging, novel functional parameters, biomarkers, and computational tools, along with the development of less invasive and more flexible interventional approaches. Prospective studies are needed to validate these innovations and to establish evidence-based guidelines tailored specifically to the MAVD population.

2.4.2 Role of Biomarkers in MAVD

Current AVD disease progression is measured using the current gold standard which is echocardiography [24]. However as previously discussed, progression rates are highly variable, difficult to predict and often subjective [11, 24]. In response to these limitations, biomarkers have emerged as a supplementary tool to manage risk classification and may have the potential to be integrated into long-term patient monitoring and care [24]. Nevertheless, biomarkers are inherently invasive, requiring blood sampling and laboratory analysis, which may limit their routine clinical use.

2.5 Patient-Specific Factors and Variability in Disease Progression

A key challenge in managing aortic valve disease is variability in patient responses to the disease. For instance, patients with preserved LVEF can still experience significant symptoms and adverse outcomes. The progression of AS and AR is influenced by factors such as age, comorbidities (e.g., hypertension, diabetes, coronary artery disease), and the presence of LV hypertrophy or fibrosis. A one-size-fits-all approach based on current parameters like LVEF does not account for these variables. There is a growing recognition that individualized risk assessment is necessary, but current tools are inadequate in this regard.

3 | Left Ventricular Efficiency - Pediatric Cardiology

Preface

Before investigating the behavior of our new proposed parameter in the context of MAVD, we first needed to validate its performance using patient data. To do this, we collaborated with St. Justine Hospital and pediatric cardiologists Dr. Mawad and Dr. Dahdah. Our goal was to compare our model against established clinical guidelines for isolated aortic valve disease prognosis and risk stratification, using the established biomarker NT-proBNP. Our findings were accepted and published in a peer-reviewed journal, which is included below [30]. This article also outlines the methodology used to develop and calculate our left ventricular efficiency parameter, providing a comprehensive overview of its derivation and validation. The subsequent chapter builds on this work by examining its results in the context of MAVD, with a particular focus on moderate MAVD.

On Left Ventricle Stroke Work Efficiency in Children with Moderate Aortic Valve Regurgitation or Moderate Aortic Valve Stenosis

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Please cite as: Asaadi, M., Mawad, W., Djebbari, A., et al. (2022, January). On Left Ventricle Stroke Work Efficiency in Children with Moderate Aortic Valve Regurgitation or Moderate Aortic Valve Stenosis. *Pediatric Cardiology, 43*, 45–53. https://doi.org/10.1007/s00246-021-02690-2.

Keywords: Moderate aortic valve disease · Moderate aortic stenosis · Moderate aortic regurgitation · Mathematical modeling · Left ventricle energy performance

3.1 Abstract

The optimal timing for management of pediatric patients with moderate aortic valve disease [moderate aortic stenosis (modAS) or moderate aortic regurgitation (modAR)] remains unknown and largely unexplored. Although usually asymptomatic, the risk of increased left ventricular (LV) wall stress, irreversible myocardial fibrosis, and sudden death in untreated moderate conditions warrants clearer risk stratification for appropriate timely intervention. In this study, we explore the use of a patient-specific mathematical model to introduce a new evaluative parameter of LV performance in patients with moderate aortic valve disease. Synthetic patient data ($N = 520$) representing healthy patients, and patients with modAS or modAR were first generated. Then, data from twenty-five pediatric patients were included in this study (healthy: $n = 9$; modAS: $n = 8$; modAR: $n = 8$). The effect of modAS or modAR on LV performance was evaluated by LV stroke work (LVSW) efficiency, a new non-invasive parameter. The results demonstrate that healthy patients possess a very high LVSW efficiency (synthetic data: 91±2%, in vivo data: 92±3%). However, modAS patients have a significant reduction in LVSW efficiency (synthetic data: $78 \pm 2\%$, in vivo data: $76 \pm 5\%$, $p < 0.05$), whereas modAR patients had the lowest LVSW efficiency (synthetic data: $58 \pm 3\%$, in vivo data: $66 \pm 7\%$; $p < 0.05$). This highlights that patients with moderate aortic valve disease require careful myocardial assessment, regardless of the onset of clinical symptoms, as their LV performance is significantly reduced. The evaluation of LVSW efficiency offers a promising avenue for future stratification of mixed aortic valve disease for optimal timing of management and intervention.

3.2 Introduction

Congenital aortic valve disease (AVD) represents approximately 5% of all congenital heart diseases. The reported incidence ranges between 0.04 and 0.38 per 1000 live births. The most common forms of congenital aortic valve disease are aortic valve stenosis (AS) and aortic valve regurgitation (AR). The management of pediatric patients with AVD remains challenging because recommendations are mainly extrapolated from adult population guidelines and based on limited pediatric series. Although there is a consensus regarding the optimal management and timing of intervention in patients with

severe symptomatic AVD, the management of patients with moderate AVD remains unclear as it mainly relies on patient-reported symptomatology. This symptoms-based approach may be sub-optimal because children tend to adapt to their condition and underestimate their intolerance to exercise. Studies in adult populations have clearly demonstrated higher risks of events in patients with even mild or moderate aortic stenosis, compared to the general population [53–56]. Rosenhek et al. found a mortality 1.8 times higher in adults with mild or moderate AS compared to an age and gender matched control group [54, 56]. The same controversy also exists regarding the management of moderate aortic regurgitation [57]. In the case of moderate AVD, current practice guidelines recommend follow-up visits with wide intervals [23, 58]. However, with more evidence of the elevated risks in patients with even moderate AVD, it is timely to reconsider how these patients are evaluated and develop new parameters allowing for an optimal management and stratification of such patients. In a recent study, we have shown that NT-proBNP measured in thirty pediatric patients following an exercise challenge is a promising possible biomarker capable of discriminating between moderate AS, moderate AR and control populations [26]. This represents a significant step towards developing new strategies for an optimal timing of intervention in such population. In this study, we explore the ability of patient-specific mathematical modeling to provide additional information on the work load supported by the left ventricle in the presence of moderate AS or moderate AR with the goal to further contribute to optimal stratification and subsequent management of patients with moderate AVD. We also introduce a new patient-specific parameter, left ventricle stroke work efficiency, to evaluate the burden on the left ventricle in synthetic patients first and then in a small pediatric patient cohort with moderate AVD.

3.3 Materials and Methods

3.3.1 Lumped Parameter Model

A schematic diagram of the lumped parameter model used in this study is presented in 3.1. The model includes three sub-modules: (1) left ventricle-arterial module; (2) aortic stenosis (AS) module and (3) aortic regurgitation (AR) module. This model has been thoroughly validated against in vitro

[59, 60] and in vivo patient data [61–64]. Below is a brief description of each module. For more details, the reader is referred to the above mentioned references. One unique feature of our model is that it only relies on parameters that can be measured non-invasively in patients by either Doppler echocardiography or magnetic resonance imaging (please see in vivo data further below).

3.4 Heart-Arterial Model

The left ventricle is modeled using the concept of time-varying elastance [65]:

$$E(t) = \frac{dP_{\mathrm{LV}}(t)}{V(t) - V_0} \tag{3.1}$$

where $P_{\mathrm{LV}}(t)$, $V(t)$, and V_0 are the LV pressure, the LV volume, and the unloaded volume, respectively. The amplitude of the elastance can be normalized with respect to the maximal elastance, $E_{\max}$ to give a normalized elastance,$E_N(t_N) = E(t)/E_{\max}$. Time can also be normalized with respect to the time to reach peak elastance,(T_{Emax}). This gives the following formulation: $E_{max}E_N(t/T_{Emax}) = \frac{dP_{\mathrm{LV}}(t)}{V(t)-V_0}$.

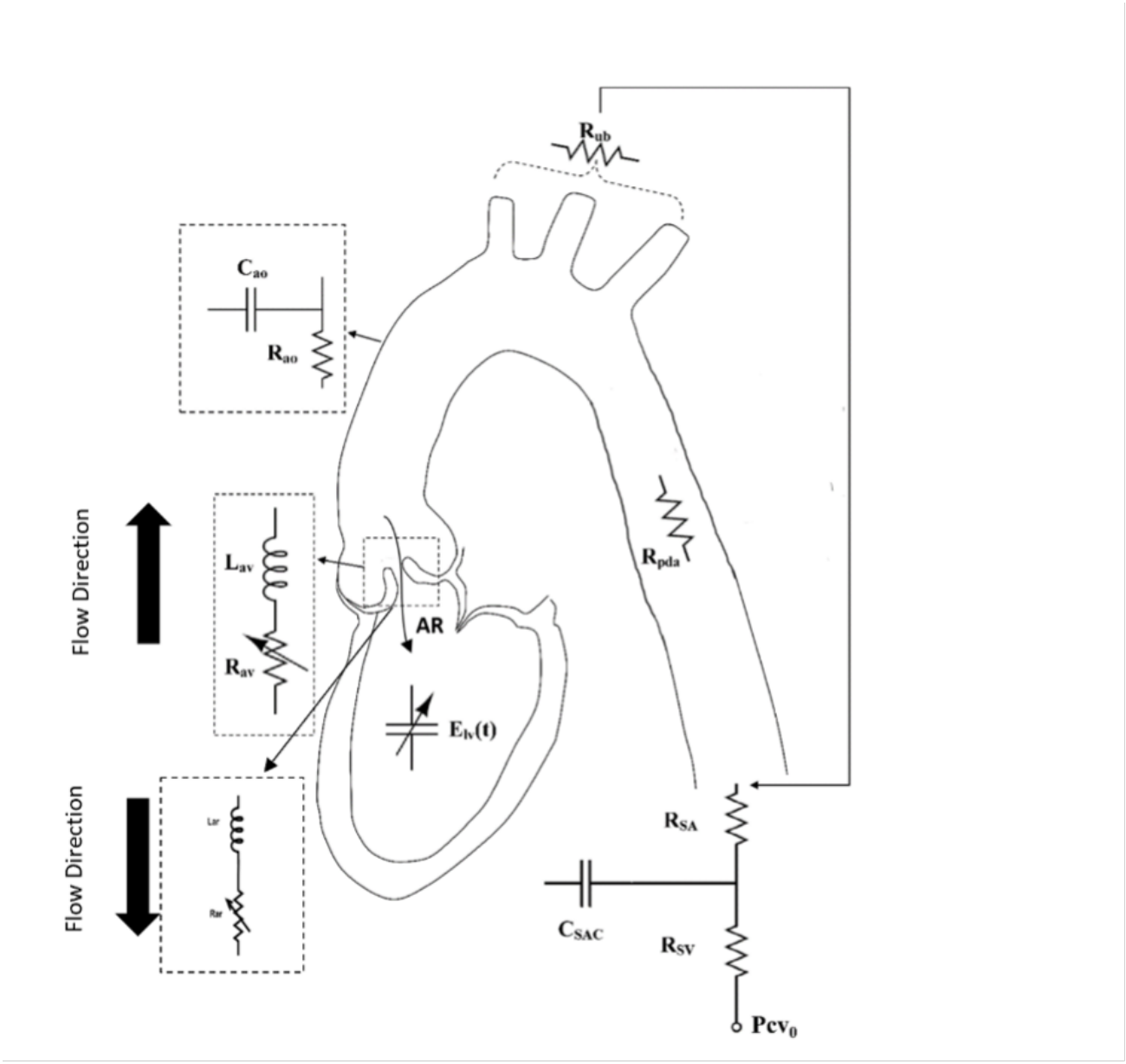


Figure 3.1: Schematic diagram of the anatomical representation of the lumped parameter model. Please see Table 3.1 for abbreviations and details.

3.4.1 Aortic Stenosis Model

The instantaneous net pressure gradient across the stenotic aortic valve ($TPG_{net}|_{AS}$) was modeled as shown below [59, 66]:

$$TPG_{net}|_{AS} = \frac{2\pi\rho}{\sqrt{E_L Co|_{AS}}}\frac{\partial Q_f(t)}{\partial t} + \frac{\rho}{2E_L Co|_{AS}^2}Q_f^2 \tag{3.2}$$

With:

$$E_L Co|_{AS} = \frac{(EOA|_{AS})A}{A - EOA|_{AS}} \tag{3.3}$$

where $E_L Co|_{AS}$, $EOA|_{AS}$, A, ρ, and $Q_f(t)$ are aortic stenosis energy loss coefficient, aortic stenosis effective orifice area, ascending aorta cross sectional area at the level of the sinotubular junction, fluid density, and forward transvalvular flow rate, respectively. $E_L Co|_{AS}$ represents the 'recovered EOA' and denotes the valve effective orifice area adjusted for the area of the aorta at the level of the sinotubular junction.

3.4.2 Aortic Regurgitation Model

Aortic regurgitation was modeled following the same approach used for AS, while considering the pressure difference ($\mathrm{TPG}_{net}|_{AR}$) controlling the regurgitant flow (Q_r) as the difference between aortic pressure and LV pressure during diastole. Additionally, the EOA used corresponds to the regurgitant orifice area $\mathrm{EOA}|_{AR}$.

$$TPG_{net}|_{AR} = \frac{2\pi\rho}{\sqrt{E_L Co|_{AR}}}\frac{\partial Q_r(t)}{\partial t} + \frac{\rho}{2E_L Co|_{AR}^2}Q_r^2 \tag{3.4}$$

With:

$$E_L Co|_{AR} = \frac{(EOA|_{AR})A_{LVOT}}{A_{LVOT} - EOA|_{AR}} \tag{3.5}$$

3.4.3 Left Ventricle Stroke Work Efficiency

In this study, we propose to evaluate the impact of moderate aortic stenosis and aortic regurgitation on LV performance by introducing a new parameter inspired by classical thermodynamic concepts.

In classical thermodynamics, the performance of pumps is evaluated using the concept of isentropic efficiency. Briefly, this efficiency represents the ratio of the work that the pump would have ideally done had it been working under perfect conditions, i.e. isentropic conditions, to the actual non-ideal work done by the pump. Transposing this concept to the evaluation of LV performance means evaluating the ratio of the stroke work developed by the LV under healthy conditions over the actual stroke work developed by the LV when subjected to pressure and/or volume overloads. This gives:

$$\eta_{LV} = \frac{\mathrm{SW}_{\mathrm{ideal}}}{\mathrm{SW}_{\mathrm{real}}} \tag{3.6}$$

$$\eta_{LV} = \frac{\int Pdv\Big|_{\mathrm{ideal}}}{\int Pdv\Big|_{\mathrm{real}}} \tag{3.7}$$

where $\mathrm{SW}_{\mathrm{ideal}}$ is the stroke work developed by the LV under healthy conditions and $\mathrm{SW}_{\mathrm{real}}$ is the stroke work developed by the LV under pathological conditions, i.e. in the presence of heart valve diseases. Now, we can move a step forward by also considering an approximation for the SW since exact values obtained using Eq. 3.7 cannot be determined non-invasively and require simultaneous measurements of LV pressure and volume waveforms. For this purpose, we approximate the SW as the product of the estimated peak aortic pressure ($P_{\mathrm{LV\_max}}$) and the forward stroke volume ($\mathrm{SV_f}$) as in [59, 67]. Equation 3.7 then becomes:

$$\eta_{LV} = \frac{\mathrm{SW}_{\mathrm{ideal}}}{\mathrm{SW}_{\mathrm{real}}} \approx \frac{(P_{\mathrm{LV\_max}} \times \mathrm{SV}_f)_{\mathrm{ideal}}}{(P_{\mathrm{LV\_max}} \times \mathrm{SV}_f)_{\mathrm{real}}} \tag{3.8}$$

Under *ideal* conditions, the LV maximal pressure should be exactly equal to the peak aortic systolic pressure, i.e. no pressure gradient is required to open the aortic valve: $(P_{\mathrm{LV\_max}})_{\mathrm{ideal}} = P_{\mathrm{sys}}$. While in the presence of an aortic stenosis, LV pressure is higher than the peak systolic aortic pressure by an amount equal to the mean transvalvular pressure gradient [67]: $(P_{\mathrm{LV\_max}})_{\mathrm{real}} \approx P_{\mathrm{sys}} + \overline{\mathrm{TPG}}$

Following the same logic, under ideal conditions in the absence of aortic regurgitation, the regurgitant volume should be subtracted from forward stroke volume: $(\mathrm{SV})_{\mathrm{ideal}} = \mathrm{SV}_f - \mathrm{SV}_{\mathrm{r}}$, where SV_f is the forward stroke volume and SV_{r} is the regurgitant volume resulting from the presence of aortic regurgitation. Substituting in Equation 3.8 gives:

$$\eta_{LV} = \frac{\mathrm{SW}_{\mathrm{ideal}}}{\mathrm{SW}_{\mathrm{real}}} = \frac{|\int P\,dv|_{\mathrm{ideal}}}{|\int P\,dv|_{\mathrm{real}}} \approx \frac{(P_{\mathrm{LV}_{\mathrm{max}}} \times \mathrm{SV}_f)_{\mathrm{ideal}}}{(P_{\mathrm{LV}_{\mathrm{max}}} \times \mathrm{SV}_f)_{\mathrm{real}}} \approx \frac{P_{\mathrm{sys}}(\mathrm{SV}_f - \mathrm{SV}_{\mathrm{r}})}{(P_{\mathrm{sys}} + \overline{\mathrm{TPG}}) \times \mathrm{SV}_f)} \tag{3.9}$$

Rearranging and naming the regurgitation fraction ($\mathrm{R_f}$) as the ratio of the SV_{r} to the SV_f gives:

$$\eta_{LV} = (1 - R_f)\frac{P_{\mathrm{sys}}}{(P_{\mathrm{sys}} + \overline{\mathrm{TPG}})} \tag{3.10}$$

Under such formulation, the LV stroke work efficiency is expected to be very close to (or 100%) under healthy conditions and continuously decreasing in the presence of valvular disease. As defined, the LV stroke work efficiency translates how far the LV performance is from its ideal performance.

3.4.4 Numerical Conditions

In this study, we evaluated the ability of our model to contribute to the stratification of patients with moderate AVD using: (1) synthetic patient data representing control patients and patients with moderate AS or moderate AR and (2) in vivo data including twenty-five pediatric patients with a healthy aortic valve (control), moderate AS or moderate AR.

3.4.5 Synthetic patient data

A total of 520 cases were generated to represent a control group, patients with moderate AS and patients with moderate AR. Control patients were simulated by assigning an aortic valve EOA between 3 cm^2 and 4 cm^2 while having no aortic regurgitation. Patients with moderate AS were simulated by assigning aortic valve EOA values ranging from 1.0 to 1.5 cm^2 with a step of 0.1 cm^2 with no aortic regurgitation. Patients with moderate AR were simulated by assigning aortic regurgitant orifice area

values ranging from 0.1 to 0.30 cm^2 with a step of 0.005 cm^2 with a normal aortic valve opening area (EOA = 3.5 cm^2). The assigned values have been selected in accordance with AHA guidelines. The simulations are performed considering a constant net stroke volume of 70 ml. It is important to note here that this means that the forward stroke volume (SV_f) ejected into the aorta, in the presence of moderate AR, will exceed 70 ml to compensate for the regurgitant volume. This is consistent with the physiological response of a left ventricle to a volume overload. Other simulation inputs used in our model are listed in 3.1. Obviously, mixed aortic valve disease (aortic stenosis + aortic regurgitation) can also be simulated using our model but this is beyond the scope of this study.

3.4.6 Patient Data

Patient data used in our previous study [26] to investigate the dynamic response of NT-proBNP and hs-cTnT to exercise challenge in pediatric patients with moderate AS or moderate AR, is used as input to our mathematical model. Briefly, our cohort includes a total of 25 gender and age-matched patients (9 control; 8 with moderate AS and 8 with moderate AR). In vivo measurements included: systolic and diastolic pressures measured by sphygmanometer, heart rate, systolic period, peak and mean transvalvular pressure gradient, forward stroke volume, aortic valve effective orifice area, aorta area at the sinotubular junction, and regurgitant fraction. The reader is referred to the original paper [26] for more details regarding the protocol and eligibility/exclusion criteria.

Table 3.1: Main numerical parameters used in the simulations

Description	Abbreviation	Value
Aortic valve parameters		
Effective orifice area	EOA	From 1.0 to 3.5 cm^2 (or from patient data)
Aortic stenosis effective orifice area	$EOA_{\|AS}$	From 1.0 to 3.5 cm^2 (or from patient data)
Aortic regurgitation effective orifice area	$EOA_{\|AR}$	From 0.1 to 0.3 cm^2 (or from patient data)
Ventricular parameters		
Net left ventricular stroke volume	LV SV	70 ml (or from patient data)
Systemic circulation parameters		
Variable resistance	R_{coa}, R_{av}, R_{ar}	
Inductance	L_{coa}, L_{av}, L_{ar}	
Aortic resistance	R_{ao}	0.05 mmHg s ml^{-1}
Aortic compliance	C_{ao}	0.5 ml/mmHg
Systemic vein resistance	R_{sv}	0.05 mmHg s ml^{-1}
Systemic arteries and veins compliance	C_{SAC}	2 ml/mmHg (or adjusted to get patient P_{sys}/P_{dia})
Systemic arteries resistance	R_{SA}	0.8 mmHg s ml^{-1} (or adjusted to get patient P_{sys}/P_{dia})
Upper body resistance	R_{ub}	Adjusted to have 15% of total flow rate in healthy case
Proximal descending aorta resistance	R_{pda}	0.05 mmHg s ml^{-1}
Output condition		
Central venous pressure	P_{CV0}	4 mmHg
Other		
Heart rate	HR	70 bpm (or from patient data)
Systolic pressure	P_{sys}	From 120 mmHg (or from patient data)
Diastolic pressure	P_{dia}	Adjusted as a function of AR

3.5 Computational Algorithm and Statistical Analysis

The computational algorithm is presented in details in our previous works [59–64]. Data are represented as mean ± standard deviation (SD). Variables were compared using a one-way repeated ANOVA. A p-value < 0.05 was considered statistically different.

3.6 Results

Considering the three cohorts simulated using our synthetic data one can compare their LV stroke work efficiency as displayed on Fig 3.2. This figure shows that on average, there is a statistical difference between the three groups in terms of LV stroke work efficiency ($p < 0.05$). The group with moderate AR is the one with the lowest LV stroke work efficiency.

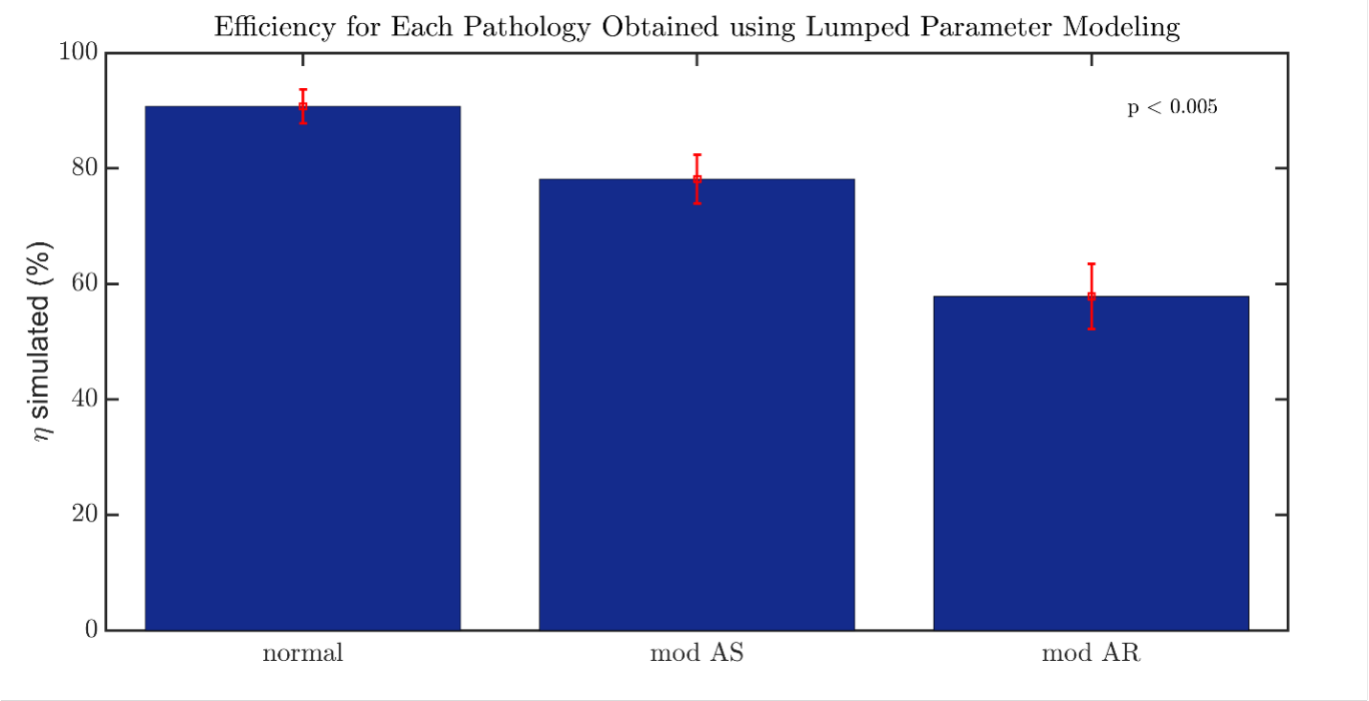


Figure 3.2: LV stroke work efficiency obtained using synthetic patient data for three different simulated cohorts: normal patients, patients with moderate aortic stenosis (mod AS) and patients with moderate aortic regurgitation (mod AR). LV stroke work efficiency was calculated using Eq.3.7.

Figure 3.3 displays the LV waveforms, aorta waveforms for three real patients: one patient with normal healthy condition, one with a moderate AS, and one with a moderate AR. Note again that the waveforms were obtained solely using non-invasive data from those patients. The corresponding LV efficiencies are 92, 86, and 75% respectively. The above reported efficiencies were obtained from the simulated actual and ideal P-V loops. It will be however more convenient for the translation to clinical practice to use the simplified formulation for the LV efficiency reported in equation 3.10.

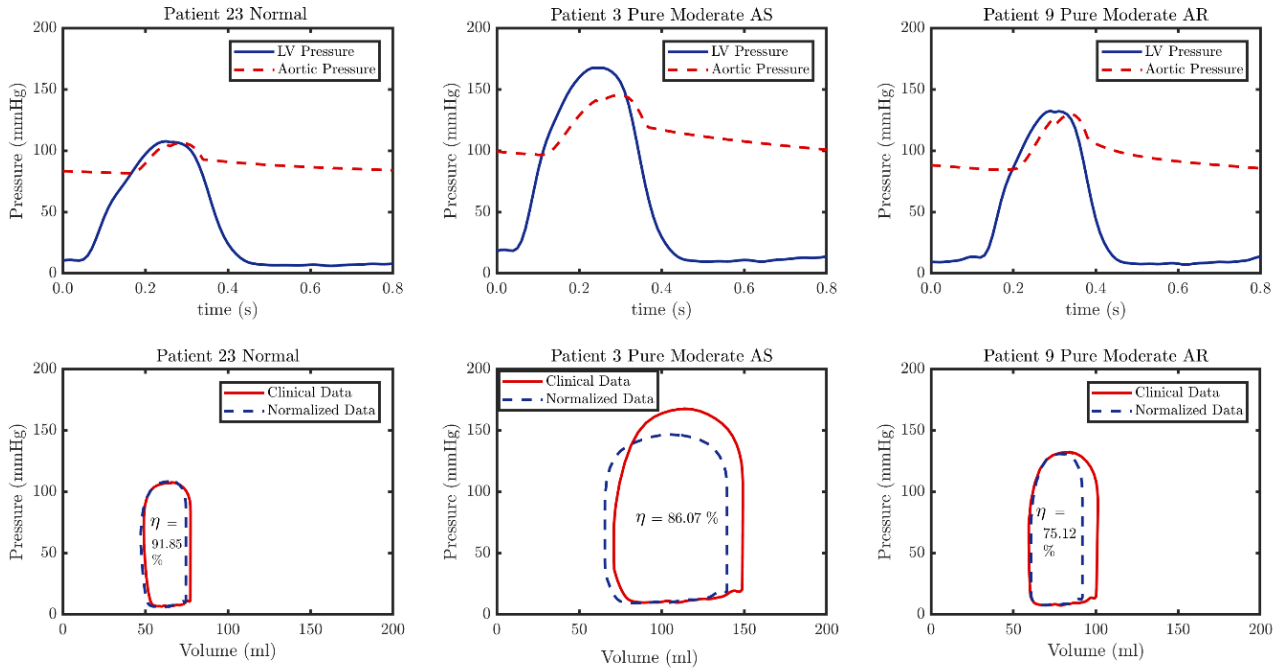


Figure 3.3: Examples of LV and aorta pressure waveforms obtained using real pediatric patient data for three different configurations of patients: (left panel) a normal patient; (middle panel) a patient with pure moderate aortic stenosis (AS); (right panel) a patient with pure moderate aortic regurgitation. The lower panel displays the actual pressure–volume loops (in red) and the ideal pressure–volume loops (in blue). The ratio between the two gives the LV stroke work efficiencies reported on the different panels as computed using Eq.3.7. SV_f forward systolic stroke volume, Rf regurgitant fraction.

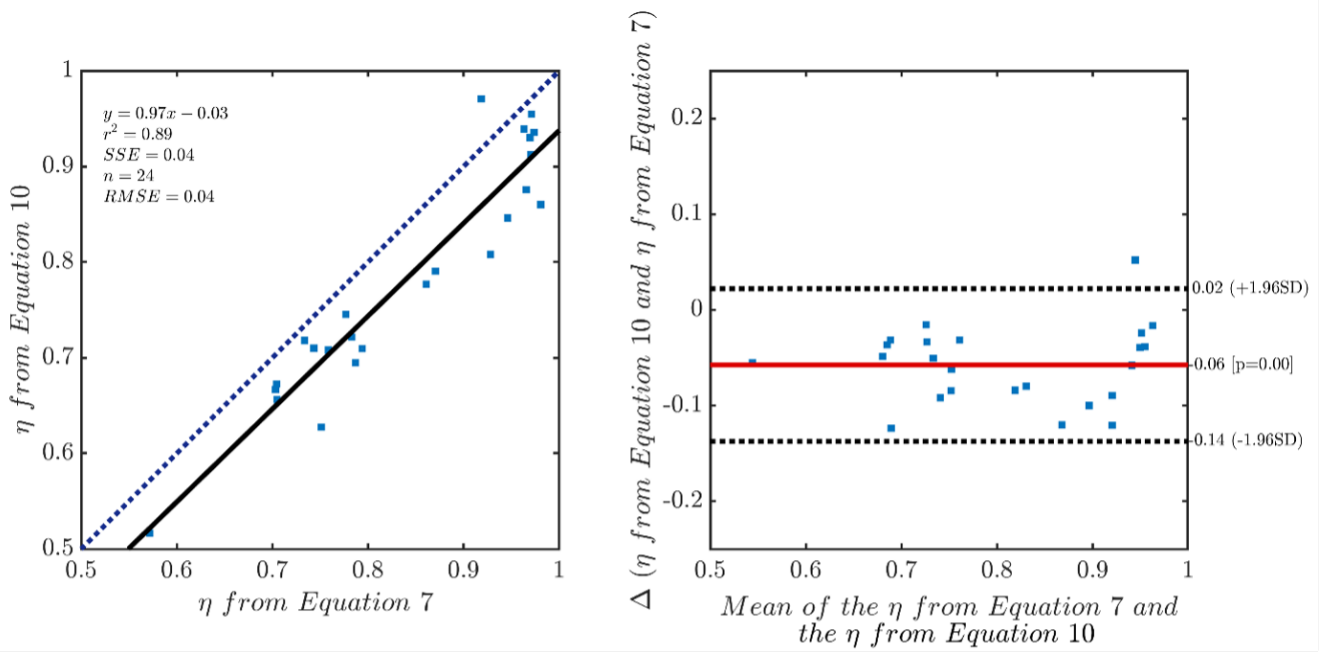


Figure 3.4: (Left panel) Correlation between LV stroke work efficiency as estimated using Eq. 3.10 and computed using Eq. 3.7 for the patient data. (Right panel) The corresponding Bland–Altman plot.

Figure 3.4 shows the correlation between LV efficiency based on in vivo data as obtained from the original equation Eq 3.7 and its approximation in Eq 3.10. There is a very good correlation and correspondence between the values for the efficiency obtained by equation 3.7 and equation 3.10) with R=0.94 and a root-mean-square error of 4%. Although both equations can be used in clinical practice, it is essential to mention that equation 3.10 cuts significantly in the number of in vivo measurement inputs required from 8 down to 3 measurements. As such, for the rest of the results, LV efficiency values obtained using the approximation reported in Eq. (3.10) will be used.

Figure 3.5 compares LV stroke work efficiency between the three different groups of patients (Normal, moderate AS, moderate AR). The results are consistent with the findings with the synthetic data where the normal group displays, on average, high LV stroke work efficiency values of 92 $\pm$ 3%, which is close to a perfect score of 100%, followed by the moderate AS group (76 $\pm$ 5%) and finally the moderate AR group (66 $\pm$ 7%). Our results show a statistically significant difference between all groups ($p < 0.05$). In the same figure, we report the individual values for LV stroke work efficiency obtained in our cohort. LV stroke work efficiency displays a clear separation between the control group and the moderate AS/moderate AR groups. It also shows some overlap between moderate AS and moderate AR, where patients at the upper bound of the moderate AR severity overlap with those at the lower bound of patients with moderate AS.

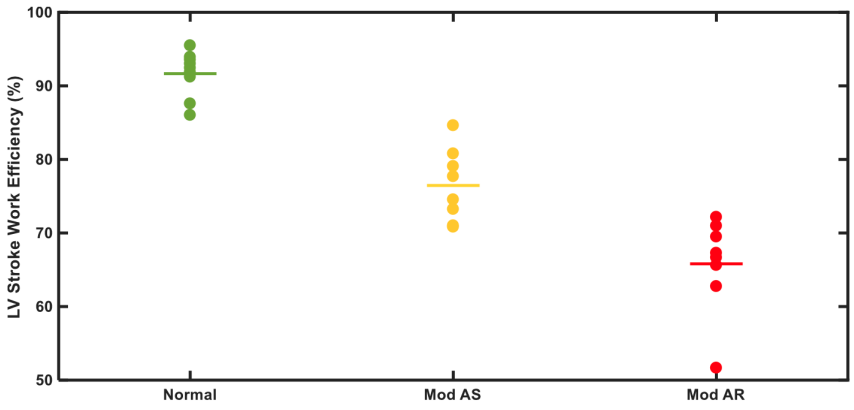


Figure 3.5: Mean values (horizontal lines) and individual LV stroke work efficiencies for the three different groups: normal patients, patients with moderate AS and patients with moderate AR (p value < 0.05 between all groups).

3.7 Discussion

The major findings in this study are: (1) Patients with moderate AR have a significantly lower LV stroke work efficiency when compared to patients with moderate AS; (2) LV stroke work efficiency seems to be a promising non-invasive parameter capable of monitoring pathology severity at all stages of progression; (3) The evaluation of LV stroke work efficiency can be considered as a first step towards a unifying approach for the classification of pure or combined heart valve disease.

3.8 The need for new clinical parameters.

Patients with moderate aortic valve disease have risks of increased mortality and sudden death that are underestimated based on symptomatology alone [53–57]. There is therefore a need for an identifying factor that can monitor the progression of the aortic valvular pathology and their impact on LV performance. Although there have been previous studies to identify markers of disease progression in adults, these studies never addressed moderate cases exclusively. One major issue when targeting cohorts with different aortic valve pathologies is the discrepancy in the parameters used to evaluate aortic valve disease in clinical practice: 1) EOA, Vmax, TPG_{mean} for the evaluation of aortic stenosis; 2) R_{f}, regurgitant EOA and pressure half-time for the evaluation of aortic regurgitation. So, we believe there is a need for a paradigm shift in the way patients with aortic valve disease are evaluated by introducing new non-invasive parameters capable of reflecting LV overload over a wide spectrum of valvular disease and severities.

In this study, we sought therefore to introduce a new parameter, LV stroke work efficiency (η_{LV}), that can be used across the different phenotypes of aortic valve disease including pure AS, pure AR and even mixed aortic valve disease. LV stroke work efficiency as estimated using Eq. (3.10) required a limited number of inputs that are routinely measured in clinical practice (Systolic pressure, mean transvalular pressure gradient and regurgitant fraction). The most challenging parameter to evaluate is regurgitant fraction but in this study this was successfully performed following the method introduced in [68]. This method evaluates the regurgitant fraction in patients with congenital heart

disease using Doppler retrograde velocity-time integral divided by antegrade velocity-time integral. Other approaches can also be used based on MRI measurements [69].

3.9 LV Stroke Work Efficiency is not Heart Efficiency.

It is worth noting that the definition of left ventricular stroke work efficiency is conceptually different from the classical definition of LV efficiency. While the classical definition of LV efficiency is the ratio of the LV work over the total myocardial O_2 consumption [70], the stroke work efficiency is the parameter used to compare between the actual performance of a device over its *ideal* performance, i.e. "isentropic" following the thermodynamic sense. In the case of aortic valvular pathologies, the ideal performance would be the work done by the left ventricle under normal conditions, i.e. in the absence of a pathology, whereas the actual performance is the left ventricular work done under the presence of a pressure and/or volume overload. In other words, it represents a measure of the deviation of the left ventricle's actual performance over its ideal potential for each individual patient.

3.10 Limitations

Our model does not currently consider physiological changes that occur overtime, such as hypertrophy or changes in left ventricular mass. Future works will attempt to include the physiological changes occurring in the cardiac muscle, including but not limited to, hypertrophy and also a validation of the simulated pressure–volume loops against in vitro measurements. The flow towards the coronary arteries during systole or diastole are neglected in our models of aortic stenosis and aortic regurgitation.

3.11 Conclusion

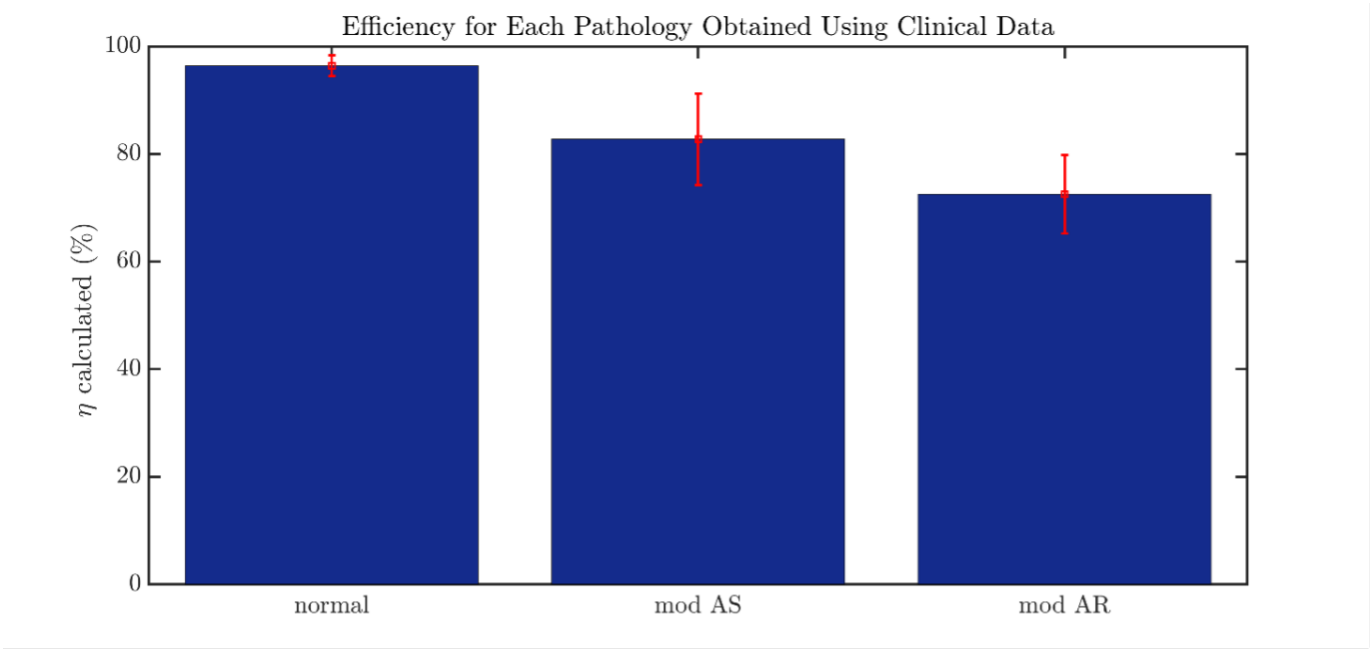
This study introduced and demonstrates the ability of LV stroke work efficiency to be used as a non-invasive parameter capable of evaluating LV overload in pediatric patients with moderate AS or moderate AR. Patients with moderate AR were found to have a significantly lower LV efficiency when compared to patients with moderate AS. LV stroke work efficiency seems to be a promising

non-invasive parameter capable of monitoring pathology severity at all stages of progression and can be conceptually considered as a first and important step towards developing a unifying approach for the classification of pure or combined heart valve disease and towards an individualized approach for AVD. However, this is a pilot study and more data are still required in order to confirm these findings and the ability of LV stroke efficiency to contribute to the optimal management of patients with aortic valvular disease.

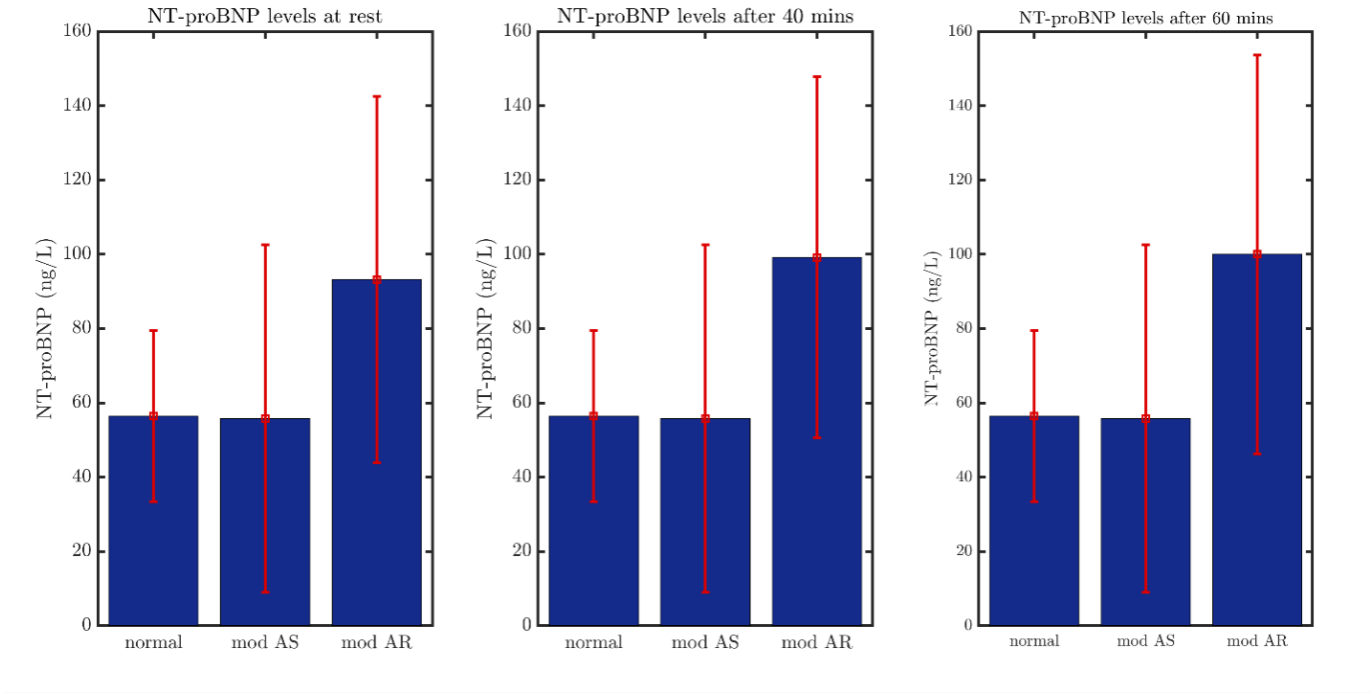
3.12 Subsequent Work - Not included in original article

3.12.1 NT-proBNP levels and LV isentropic efficiency

In our previous study [Mawad et al. 2015] [26], we have demonstrated the ability of NT-proBNP response to exercise challenge as a potential identifier for moderate AR compared to moderate AS and normal cases. In the same study, patients with moderate AR were found to display the highest values in terms of NT-proBNP at rest and after 20, 40 and 60 min after peak exercise. Our results based on the determination of LV isentropic efficiency are consistent, on average, with the results obtained with NT-proBNP measurements. More specifically, patients with moderate AR were also found to display the worst loading condition on the LV compared to control and moderate AS patients. However, we have also shown that when looking at individual patient data, LV isentropic efficiency allowed a better stratification between the different populations. This is very interesting since LV isentropic efficiency might be used clinically using non-invasive data and without the need for blood draw to provide a rapid indication of the load supported by the LV in patients with different phenotypes of aortic valve disease including pure AS, pure AR and even mixed aortic valve disease. Using a multi-modality approach including LV isentropic efficiency recording and other hemodynamic parameters will certainly contribute to a better management and stratification of pediatric patients with aortic valve disease.



(a) A



(b) B

Figure 3.6: NT-ProBNP levels post exercise challenge at rest, 40 mins into recovery, and 60 minutes into recovery for normal patients, mod AS patients, and mod AR patients.

4 | MAVD *in silico* Study

4.1 Methodology

In this study, several conditions have been tested using our model: Aortic valve effective orifice area was changed from 0.6 to 3.5 cm^2; aortic valve regurgitant orifice area from 0 to 0.7 cm^2; the LV net stroke volume (i.e., forward volume – regurgitant volume) from 50 ml to 80 ml; the heart rate from 60 to 90 bpm; systolic pressure from 120 mmHg to 140 mmHg. Table 4.1 shows the different conditions tested in this study. The cases simulated cover a wide range of aortic stenosis and aortic regurgitation severities and combinations, including mixed aortic valve disease. The cases have been selected in accordance with the AHA guidelines (see 4.1 for the definition) [51, 71]. A total of 46200 cases have been simulated in this study.

Table 4.1: Classification of the Severity of Valve Disease in Adults

Description	**Mild**	**Moderate**	**Severe**
Aortic Stenosis			
Jet velocity (m/s)	<3.0	3.0-4.0	>4.0
Mean gradient (mmHg)	<25	25-40	>40
Valve Area (cm^2)	>1.5	1.0-1.5	<1.0
Indexed Valve Area (cm^2/m^2)			<0.6
Aortic Regurgitation			
Regurgitant Volume (ml/beat)	<30	30-59	≥60
Regurgitant Fraction (%)	<30	30-49	≥50
Regurgitant Orifice Area (cm^2)	<0.10	0.10-0.29	≥0.30

4.2 Results

Please note that, for the sake of clarity, the results displayed in this section are for a normal stroke volume of 70 ml (the specific effect of variations in stroke volumes is displayed in Figure 4.7). Additionally, cases leading to unrealistically elevated values of TPGmax > 100 mmHg have been excluded.

Figure 4.1 displays LV waveforms, aorta waveforms, and pressure-volume loops for selected simulated cases representative of the different categories of patients: Normal ($AS_{EOA} = 3.5\,cm^2$; $AR_{EOA} = 0\,cm^2$); Moderate pure AS ($AS_{EOA} = 1.2\,cm^2$; $AR_{EOA} = 0\,cm^2$); Moderate pure AR ($AS_{EOA} = 3.5\,cm^2$; $AR_{EOA} = 0.15\,cm^2$); and Moderate MAVD ($AS_{EOA} = 1.2\,cm^2$; $AR_{EOA} = 0.15\,cm^2$). The corresponding LV stroke works are 0.96 J, 1.12 J, 1.41 J, and 1.82 J, and the corresponding LV efficiencies are 96.4%, 71.32%, 63.2%, and 51.80%, respectively.

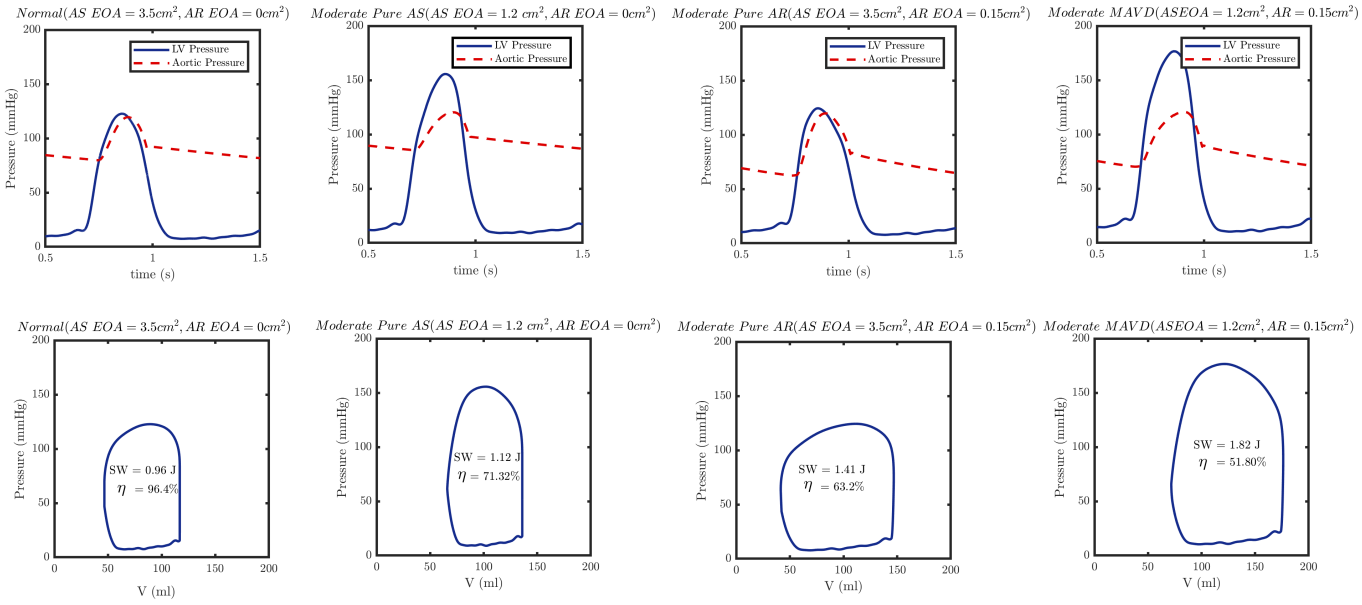


Figure 4.1: Simulated left ventricle and aortic pressure and LV stroke work in the case of: normal conditions (no pathologies), moderate pure AS, moderate pure AR and concurrent moderate AS and AR (moderate MAVD). For all cases, SV= 70 ml; HR=70 bpm.

Figure 4.2-A shows the correlation between the LV efficiency as computed using equation 3.8, i.e. integration of the pressure-volume loops, and equation 3.7 making use of the approximation of the LV stroke work. There is a very good correlation between the two (R = 0.99) with a SEE of 2.4.

Figure 4.2-B shows the corresponding Bland-Altman plot for the results in 4.2-A. It appears that equation 3.7 represents a very good approximation for equation 3.8 for low LV efficiencies ($< 40\%$) and lead to a slightly underestimation for higher efficiencies.

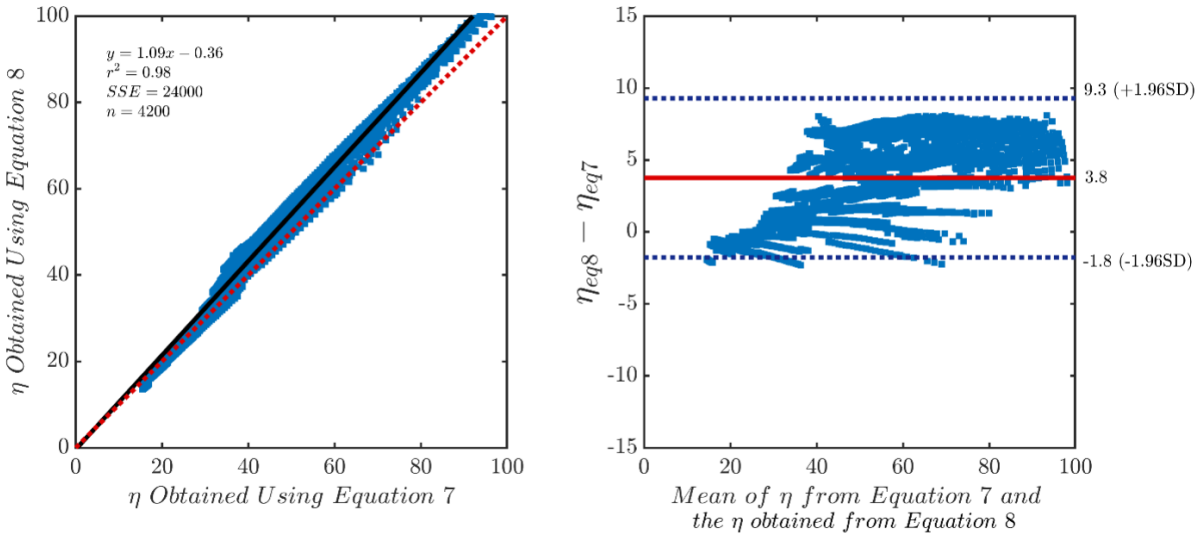


Figure 4.2: (A) Correlation between LV efficiency as estimated using equation 3.8 and computed using equation 3.7. (B) Corresponding Bland-Altman plot. SV= 70 ml; HR=70 bpm.

Figure 4.3 shows the relationship between LV stroke work and LV efficiency. It appears that there is an interesting non-linear relationship (power-law type) between the two variables, with a more pronounced decreases in LV efficiency as a result of LV stroke work increases for values higher than 1.5 J.

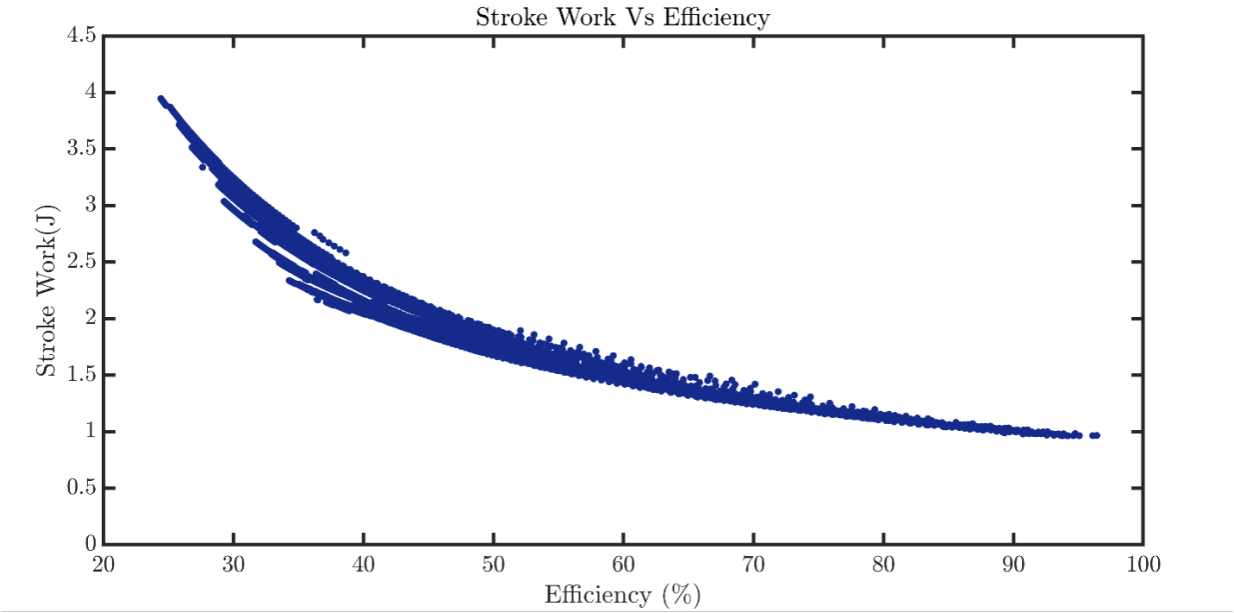


Figure 4.3: Relationship between LV stroke work & LV efficiency. The plot is for cases where TPGmean $\leq$ 100 mmHg, SV = 70 ml & HR = 70 bpm.

Figure 4.4 represents a contour plot of the LV efficiency as computed using equation 3.7 for AS_EOA ranging from 0.6 cm^2 to 3.5 cm^2 and AR_EOA ranging from 0.001 cm^2 to 0.7 cm^2, with the net stroke volume fixed at 70 ml. Figure 4.5 provides an expanded view of Figure 4.4, focusing on values corresponding to moderate mixed aortic valve disease (MAVD) severity as defined by clinical guidelines. Interestingly, within the same class of severity, specifically moderate AS and AR in this case, the LV efficiency varies significantly from 60% down to 35%. This observation indicates that using ordinal variables to evaluate the severity of MAVD might lead to considerable variability in hemodynamic conditions and outcomes within a single class of patients with aortic valve disease.

Figure 4.6 shows the interesting mapping in terms of LV efficiency between moderate MAVD cases and equivalent pure AS cases. This clearly demonstrates that patients with moderate MAVD have LV efficiencies that are similar to those of patients with severe pure AS (EOA $< 1.0\,cm^2$). In other words, our results show that, considering LV efficiency alone, patients with MAVD even at moderate level should be classified as equivalent to patients with severe pure AS.

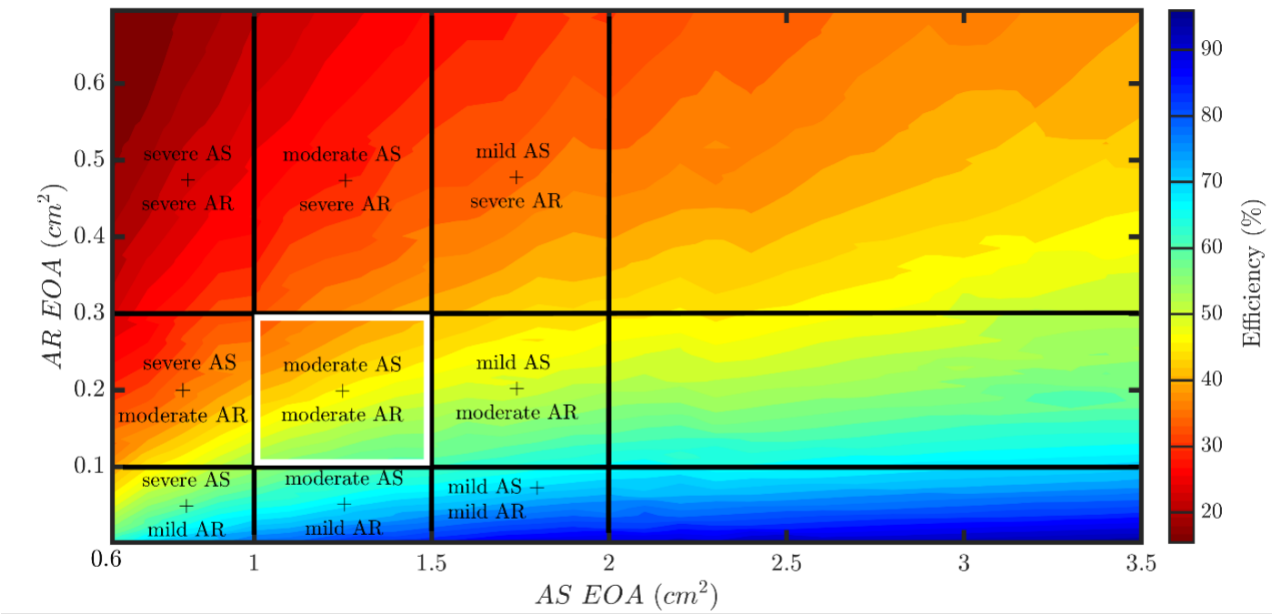


Figure 4.4: Contour map of the LV efficiency corresponding to different combinations of AS and AR severities.

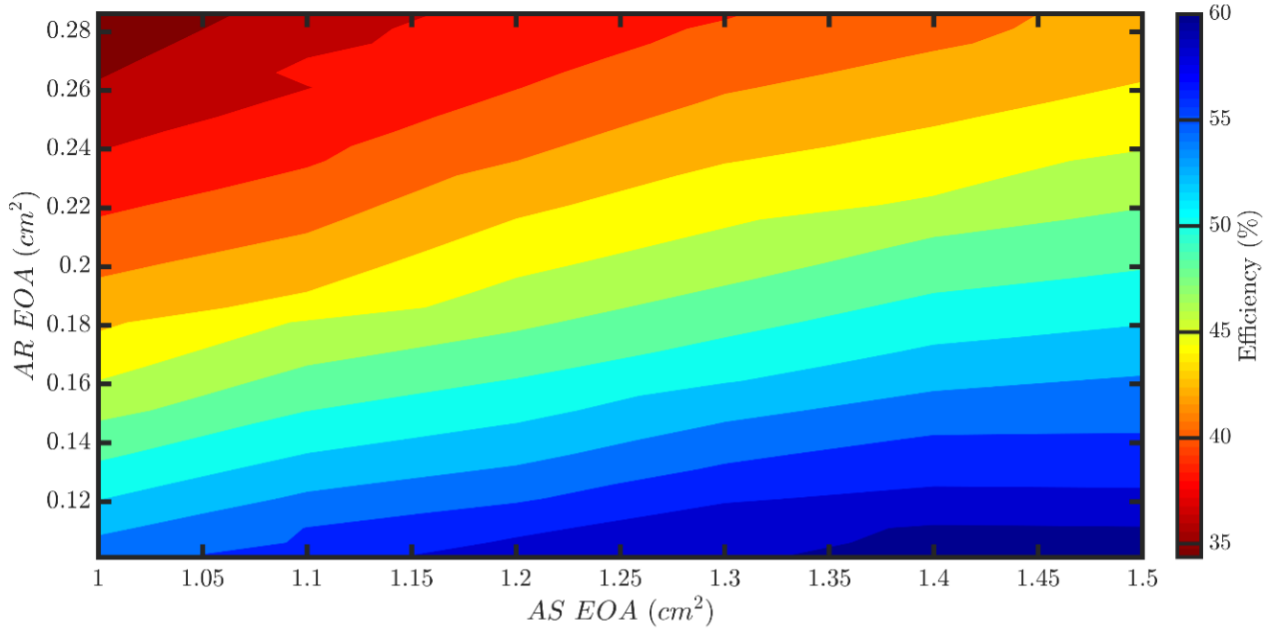


Figure 4.5: Expanded contour map of LV efficiency corresponding to moderate mixed aortic valve disease.

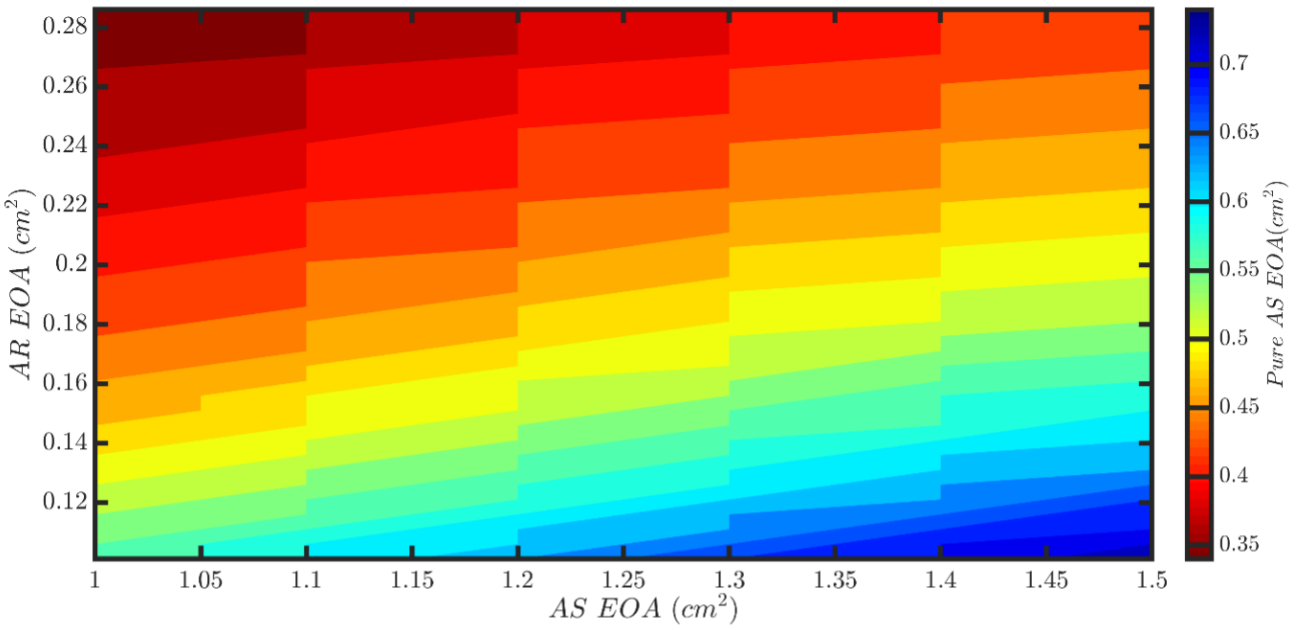
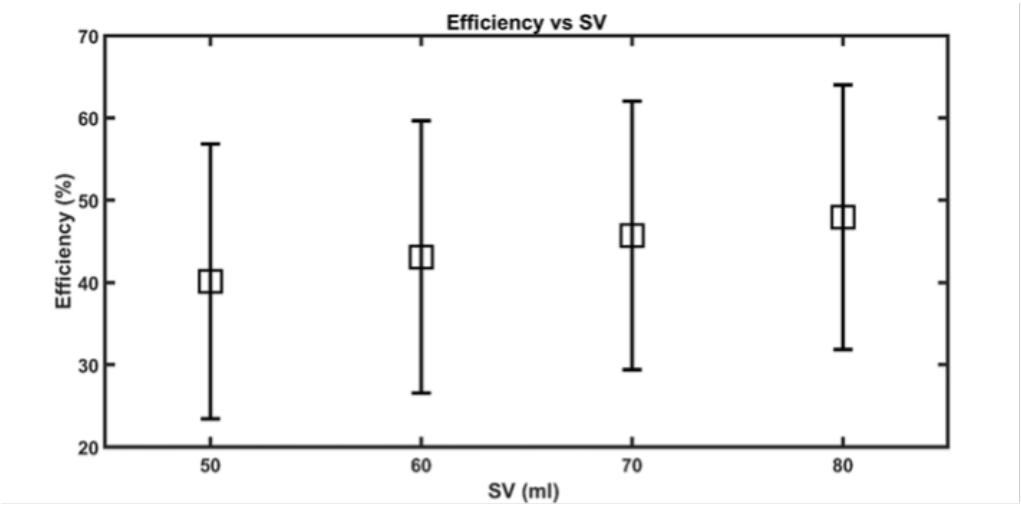
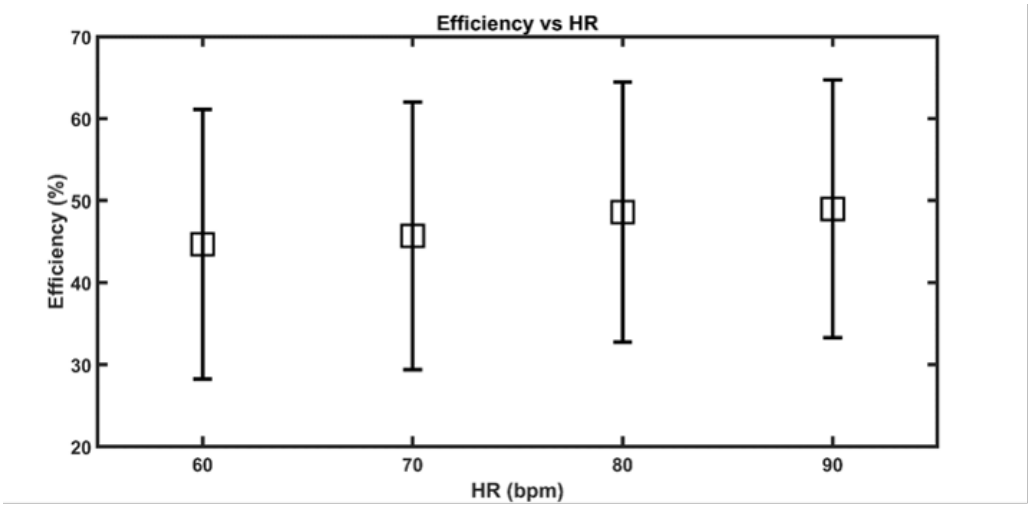


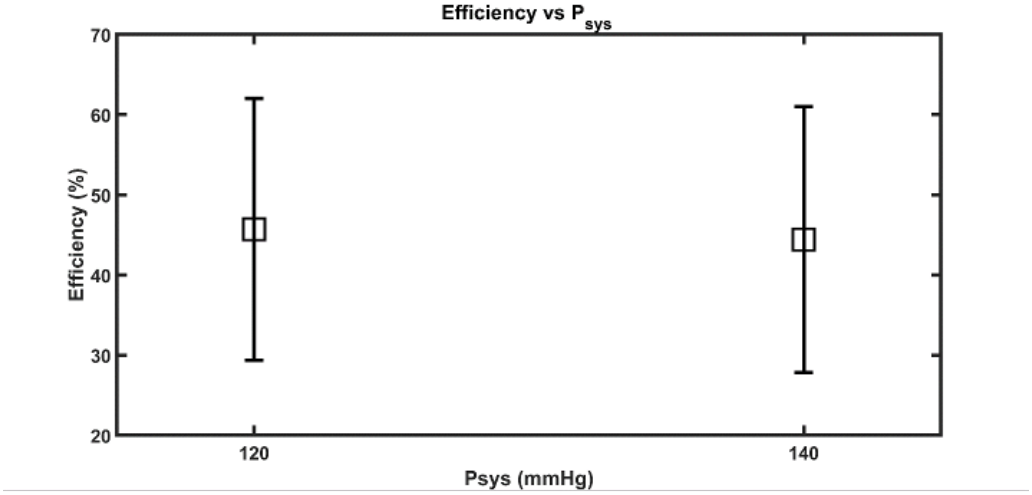
Figure 4.6: Mapping in terms of LV efficiency between values for mixed aortic valve disease cases and equivalent pure aortic valve stenosis cases.



(a) Stroke volume



(b) Heart rate



(c) Systolic pressure

Figure 4.7: Effects of variations in (A) stroke volume, (B) heart rate, (C) systolic pressure on LV efficiency.

Figure 4.6 shows the mapping of LV efficiency between moderate MAVD cases and equivalent pure AS cases. This clearly demonstrates that patients with moderate MAVD have LV efficiencies similar to those of patients with severe pure AS (EOA < 1.0 cm^2). In other words, our results suggest that, considering LV efficiency alone, patients with MAVD, even at a moderate level, should be classified as equivalent to patients with severe pure AS. Our findings are consistent with the clinical observations reported by *Dr. Mantovani and colleagues*, whose work draws from their direct experience and research in their medical practice [39]. Their study examines the epidemiologic, hemodynamic, and pathophysiologic implications observed in cases of mixed and combined valvular disease [39].

Figure 4.7 displays the effects of variations in stroke volume (SV) from 50 ml to 80 ml, heart rate (HR) from 60 bpm to 90 bpm, and systolic pressure from 120 mmHg to 140 mmHg on LV efficiency. It appears that there is a statistically significant difference ($p < 0.05$) in LV efficiency due to changes in SV, HR, and peak systolic pressure. However, the variations are relatively small ($< 5\%$ in absolute values), indicating the need for a clinical study to evaluate whether these variations are clinically relevant.

4.3 Discussion

4.3.1 MAVD findings

The major findings of this study are: 1) MAVD even at a moderate level leads to significantly elevated loads on the LV; 2) Moderate MAVD leads to LV overloads that are equivalent to those induced by severe pure aortic stenosis; 3) LV efficiency appears to be a promising parameter capable of unifying the classification of valve disease severity in the presence of pressure and/or volume overloads.

4.3.2 The curious case of mixed aortic valve disease

Several previous studies have investigated the impact of pure AS or pure AR on LV systolic and diastolic functions. However, little was known until quite recently, about the LV response to mixed aortic valve disease and more specifically to moderate mixed aortic valve disease [52]. Patients with moderate mixed aortic valve disease were not regarded as patients at risk simply because none of the valve diseases (AS or AR) had reached a severity justifying an aortic valve replacement [45, 70, 72]. However, recent studies clearly questioned this approach [46, 49, 73]. Patients with moderate MAVD must overcome the combined loads (pressure load + volume load) induced by aortic stenosis and aortic regurgitation [52]. Consequently, they have been shown to have a significant increase in LV mass and a more rapid progression of symptoms requiring aortic valve replacement when compared to patients with moderate AS or moderate AR [48, 50].

4.3.3 The need for new clinical parameters

The coexistence of AS and AR in patients with MAVD raises the question regarding which parameter to use for decision making and follow up in such patients [52]. LV mass in patients with moderate MAVD has been found to be significantly higher than in patients with isolated AS or AR but using this parameter may be challenging because of the limited resolution of Doppler echocardiography systems [52]. Another interesting parameter suggested to evaluate patients with MAVD is Doppler peak systolic velocity [45, 73]. The rationale behind suggesting this parameter was that it can capture the combined effects of AS and AR. A Doppler peak systolic velocity > 4 m/s or severe MAVD (the

presence of severe AR or severe AS) were found to be the most significant predictors of clinical events (death or need for AVR) in patients with MAVD [45, 46, 73]. Although, peak aortic valve velocity represents a simple and reproducible parameter its flow dependent nature may limit its application to large cohorts. Furthermore, Doppler peak aortic velocity can be useful in pure AS and MAVD but not in pure AR. This last issue illustrates the discrepancy in the parameters used to evaluate aortic valve disease in clinical practice: 1) EOA, Vmax, $\overline{TPG}$ for the evaluation of aortic stenosis; 2) Rf, regurgitant EOA and pressure half-time for the evaluation of aortic regurgitation. In this study, we sought therefore to introduce a new parameter (η_{LV}) that can be used across the different phenotypes of aortic valve disease including pure AS, MAVD, and pure AR. This represents, at least from a fundamental point-of-view, a paradigm shift in the way aortic valve disease can be evaluated by introducing a patient-specific parameter that can potentially unify the decision-making process in patients with aortic valve disease.

4.3.4 Moderate AS + Moderate AR $\geq$ pure Severe AS.

Our results (see Figure 4.4 Contour map of the LV efficiency corresponding to different combinations of AS and AR severities; Figure 4.5) show that when moderate AS and moderate AR coexist, this leads to a LV stroke work and efficiency which are equivalent or worse than for a severe isolated AS. For example, the best case scenario for the subgroup with moderate MAVD (AS EOA of 1.5 cm^2 and an AR EOA of $0.101cm^2$) results in a LV efficiency wish is equivalent to the one generated by a severe pure AS of 0.74 cm^2. This is very significant as physicians currently base their clinical decisions, when treating MAVD, on the predominant lesion while a severe case of pure AS would unquestionably warrant intervention and subsequent valve replacement according to the current guidelines [51, 71, 73]. This result is consistent with clinical studies showing that patients with MAVD experience more severe hemodynamic events compared to patients with severe isolated AS [49, 52, 73–75]. Our results also advocate for a closer follow up of patients with moderate MAVD which is consistent with some recent clinical recommendations that even suggested earlier valve replacement in patients with MAVD [48, 50, 59, 73].

4.3.5 A closer look at the immense variation within Moderate MAVD group.

Our results show that moderate MAVD cases alone results in LV efficiencies ranging from 61.71% down to 34.36%. The fact that there is such a drastic range within moderate MAVD efficiency and that the work exerted by the left ventricle can vary so dramatically depending on the respective combinations of the AS and AR severity, is a testament to the importance of better understanding the vastly different cases within moderate MAVD and introducing guidelines that are better suited for cases of concurrent AS and AR.

4.3.6 The significance of volume overload in stroke work and cardiac efficiency.

In the presence of MAVD, AR plays a peculiar role in increasing the LV stroke work and lowering LV efficiency. The real LV stroke work as approximated in equation 3.9 displays a cubic dependence with respect to stroke volume, or flow rate. As consequence, even small variations in AR severity and volume overload lead to significant changes in LV stroke work. This further exaggerated when AR coexists with AS as in patients with MAVD.

It is worth noting that the new definition of left ventricular isentropic efficiency is conceptually different from the classical definition of LV efficiency. While the classical definition of LV efficiency is the ratio of the LV work over the total myocardial O_2 consumption [70], the isentropic efficiency is the parameter used to compare between the actual performance of a device over its ideal i.e. isentropic performance. In the case of aortic valvular pathologies, the ideal performance would be the work done by the left ventricle under normal conditions, i.e. in the absence of a pathology, whereas the actual performance is the left ventricular work done under the presence of a pressure and/or volume overload. In other words, it represents a measure of the deviation of the left ventricle's actual performance over its ideal potential.

5 | Conclusion and Future Work

While this thesis introduces a novel framework for modeling aortic valve disease (AVD) and assessing patient-specific left ventricular (LV) efficiency, several limitations must be acknowledged. At the core of this work is the introduction of LV isentropic efficiency as a promising non-invasive parameter capable of evaluating LV overload in patients with moderate aortic stenosis (AS), aortic regurgitation (AR), particularly in pediatric cases. Our findings indicate that patients with moderate AR exhibit significantly lower LV efficiency compared to those with moderate AS. This parameter not only captures differences in hemodynamic burden but may also serve as a unifying metric for tracking disease severity across the spectrum of pure and mixed valve pathologies. Its conceptual foundation lays important groundwork for an integrative approach to heart valve disease classification.

Despite these promising results, several modeling and data-related limitations must be addressed. First, the current models do not incorporate time-dependent physiological remodeling of the myocardium, such as hypertrophy, fibrosis, or changes in LV mass and compliance. These adaptations are essential for simulating long-term disease progression in response to chronic pressure or volume overload and will be critical for increasing the physiological fidelity of future simulations.

Second, the models currently assume simplified hemodynamics and do not include coronary artery flow during systole or diastole. As coronary perfusion is key to myocardial energetics, particularly in cases of LV hypertrophy or dysfunction, its omission may affect the accuracy of pressure-volume analyses and energetic assessments under real-world conditions.

Third, while the AR model has been validated in isolated AR, it has not yet been tested in patients with mixed aortic valve disease (MAVD), especially those with concurrent AS. This is largely due to the retrospective nature of most MAVD studies and the inconsistent reporting of key AR parameters

such as regurgitant fraction (RF), forward stroke volume, and regurgitant stroke volume in clinical records. These values are often omitted or calculated inconsistently, creating major barriers to model validation. A prospective study that systematically captures these parameters from the outset is needed to evaluate the model in mixed disease states.

Additionally, although echocardiographic Doppler measurements are commonly used in the clinic to estimate disease severity, RF and other derived metrics are not always reliably reported in routine imaging. This inconsistency limits both the input data available for simulations and the reference standards required for model validation. Furthermore, our models are currently derived from controlled, synthetic simulations that do not yet reflect the full heterogeneity of real-world patients, such as comorbidities, anatomical variability, or interobserver differences in data acquisition. These factors may limit the immediate clinical translation without further refinement and testing.

Future efforts will aim to address these limitations through both clinical data acquisition and model expansion. A key next step is the development or collaboration on a prospective MAVD study in which RF, forward stroke volume, and regurgitant stroke volume are measured in a standardized fashion. This would provide essential data for validating the AR component of the model in mixed valve disease and enable more robust comparison between predicted and observed outputs.

To address the incompleteness of Doppler-derived measurements in retrospective datasets, machine learning (ML) will be explored as a tool to estimate missing values. Predictive models trained on a combination of synthetic simulations and available patient data could infer missing hemodynamic parameters and improve the model's clinical utility. Beyond data imputation, ML may also identify hidden hemodynamic patterns that support more personalized diagnostic and treatment pathways.

In parallel, future iterations of the model will incorporate physiological adaptations such as myocardial hypertrophy, fibrosis, and compliance changes. Integrating coronary perfusion dynamics (currently excluded) will further enhance the model's accuracy in simulating myocardial energetics. Lastly, the framework will be expanded to encompass additional valvular pathologies, such as mitral valve

disease, broadening the model's applicability to a wider range of mixed valve conditions.

Collectively, these efforts aim to transform LV efficiency into a clinically viable, non-invasive parameter for evaluating and monitoring AVD severity across a range of patient populations and disease presentations.

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A | Tables

Table A.1: Clinical classification of the severity of valve disease in children.

Category	Criteria
Moderate AS	Mean Doppler Pressure Gradient of 20-39 mmHg with normal left ventricular function No more than Mild AR, if any No reported symptoms
Moderate AR	Retrograde to anterograde velocity time integral ratio of 20-40% at the level of the thoracic aorta Absent or mild Doppler Pressure Gradient (mean gradient <25 mmHg)
Normal	LVEF greater than 55%
CTL	Asymptomatic children with physiological murmur

Table A.2: Stages of Valvular Heart Disease (VHD). Reproduced from Otto, C.M., Nishimura, R.A., Bonow, R.O., et al. *2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease*, Circulation, 2021;143:e72-e227 [23]. © 2021 American Heart Association, Inc. Used under fair dealing for educational purposes.

Stage	Definition	Description
A	At risk	Patients with risk factors for the development of VHD
B	Progressive	Patients with progressive VHD (mild to moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who meet criteria for severe VHD: C1: Asymptomatic with severe VHD, where the LV or RV remains compensated C2: Asymptomatic with severe VHD, with decompensation of the LV or RV
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

Table A.3: Stages of Valvular Heart Disease (VHD). Reproduced from Otto, C.M., Nishimura, R.A., Bonow, R.O., *et al.*, *2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease* Circulation, 2021;143:e72-e227 [23]. © American Heart Association. Reproduced under fair dealing for educational purposes.

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	BAV (or other congenital valve anomaly) Aortic valve sclerosis	Aortic V_{max} < 2 m/s with normal leaflet motion	None	None
B	Progressive AS	Mild to moderate leaflet calcification/fibrosis of a bicuspid or trileaflet valve with some reduction in systolic motion Rheumatic valve changes with commissural fusion	Mild AS: aortic $V_{max} = 2.0 - 2.9$ m/s or mean $\Delta P < 20$ mm Hg Moderate AS: aortic $V_{max} = 3.0 - 3.9$ m/s or mean $\Delta P = 20 - 39$ mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg AVA typically ≤ 1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2)	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV systolic dysfunction	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg AVA typically ≤ 1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2)	LVEF < 50%	None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification/fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg AVA typically ≤ 1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2) but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea, decreased exercise tolerance, or HF Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA ≤ 1.0 cm^2 with resting aortic $V_{max} < 4$ m/s or mean $\Delta P < 40$ mm Hg Dobutamine stress echocardiography shows AVA ≤ 1.0 cm^2 with $V_{max} \geq 4$ m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF < 50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification/fibrosis with severely reduced leaflet motion	AVA ≤ 1.0 cm^2 (indexed AVA ≤ 0.6 cm^2/m^2) with an aortic $V_{max} < 4$ m/s or mean $\Delta P < 40$ mm Hg AND stroke volume index < 35 ml/m^2 Measured when patient is normotensive (systolic blood pressure < 140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF $\geq$ 50%	HF Angina Syncope or presyncope

B | Figures

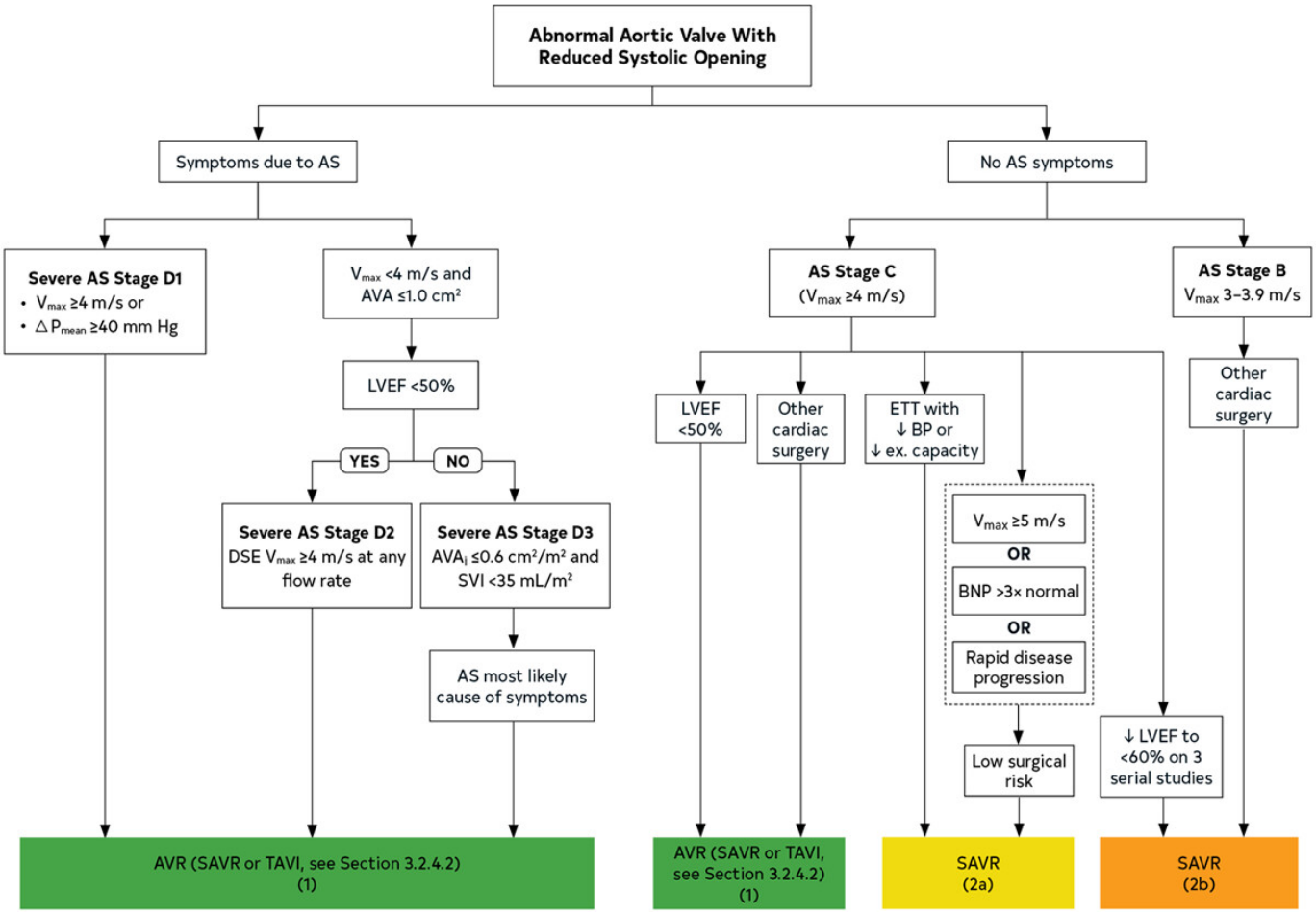

Figure B.1: AVD management and intervention process flowchart. Reproduced from *2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease*, Circulation, 2021 [23]. Copyright © 2021 American Heart Association. Reproduced under fair dealing for educational purposes.