

Novel assessment of cardiorespiratory interactions in aortic stenosis

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*” Croyez ceux qui cherchent la vérité,
doutez de ceux qui la trouvent;
doutez de tout, mais ne doutez pas de vous-même. ”*

*” Believe those who seek the truth,
doubt those who find it;
doubt all, but do not doubt yourself. ”*

*André Paul Guillaume Gide, 1952
Ainsi soit-il; ou, Les Jeux sont faits*

I dedicate this work to my family.

Declarations and Acknowledgments

I, Marzia Rigolli, declare that the work presented in this thesis is my own, unless stated otherwise, and is in accordance with the University of Oxford's regulations for the degree of Doctor of Philosophy.

This thesis was possible thanks to my supervisors Saul Myerson, Associate Professor in Cardiovascular Medicine, and Mona Bafadhel, Associate Professor in Respiratory Medicine to whom I am grateful. In addition, I thank my collaborators who have helped me in this journey. Their contributions are here listed:

Chapter 3 – Respiratory Function in Aortic Stenosis

Multi-centre Retrospective Oxford-Italy Study

I designed the multi-centre retrospective study and collaborated with Dr. Faggiano and colleagues who provided the Italian arm data. I collected the Oxford arm data, performed and interpreted the analyses.

Chapter 4 – Cardiac Function in Aortic Stenosis

Single-centre Prospective Oxford Study

I designed the study and recruited part of the aortic stenosis participants. Dr. Mahmod, Dr. Bull and Dr. Loudon provided the ethics and recruited part of the aortic stenosis participants. Dr. Wijesurendra and Dr. Ariga provided the healthy controls. Dr. Sivalokanathan performed the second operator blinded analyses for the inter-observer analyses and the first operator blinded biventricular functional and strain analyses.

Multi-centre BSCMR UK Outcome Study

The British Society of Cardiovascular Magnetic Resonance (BSCMR) Valve Consortium provided the data for the collaborating UK Centres. I collected the Oxford data with the assistance of Dr. Loudon. I performed the blinded biventricular volumetric, mass and functional analyses as part of the BSCMR core-lab. I designed the sub-analysis study presented, analysed and interpreted the data.

Chapter 5 and 6 - Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis: The AMICA-AS Study

Single-centre Prospective Oxford AMICA-AS Study

This was devised, coordinated and run by me, including the ethical approval, recruitment of all subjects, data acquisition, analysis and interpretation. As the study involved complex advanced imaging techniques, additional technical support was required. Participants were assisted by research nurses Ms. Delos Santos and Ms. Farras. I performed the clinical assessment and the magnetic resonance scans with the support of radiographers Ms. Francis and Ms. Leal. The four-dimensional flow sequence was optimised by Dr. Hess. The Xenon hyperpolarisation was performed by the gas production team. Xenon magnetic resonance scans were performed by Mr. McIntyre with the help of Mr. Jacob for gas administration. Funding for the imaging developing arm was provided by Prof. Gleeson. Dr. Doganay coded the sequence for gas exchange. Dr. Martin and Dr. Chen provided training for the Pulmonary Toolkit developed by Dr. Doel. The respiratory functional testing was performed by lung physiologists Dr. Bruce, Mr. Pacpaco and Mr. Guan. The computed tomographic images were collected by the Churchill radiographers. Dr. Bruce provided the operator blinded morphological lung analyses and helped assisting the participants during their respiratory visit.

Abstract

The outcome in aortic stenosis (AS) depends on the correct timing of valve replacement. Currently, this is based on symptoms and cardiac response to pressure overload. In patients with multiple medical conditions, uncertainty exists concerning symptomatic onset and in distinguishing cardiac from respiratory causes of breathlessness. An accurate assessment of lung disease and optimal tools to discriminate between cardiac and respiratory dyspnoea are needed in AS, in whom decompensation may confound respiratory assessment, and conversely chronic obstructive pulmonary disease (COPD) is a major reason for delay or avoidance of surgery. Mis-treatment can therefore result from inaccurate diagnoses. Advanced imaging allows the assessment of cardiac and respiratory co-morbidities, potentially reducing the misinterpretation of symptoms, and may enable more appropriate treatment.

In chapter 3, I explore the limitations of standard respiratory assessments in patients with AS. The discrepancy between apparent and confirmed airflow limitation, their relationship with aortic treatment and mortality were assessed. It was found that these are distinct entities with different prevalence and prognosis: apparent COPD was a powerful independent predictor of mortality in severe AS and this may reflect its ability as a combined cardiac and respiratory disease marker. However, when COPD was assessed more accurately, airflow limitation was only mild-moderate in severity and not showing prognostic impact.

The right ventricle not conventionally assessed in AS and often influenced by COPD was examined in chapter 4. A hyperdynamic right ventricle was a marker of decompensation

and cardiac recovery. In addition, even mild right ventricular dysfunction was a predictor of late mortality after aortic replacement. Therefore, the right ventricle may prove useful as an indicator of decompensated AS when symptoms are difficult to assess and may help identify those suitable for early surgery.

Advanced lung functional testing and novel lung imaging methods were studied in chapter 5 and 6 to discriminate between decompensated AS and symptomatic lung disease. I discovered a significant promise for direct lung imaging and functional measures which were able to differentiate symptomatic AS who most benefitted from aortic replacement.

In summary, this thesis demonstrates the role of cardio-respiratory assessment in AS, including a novel morpho-functional evaluation of the cardio-respiratory interactions in AS. Patients with advanced lung disease who would not likely improve after valve replacement may avoid in the future a high-risk futile intervention. On the contrary, those with an hyperdynamic right ventricle and apparent respiratory dysfunction determined by cardiac disease might avoid under-treatment.

List of Awards, Publications and Presentations

Parts of the original research presented in this thesis have been disseminated via publications in peer-reviewed journals and presentations at national and international meetings. Below a list of awards, publications and presentations directly arising from this doctoral work:

Awards

- **Rigolli M.** Winner of the *Young Investigator Award* of the *British Heart Valve Society* 2018, presenting part of the research findings described in Chapter 4 - Cardiac Function in Aortic Stenosis published in the article “A Hyperdynamic Right Ventricle is an Early Marker of Clinical Decompensation and Cardiac Recovery in Aortic Stenosis with Normal Ejection Fraction” (September 2018)
- **Rigolli M.** Finalist of the *Young Investigator Award* of the *British Research Council Cardiovascular Theme* 2015, presenting part of the proposal for my doctoral studies (October 2015)

Publications

Original Research Papers

- **Rigolli M**, Sivalokanathan S, Bull S, Wijesurendra R, Loudon M, Francis JM, Karamitsos T, Neubauer S, Mahmood M, Myerson SG. *A Hyperdynamic Right Ventricle is an Early Marker of Clinical Decompensation and Cardiac Recovery in Aortic Stenosis with Normal Ejection Fraction*. JACC Cardiovasc Imaging. 2018 Nov 8; Epub ahead of Print. Research findings described in Chapter 4 - Cardiac Function in Aortic Stenosis
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Law G, Moon JC, Greenwood JP. *Myocardial Scar and Mortality in Severe Aortic Stenosis. Data from the BSCMR* (British Society of Cardiovascular Magnetic Resonance Valve Consortium). *Circulation* 2018, Oct 30;138(18):1935-1947. New research findings described in Chapter 4 - Cardiac Function in Aortic Stenosis

- Doganay O, Chen M, Matin T, **Rigolli M**, Phillips J, McIntyre A, Gleeson F. *Magnetic resonance imaging of the time course of hyperpolarized ¹²⁹Xe gas exchange in the human lungs and heart*. *Eur Radiol*. 2018 Dec 5; Epub ahead of Print. New research findings described in Chapter 5 and 6.
- Bruce RM, Phan PA, **Rigolli M**, Pacpaco E, Rahman NM, Farmery AD. *Assessment of ventilatory heterogeneity in chronic obstructive pulmonary disease using the inspired sinewave technique*. *Chest* 2018 Dec. Under Review. New research findings described in Chapter 5 - Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis: The AMICA-AS Study

Abstracts (only first name and published are listed)

- **Rigolli M**, Rossi A, Temporelli P, Benfari G, Cioffi G, Nistri S, Gaibazzi N, Guidetti F, Myerson S, Bafadhel M, Faggiano P. *Chronic Obstructive Pulmonary Disease in Symptomatic Aortic Stenosis: the importance of correct assessment for defining prognosis*. *European Heart Journal* 2018; 39: supplement 1. Research findings described in Chapter 3 - Respiratory Function in Aortic Stenosis
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- **Rigolli M**, Rossi A, Temporelli P, Benfari G, Cioffi G, Nistri S, Gaibazzi N, Guidetti F, Bafadhel M, Faggiano P. *Chronic Obstructive Pulmonary Disease in Symptomatic Aortic Stenosis: A Main Underlying Diagnostic Confounder and Prognostic Factor*. Thorax 2017, 72, Supplement 3: A134-A135. Research findings described in Chapter 3 - Respiratory Function in Aortic Stenosis.
- **Rigolli M**, Rossi A, Temporelli P, Benfari G, Cioffi G, Nistri S, Gaibazzi N, Guidetti F, Vassanelli C, Metra M, Tavazzi L, Faggiano P. *Prognostic impact of chronic obstructive pulmonary disease in severe symptomatic aortic stenosis*. European Respiratory Journal 48 (Suppl 60) September 2016. Research findings described in Chapter 3 - Respiratory Function in Aortic Stenosis.

Oral Presentations at National and International Conferences

- **Rigolli M**. A hyperdynamic right ventricle is an early marker of clinical decompensation and cardiac recovery in aortic stenosis with normal ejection fraction. BHVS2018: British Heart Valve Society – Birmingham 09/2018 (awarded Young Investigator Award of the year) described in Chapter 4.
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- **Rigolli M**. The right ventricle in aortic stenosis: RV hypercontractility assessed by CMR is an early marker of clinical decompensation and cardiac recovery in as with normal left ventricular function. CMR2018: Joint Annual American/European Cardiovascular Magnetic Resonance Congress– Barcelona 01/2018 described in Chapter 4.

- ***Rigolli M.*** Chronic obstructive pulmonary disease in symptomatic aortic stenosis: a main underlying diagnostic confounder and prognostic factor. BTS2017: British Thoracic Society – London 12/2017 described in Chapter 3.
- ***Rigolli M.*** Recent high impact findings in chronic obstructive pulmonary disease comorbidities: prognostic impact of chronic obstructive pulmonary disease in severe symptomatic aortic stenosis. Oral presenter aged 35 and under. ERS2016: European Respiratory Society– London 09/2016 described in Chapter 3.

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List of Abbreviations

AMICA-AS:	Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis Study
AS:	Aortic Stenosis
AV:	Aortic Valve
AVA:	Aortic Valve Area
AVR:	Aortic Valve Replacement
BNP:	Brain Natriuretic Peptide
BP:	Blood Pressure
CLD:	Chronic Lung Disease
CMR:	Cardiovascular Magnetic Resonance
CMR-TT:	Cardiovascular Magnetic Resonance Tissue Tracking
COPD:	Chronic Obstructive Pulmonary Disease
COPD-GOLD:	Chronic Obstructive Pulmonary Disease diagnosed with the Global Initiative for Chronic Obstructive Lung Disease criteria
COPD-STs:	Chronic Obstructive Pulmonary Disease diagnosed with the Society of Thoracic Surgeons criteria
EUROSCORE:	European System for Cardiac Operative Risk Evaluation
FEF:	Forced Expiratory Flow
FEV ₁ :	Forced Expiratory Volume in one second
FVC:	Forced Vital Capacity
HP:	Hyperpolarised
IQR:	Inter Quartile Range
LGE:	Late Gadolinium Enhancing

LV:	Left Ventricle
LVEF:	Left Ventricular Ejection Fraction
MRI:	Magnetic Resonance Imaging
NPV:	Negative Predictive Value
PEF:	Peak Expiratory Flow
PFT:	Pulmonary Functional Testing
PPV:	Positive Predictive Value
ROC:	Receiver Operator Characteristic
RV:	Right Ventricle
RVEF:	Right Ventricular Ejection Fraction
RVSD:	Right Ventricular Systolic Dysfunction
SAVR:	Surgical Aortic Valve Replacement
SOP:	Standard Operator Procedure
SPAP:	Systolic Pulmonary Artery Pressure
STS:	Society of Thoracic Surgeons
TAPSE:	Tricuspid Annular Plane Systolic Excursion
TAVI:	Transcatheter Aortic Valve Implantation
XE:	Xenon

Chapter 1 - Introduction

OUTCOME IN AORTIC STENOSIS

Aortic stenosis (AS) is the most common heart valve disease characterised by progressive left ventricular outflow tract obstruction and systemic pressure overload. Its prevalence increases dramatically with age, reaching almost 10% in octogenarians (1). Moreover, if severe valve obstruction is left untreated, it severely impacts outcome with a mortality rate as high as 90% at five years after symptomatic onset (2). Since no medical therapy is currently available to treat or reduce the disease progression, improving outcomes relies on ensuring the most appropriate timing for aortic valve replacement (AVR). Currently, this decision depends on two factors affecting mortality in severe AS (3):

- 1. Symptoms**

- 2. Cardiac response to pressure overload.**

However, uncertainty exists in the evaluation of both manifestations.

In the following introductory sections, the importance of lung disease which may confound *symptoms* and, consequently, outcome in AS is discussed. Secondly, novel ways of discriminating between respiratory and cardiac effects in AS are introduced. Lastly, the importance of the *cardiac* right ventricular *response* which may be affected by *pressure overload* and result a determinant of outcome in AS is explored. Each section corresponds to a following result chapter and ends with the pertaining research questions which are further explored in the appropriate result chapters.

SYMPTOMS

1.1.1 Dyspnoea in Aortic Stenosis

The onset of symptoms has been the key element indicating the need of invasive treatment in severe AS. Untreated AS is characterised by a long pre-symptomatic period and dismal outcome after symptomatic onset (4). In addition, AVR in symptomatic valvular disease was proven to reduce mortality with robust evidence in severe AS, regardless of the type or severity of symptoms or the response to medical therapy (5–8). However, the typical initial manifestations of AS are exertional dyspnoea and decreased exercise tolerance, both highly non-specific and relatively common symptoms. These may often arise in physiological ageing or be caused by other co-morbidities. Due to the slow, progressive nature of the aortic valve obstruction, patients may also not recognise symptoms because they may have gradually limited their daily activity levels (9,10).

Therefore, the most important early indications of valve obstruction are also the least easy to identify, in contrast to the more specific classical symptoms. The latter are represented by syncope, angina, and heart failure, which are often seen at a later stage when symptomatic onset has not been properly recognised and, consequently, treatment delayed. In addition, due to the population ageing and the wider availability of less invasive AVR treatment options (11,12), patients age at the time of intervention has significantly increased, intensifying the need of correctly assessing a newly complex clinical group with co-existing pathologies.

Dyspnoea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity... [it] derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses” (13). The intrinsic subjective nature of dyspnoea and its frequent occurrence in the clinical setting are the main challenges confronting the clinician when assessing symptomatic patients with multiple potential underlying causes of symptoms. In the general population, 10% complain to their family doctor of dyspnoea when walking on flat ground and up to 25% on more intense exertion such as climbing stairs (14,15). For 1–4% of patients, shortness of breath is the main reason for consulting a doctor (14,16).

While dyspnoea at rest and pulmonary oedema are typical and often clearly recognisable manifestations of decompensated AS and other types of heart failure, exertional symptoms are difficult to assess, and their underlying pathophysiological mechanisms not fully understood. The classic notion that exertional dyspnoea and exercise intolerance in patients with heart failure is caused by the inability of the cardiac pump to support the increased metabolic demand of the exercising muscles determining exertional fatigue and its inability to do so without abnormal increases in pulmonary venous pressures causing dyspnoea (17,18) has been challenged. Studies have shown that ventricular systolic and diastolic functional parameters are poorly related to exertional symptoms (19–21) and that therapeutic interventions improving the cardiac haemodynamic response do not impact on exertional dyspnoea (22–25). Respiratory abnormalities contribute to exertional dyspnoea in heart failure with demonstrated excessively increased ventilatory demand and critical mechanical ventilation limitation due to abnormal restrictive

constraints on tidal volume expansion (26,27). Some research has also shown that interventions acting on the above mechanisms by reducing the ventilatory response to exercise and improving respiratory mechanics were able to benefit heart failure patients with exertional symptoms (26–28).

Therefore, dyspnoea is not determined by cardiac factors alone, but likely depends on complex cardio-pulmonary interactions (29). The study of these cardiac and respiratory interactions is needed to provide a more effective management of such a common and disabling symptom which awaits a better understanding of its underlying pathophysiology.

1.1.2 Dyspnoea in the Elderly: Multi-morbidity

Patients with chronic dyspnoea account for 15–50% of those seen in the cardiology setting and approximately 60% of those referred to pneumonologists (30). Chronic dyspnoea is usually due to one of the following common causes: chronic obstructive pulmonary disease (COPD), congestive heart failure, bronchial asthma, interstitial lung disease, pneumonia, and mental disorders (31,32). However, in the elderly and multi-morbid patient it is challenging to ascribe dyspnoea to a single cause. The increasing prevalence of chronic progressive disease due to prolonged life expectancy is leading to highly complex cardiovascular patients with significant co-morbidities (33,34).

Of the potential causes of dyspnoea, AS has become the most common valvular heart disease in Europe and North America (1,35). The prevalence of AS is 0.2% among adults between the ages of 50 and 59 years but steeply increases to around 10% in octogenarians,

with an overall prevalence of 2.8% in adults older than 75 years of age (36,37). Dyspnoea is also a cardinal symptom of COPD, being its major cause of anxiety and disability (38). COPD is the third leading cause of mortality (39), claiming 3.0 million lives in 2016 worldwide (40). In the United Kingdom, the reported population prevalence of spirometry-diagnosed COPD is 13.3%, with 80% of subjects denying any respiratory diagnosis (41). In addition, the prevalence of COPD also increases with age to reach over 19% of people over 75 (42). These figures confirm that both COPD and AS are a significant public-health burden in the elderly and may largely go unrecognised by those affected.

The treatment of elderly and co-morbid patients is not routinely standardised. Guidelines for the management of AS define the assessment of comorbidity as being directed by clinical evaluation (section 3.1.4 in the European Guidelines for the management of valvular heart disease 2017) (43). The lack of protocols and common ground to diagnose and classify lung disease in AS determines a variable choice of specific examinations to risk stratify the patient with valvular disease. Guidelines for COPD management also do not take into account heart valve disease although COPD often coexists with other diseases that may have a significant impact on prognosis (44). Of these, cardiovascular diseases are the most frequent and important comorbidity affecting outcome in COPD (45,46). Cardiovascular disease, AS and COPD share similar risk factors and may be causally related by mutually increasing the risk or severity of disease. It is also recognised that some COPD features such as symptoms may be shared with other disease and, as such, this mechanism may represent a link between COPD and AS (46).

1.1.3 Shared Risk Factors and Pathophysiology in Aortic Stenosis and COPD

Clinical factors associated with calcific aortic valve disease mirror those associated with cardiovascular disease, and coronary artery disease is common among AS patients (47). Population-based studies have shown associations between AS and older age, male sex, low-density lipoprotein cholesterol and lipoprotein(a), hypertension, smoking, diabetes, and the metabolic syndrome (48,49). In addition, populations at increased risk for AS include those with a history of renal failure, familial hypercholesterolemia, or calcium metabolism alterations (50).

Smoking, cardiovascular disease, diabetes, metabolic syndrome and calcium metabolism disorders are also directly linked to COPD (38). Although smoking is the most studied and prevalent risk factor of chronic lung disease, non-smokers may develop COPD and evidence showing strong associations with other underlying diseases is available (51). Less than 50% of heavy smokers develop COPD during their lifetime (52) and, therefore, other mechanisms are likely involved. Cardiovascular disease has been recognised as the most frequent comorbidity in COPD (45,46). Previous studies have also shown that diabetes and metabolic syndrome are more frequent in COPD patients than the general population and impact on prognosis (53,54). Osteoporosis is also a common comorbidity in COPD associated with emphysema and low body mass index (55,56).

Several lines of evidence suggest that both AS and COPD are not localised diseases but systemic conditions. AS is not a simple mechanical disease limited to the valve leaflets given that adverse outcomes are present in calcific aortic disease even in the absence of significant valve obstruction: the presence of aortic sclerosis in adults over the age of 65

years without known coronary artery disease was associated with a 52% increase in cardiovascular mortality risk and a 40% increase in the risk of myocardial infarction, independently from known cardiovascular disease risk factors (57). Aortic valve sclerosis in patients without known coronary artery disease was also associated with a doubling of cardiovascular risk in the higher-risk hypertensive population (58). Aortic valve calcifications were associated with a 50% increase in cardiovascular events in the MESA study (49) and the degree of these provided additive value to the Framingham Heart Study risk factors for the prediction of events (59). Further studies are needed to explore whether AS is a marker of cardiovascular disease or whether it reflects a shared underlying pathophysiological mechanism, such as systemic inflammation.

Systemic inflammation is also pivotal in the pathophysiology of COPD. Inhalation of cigarette smoking or other noxious gases causes lung inflammation and this inflammatory response appears to be increased in patients affected by COPD (44). Chronic inflammation induces the pathological lung parenchymal destruction which results in emphysema, and the disruption in defence mechanisms leading to small airway fibrosis (44). The pathological changes in COPD include elevated numbers of inflammatory cells in the lung, and morphological changes induced from repeated injury and repair (60). Patients with COPD, particularly when reaching the severe stages of disease and during active exacerbation, have also other evidence of systemic inflammation: increased circulating cytokines, chemokines and acute-phase proteins, or abnormalities in circulating cells were demonstrated (61,62). Systemic inflammation could, therefore, play an important role in both COPD and AS disease and also help explain the high prevalence of other comorbidities associated with COPD (63).

In addition to the above mechanisms, other common pathways in COPD and decompensated AS may cause disease overlap and progression. For example, the renin-angiotensin system (RAS) is overactivated in both conditions (64,65). This has been extensively studied in heart failure and its compensatory mechanisms (66), but the RAS is not only present in the systemic circulation. RAS mediators have been demonstrated in multiple organs and, particularly, in the lungs (65,67). Angiotensin-II is a potent mediator of pulmonary airway constriction and can activate apoptosis in lung epithelial cells and mitogenic effects in lung fibroblasts (68). Reported higher levels of angiotensin-II in the lungs have been associated with decreased gas exchange and increased lung inflammation and pulmonary vasoconstriction (67–69). Another important common mechanism is the shared metabolic modulation shift from glucose to lipid metabolism, resulting in muscle dysfunction and cachexia in the end stage of both disease (66,70,71).

Shared risk factors, overlapping symptoms, systemic inflammation and other common pathophysiological pathways in COPD, AS and cardiovascular disease may explain the important cardio-respiratory associations present in the co-morbid dyspnoeic patient.

1.1.4 Associations and Interactions between Aortic Stenosis and COPD

Unsurprisingly, AS and COPD frequently co-exist: almost 20% of patients with severe AS undergoing cardiac surgery for valve replacement were diagnosed with COPD (72). Understanding the cause of dyspnoea and formulating the correct diagnosis regarding the underlying respiratory conditions in these complex patients is extremely challenging. However, these two conditions are often studied separately, while their association may entail significant diagnostic and prognostic implications.

AS and COPD may co-exist either explicitly or as underlying undiagnosed conditions. These two diseases may overlap in terms of risk factors (elderly age, smoking and inflammation), symptoms and signs. Given the common presence of COPD in the same population that is also prone to AS, a significant proportion of AS patients may have COPD which could confound the assessment of symptoms. One disease may confound the diagnosis, classification and risk assessment of the other.

The prevalence of comorbidities in COPD patients varies significantly according to their definition, diagnosis, collection methods and population selection. Cardiovascular comorbidities which are the most common in COPD (73–75) emerged as the leading cause of mortality in patients with mild-moderate stages of COPD: their presence is associated with poor outcome, with those affected being more likely to die from the comorbid cardiovascular disease rather than their respiratory condition (76).

However, specific data on heart valve disease prevalence in patients affected by COPD is unknown. Most of the literature has been focused on the association between COPD and cardiovascular disease. For example, the prevalence of COPD in heart failure patients who share similar age and decompensation features with AS varies substantially between less than 10% to more than 50% (77), underlying the complexity in distinguishing lung disease in elderly co-morbid patients with various degrees of frailty and lung congestion.

Congestive heart failure is a common and complex clinical syndrome which represents the most significant manifestation of decompensated AS. In fact, the average survival rate after the onset of heart failure in severe AS is only 1.5 years (78), the lowest survival

of the classical AS symptomatic onsets. The coexisting prevalence of COPD and heart failure is extraordinarily variable depending on the COPD definition and patient population selection (33,79). Elderly patients with known COPD manifest a 4.5 fold higher risk of developing heart failure and one-fifth of them has unrecognised heart failure (80). Instead, about one-third of patients with heart failure were found to be affected by COPD (80,81). The inconsistency between studies in prevalence and prognosis underlies how complex it is to develop a correct diagnosis in this type of population.

1.1.5 Diagnosis and Classification of COPD in Aortic Stenosis

Data on COPD prevalence in AS is extremely limited. Our knowledge on COPD in symptomatic AS is based on retrospective sub-analyses of larger trials with dubious lung disease diagnosis and classification (82,83). The previous literature is severely limited by the adopted definition of COPD in the cardiology setting. This is based on risk scoring (84), mainly the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (85,86) and derivatives of the EuroSCORE (87–89) rather than on the standard diagnosis of COPD with spirometry, as defined by the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines (90).

The STS score has been largely used for the selection of patients undergoing large randomised trials investigating transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement (SAVR) in high and intermediate risk patients (5,91,92). TAVI is widely adopted in symptomatic AS patients with multiple co-morbidities and, therefore, these trials have been used to retrospectively assess COPD

impact based on the information collected during the cardiac surgery risk assessment, creating a particular diagnosis of “COPD” which has been in this thesis renamed COPD-STS for clarity.

A summary of differences between COPD definitions and classifications is provided below in Table 1.1.

Table 1-1. Definition and classification of COPD-GOLD and COPD-STS according to guidelines and commonly adopted risk scores.

	GOLD	STS
<i>Definition</i>	Common, preventable and treatable disease characterised by - persistent respiratory symptoms AND - airflow limitation due to airway and/or alveolar abnormalities	Disease defined based on either - spirometry ($FEV_1 \leq 75\%$ predicted) AND/OR - medical therapy (bronchodilators, long-term cortocosteroids therapy, home oxygen therapy)
<i>Classification</i>	Classified based on airflow limitation assessed by spirometry which is required to make the diagnosis: - Mild: $FEV_1 \geq 80\%$ - Moderate: $50 \leq FEV_1 < 80\%$ - Severe: $30 \leq FEV_1 < 50\%$ - Very Severe: $FEV_1 < 30\%$	- Mild: FEV_1 60-75% OR inhaled/oral bronchodilator - Moderate: FEV_1 50-59% OR steroid therapy - Severe: $FEV_1 < 50\%$ OR room air $pCO_2 > 50$ Oxygen - Unknown: history of chronic inhalation reactive disease

1.1.6 Prognostic Impact of COPD in Aortic Stenosis

Previous sub-analyses of randomised trials and large registries conducted mainly in TAVI patients have assessed the prognostic impact of COPD in AS (82,83,93,94). COPD resulted an independent predictor of mortality after TAVI with adjusted hazard ratio (HR) ranging from 1.23 (95% CI: 1.04 – 1.47) (82) to 1.84 (95% CI: 1.08 – 3.13) (83). Therefore, COPD patients are currently recognised as high-risk patients for invasive treatment of their aortic valve disease. If intervention is futile, as recognised in almost half of the AS patients with lung disease (43% in Mok et al. study (83)), this may expose these patients to premature mortality.

However, all the above studies were severely limited by the definition of COPD, as discussed in the above paragraph. Sometimes referred as chronic lung disease (CLD), COPD was mostly defined clinically by the presence of respiratory symptoms (e.g., progressive dyspnoea) requiring long-term use of bronchodilators, steroids or oxygen. This definition is derived from the information acquired from the commonly adopted cardiac STS scoring system used to evaluate the optimal aortic valve management option.

The only previous study assessing the association between airway obstruction and mortality after TAVI found an adjusted cumulative HR of 1.44 (95% CI 1.150-1.793). However, this impact was mainly driven by severe stages of COPD and mild lung disease manifested a survival distribution similar to non-COPD patients (94). Therefore, a simplified and dichotomous definition of COPD may be deleterious for patients in need of invasive aortic treatment who may be excluded from it based on a perceived increased risk.

1.1.7 Confounding Effect of COPD in Aortic Stenosis

Even objective measurements of respiratory function with spirometry may fail to distinguish between ageing, COPD and symptomatic AS. Currently, spirometry is required to make the diagnosis of COPD (90). The presence of a post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) <0.70 confirms the presence of persistent airflow limitation. However, the fixed criterion may be too simplistic in this group of patients. In the elderly, it overestimates the disease, as it declines with ageing even in healthy never smokers (95). Moreover, although restrictive ventilation is the hallmark of chronic heart failure, airflow obstruction is typical in pulmonary oedema (96) which is the decompensated stage of AS. This may explain why the prevalence of COPD in heart failure varies substantially between less than 10% to more than 50%, emphasising the high complexity of lung disease diagnosis in this class of patients (77). In addition, the FEV_1 -based classification fails to recognise that in elderly patients with stable or acute heart failure a significant reduction in FEV_1 may be present and airflow obstruction overrated on spirometry (97–99).

The confounding effect between cardiac and respiratory disease on spirometry has also been confirmed by the observation that patients with severe AS were diagnosed with COPD on the basis of lung functional testing with no history of previous hospitalisation or known lung disease (100). Furthermore, almost half of all the patients undergoing AVR improved lung function on spirometry after the valve operation (100) and patients with heart failure may normalise their lung function just by diuresis (99). Both of these studies indicate that lung congestion secondary to left-sided heart disease (including AS) can result in altered lung spirometry, giving the false impression of COPD. While a

significant change in pulmonary functional tests following cardiac interventions would not be expected in patients with underlying COPD, an improvement could be explained in those with misdiagnosed COPD and congestive heart failure which can be determined by the AS itself. The importance of better defining COPD to discriminate true lung disease effects in patients with AS needs to be investigated and better evaluations are required.

1.1.8 Distinguishing between Cardiac and Respiratory Dyspnoea: Advanced Lung Assessment

Cardiac and respiratory causes of dyspnoea may be simultaneously present in the elderly co-morbid patient. The prevalence of cardiovascular disease in COPD subjects is high, around 20-22% compared to only 9% in those without COPD (101). Similarly, COPD patients characterised by a higher degree of dyspnoea (GOLD categories B and D) had a five to eight times higher mortality from cardiovascular diseases than A and C groups (102). In the ECLIPSE study, cardiovascular disease defined as “heart trouble” was reported in 26% of the over 2000 patients with COPD compared to 11% of the smokers without airflow obstruction (74).

COPD is characterised by progressive airflow limitation caused by a variable combination of small airways disease and lung parenchymal destruction (103). Spirometry, the standard method to diagnose and classify COPD, provides information on global lung function. It does not provide regional nor direct information about the lung and, most importantly, spirometry can be severely confounded by heart failure and ageing in cardiac patients. In addition, changes detected by spirometry are not associated with

patient symptoms which are important in predicting mortality in both COPD (104) and AS (105). Therefore, additional methods to diagnose and objectively quantify lung disease would be beneficial in this complex group of patients to prevent the above confounding effects and potentially be better associated with outcome.

COPD includes a broad range of pulmonary disease. The progressive airflow limitation in COPD is due to two major pathological processes: the remodelling and narrowing of the small airway disease, and the destruction of lung parenchyma. The latter is called lung emphysema which is a subset of the heterogeneous COPD disease and it is defined anatomically as a permanent enlargement of air spaces distal to the terminal bronchiole with destruction of their walls. The ability of radiographic scans to identify emphysema has focused the attention on imaging to diagnosis and categorise morphological lung alterations. Computed tomography (CT) has been advocated for its efficacy in detailed diagnosis of emphysema and was correlated with gross pathology (106), with excellent in-vitro correlations between CT emphysema score and pathological emphysema grade and in-vivo correlations in the range of 0.8-0.9 (107). CT assessment for emphysema in smokers and COPD subject was adopted for two important large studies which analysed the associations of emphysema with symptoms and lung function characteristics, and changes over time. In the MESA-COPD study (108) around half of the smokers presented a degree of COPD and 51% of these had emphysema on CT assessment. In addition, 17% of the smokers with no COPD manifested a degree of lung emphysema, with an overall prevalence of emphysema in smokers of 27%. Centrilobular and panlobular emphysema types presented greater symptoms, greater hyperinflation and reduced diffusing capacity. The ECLIPSE study (109) was a longitudinal study designed to assess change in CT lung

density and biomarkers in smokers over time. Baseline lung density assessed by CT was influenced by smoking status, gender, age, BMI and FEV1. The decline in lung density was more rapid in smokers and females. A CT diagnosis of emphysema was also associated with important clinical outcomes, including mortality (110). Nowadays, CT is the reference standard for the diagnosis of emphysema and any other morphological lung disease. It is clinically and widely available and may help discriminate true lung disease in a complex AS population with other causes of dyspnoea and shared risk factors such as age and smoking. Although widely used in radiology and respiratory medicine for COPD assessment, chest CT has not been previously adopted for this purpose in cardiology and may entail important diagnostic and prognostic implication in a difficult to assess multi-morbid population.

While chest CT can provide morphological information and may distinguish true underlying lung alteration from cardiac decompensation, exposure to ionising radiation renders it an unfavourable modality for multiple follow-up scans. In addition, spatial resolution limits the assessment to the macro-structural lung changes. Hyperpolarised Xenon Magnetic Resonance Imaging (HP-Xe MRI) is a novel imaging technique adopted in a limited number of centres worldwide and available in Oxford (111). HP-Xe MRI provides a unique method for evaluating regional lung function by direct visualisation of the lung airspaces. HP-Xe MRI is free from ionising radiation, and therefore safe for repeated assessment. Conventional proton MRI has limited use in respiratory disease because the lung is largely composed of air which has few hydrogen atoms and thus does not generate signal (112). Inhalation of hyperpolarised xenon (Xe-129), an inert noble gas, enables direct visualisation of the lung airspaces on MRI. In addition, the high

solubility of Xe-129 in biological tissues and its chemical shift (113,114) render the technique ideal for assessing the primary lung function: gas exchange. Therefore, HP-Xe MRI is safe and can provide a unique strategy for regionally quantifying ventilation, diffusion and gas transfer to provide comprehensive in vivo global and regional assessment of lung structure and function.

1.1.9 Research Hypotheses

Chapter 3 – Respiratory Function in Aortic Stenosis

- The prevalence of confirmed respiratory dysfunction in patients with symptomatic AS is high and different from the known prevalence of apparent lung disease.
- Both under-diagnosis of COPD leading to unnecessary AVR at higher risk, and over-diagnosis of COPD leading to over-estimate of operative risk and surgical denial, exist in a significant proportion of symptomatic AS patients. The co-existence of AS and COPD in patients with symptoms have important implications for AVR management and, thus, indirectly and/or directly affect survival.
- The impact of confirmed respiratory dysfunction is different from the known prognostic impact of apparent lung disease in AS.

Chapter 5 – The AMICA-AS Study

- Current methods for assessing lung disease in AS are inadequate and novel imaging modalities enable a direct morphological and functional lung assessment to distinguish between respiratory and cardiac effects in AS.
- The degree of morphological lung disease is associated with AVR futility demonstrated by reduced functional capacity improvement post-AVR.

- Hyperpolarised xenon magnetic resonance is feasible in a multi-morbid population with cardio-respiratory disease.

1.1.10 Research Aim

The objective of this research branch was to assess the prevalence and prognostic role of COPD defined by the “gold standard” respiratory functional assessment compared to the conventional clinical “risk stratification” definition in patients with severe AS undergoing different aortic valve treatment strategies (Chapter 3 – Respiratory Function in Aortic Stenosis).

In addition, the research explored novel ways of discriminating the confounding effect of lung disease in symptomatic AS patients who may either be inappropriately excluded from cardiac treatment in the absence of lung disease or may endure futile higher-risk AVR in case of respiratory symptoms (Chapter 5 – The AMICA-AS Study).

CARDIAC RESPONSE TO PRESSURE OVERLOAD

1.1.11 Limitation of Left Ventricular Function in Aortic Stenosis

AS is characterised by LV pressure overload which results in compensatory LV hypertrophy. Both LV function and hypertrophy have been extensively researched in AS. Previous studies have proven that patients with a normal LV ejection fraction (LVEF) but a decreased mean transvalvular gradient have a significantly higher afterload, and the LVEF does not satisfactorily reflect LV performance under these circumstances (115). Importantly, LV pressure overload in AS induces myocardial alterations and fibrosis that mainly affect the subendocardial layers responsible for longitudinal function and not well reflected by global LVEF (116). Hermann et al. further demonstrated that LV systolic function based on endocardial displacement could remain normal despite significant myocardial damage (117). However, guidelines consider LVEF as the only index to identify LV systolic dysfunction. Unfortunately, this evaluation markedly underestimates the extent of cardiac impairment in the presence of LV hypertrophy such as it is often the case with AS. This is why there is a need of other types of assessment of cardiac involvement in AS to target early impairment for a better timing of intervention and therapy.

1.1.12 Right Ventricular Function in Aortic Stenosis

Cardiac pressure overload in AS results in LV hypertrophy, stiffness and increased LV filling pressures. These may lead to pulmonary hypertension and, ultimately, right ventricular (RV) dysfunction (118,119). Pulmonary hypertension is frequent in AS: elevated pulmonary pressures are present in almost half of the invasively assessed severe AS (120). Pulmonary hypertension has also been recently recognised as an important prognostic predictor (121),

becoming a new indication for AVR in asymptomatic severe AS (43). Both pulmonary hypertension and RV impairment are well-recognised predictors of poor prognosis in heart failure (122–124) and other valvular diseases (125). However, pulmonary pressures are not routinely invasively assessed and significant RV afterload may be missed or underestimated, given the limitations in non-invasive afterload assessment that render it difficult to identify (126).

The RV is extremely sensitive to increased afterload and this may stimulate increased RV contractility (127). Although RV *dys*function is the typical response to *acute* pulmonary pressure increases, the RV adapts to *chronically* rising afterload by increasing its contractility (128,129). Thus, in chronic afterload elevation driven by progressive valve obstruction, a compensatory increase in RV function may be anticipated. RV changes may be noticeable in earlier stages of AS, preceding overt or undetected pulmonary hypertension, and these may help unmask pulmonary afterload increase. Therefore, increased RV function may not only reflect RV adaptation to increased afterload (130,131) but also result in a better marker of disease progression than estimated pulmonary pressures.

1.1.13 The Neglected Right Ventricle in Aortic Stenosis

RV impairment typically occurs only in advanced stages, often associated with LV dysfunction (118,121,132,133). Therefore, RV assessment has been overlooked in AS with normal LVEF. However pulmonary hypertension is common at this stage (120) and increased afterload may impact on the RV before overt LV systolic dysfunction.

The RV is also a strong outcome predictor in other diseases (122–124,134) including conditions in which high LV filling pressure result in increased pulmonary afterload (135,136).

RV dysfunction by echocardiographic parameters has been previously proven to be a determinant of outcome in AS after surgery (137) and, more recently, was associated to cardiovascular death post TAVI (138). There is also some previous evidence in systemic hypertension supporting an earlier and direct relationship between physiological RV changes and increased LV afterload (139,140)

Given these previous findings suggesting the importance of the RV in left-sided increased afterload, efforts should be directed to better and early assess RV function and potentially unmask RV dysfunction when conventional echo parameters are normal. Thus, early RV functional changes may be significant in AS and may reflect on clinical compensation just prior to decompensation and/or outcome.

1.1.14 Novel Assessment of Right Ventricular Function in Aortic Stenosis

In addition to the common belief that right effects are limited to a direct consequence of long-standing pulmonary hypertension and LV dysfunction (141–143), the lack of data on RV performance in AS may also be due to the difficulty in assessing the right side. RV imaging has been long recognised as technically challenging by echocardiography (144–146) due to the particularly complex right-sided chamber shape (147). Despite this, echo-doppler imaging is the routinely adopted method for right assessment due to its wide availability and ease of measurement (148). However, echocardiographic evaluations in terms of tricuspid annular plane systolic excursion (TAPSE), tissue doppler and fractional area change are limited (149). These methods do not measure myocardial contraction, are affected by the complex RV geometry and have limited reproducibility (149).

Cardiovascular magnetic resonance (CMR) is the most accurate non-invasive imaging modality available for in-vivo cardiac evaluation (150,151): considered the gold standard for ventricular volumetric assessment for its high spatial resolution and precision in distinguishing myocardial trabeculations along endocardial borders, CMR is a three-dimensional modality unaffected by geometrical assumptions, insonation angle and patient acoustic window (150,151). Therefore, CMR imaging is recognised as the most accurate modality for RV volumetric and functional assessment.

CMR also enables detection of subtle contraction abnormalities by assessing myocardial deformation parameters (152). Although CMR-tagging is conventionally adopted as the reference standard to measure cardiac strain, this technique is not exploitable in the RV due to its wall thinness which does not allow tagging (153). Recently, CMR tissue-tracking (CMR-TT) has been proposed as a novel technique to quantify LV myocardial deformation, showing good agreement with CMR-tagging strain values (154). Moreover, CMR-TT can measure RV strain by overcoming the limitations of CMR-tagging and may provide unprecedented capability to visualise the RV myocardial deformation (155).

CMR-TT has been shown to be reproducible for RV strain assessment in other conditions (156–159). For example, in the setting of heart failure, RV strain has proven useful to unmask RV dysfunction in 25% of patients in whom RV systolic function was deemed normal by TAPSE (160). CMR-TT relies on tracking borders rather than myocardial features (155) and, therefore, may be superior in the right trabeculated thinned-wall. Moreover, CMR-TT is a practical post-processing method that relies on routinely acquired cine images and can be easily incorporated into clinical protocols and applied to previously acquired images.

1.1.15 COPD, Pulmonary Hypertension and the Right Ventricle in Aortic Stenosis

Increased RV afterload and overt pulmonary hypertension are common in COPD, with an overall reported prevalence which ranges from 20 to 63% (161–163). Pulmonary hypertension is associated with worse forced expiratory volume in one second (FEV₁), functional class and hypoxaemia (164–166). In addition, pulmonary hypertension in COPD is more commonly described in elderly patients but whether this association is directly attributable to age or to other contributing co-morbidities is unknown (163,167). For instance, severe AS is commonly associated to pulmonary hypertension and both diseases may be present in the elderly. The degree of pulmonary hypertension in COPD is usually mild to moderate but “out of proportion” severity to the degree of airflow obstruction is increasingly reported (165). This may represent a particular clinical manifestation or be the expression of multiple and interacting co-morbidities which affect the pulmonary circulation and potentially impact on the RV. Pulmonary hypertension is suggestive of morbidity in COPD, with previous research correlating it to exercise-induced desaturation and reduced exercise performance (168,169) and increased risk of exacerbations and hospitalisations (170,171). In addition, the presence of pulmonary hypertension is associated with poor prognosis in COPD (161,168,172–175).

The underlying pathophysiological mechanism to pulmonary hypertension in COPD is not completely understood but there is evidence that this includes vascular remodelling, endothelial dysfunction, systemic inflammation, pulmonary mechanics and genetic factors. Vascular remodelling is led by alveolar hypoxia in severe COPD with consequent vasoconstriction and thickening of the small arterioles (176–180). These changes are present in mild, normoxaemic heavy smokers and, thus, may also be driven by smoking itself in the absence of significant chronic hypoxia (181,182). Endothelial dysfunction was shown in smokers and COPD patients: downregulation of the vasodilatory mediator nitric oxide (NO) was found with reduced

expression of endothelial nitric oxide synthase (eNOS) (183). Reduced eNOS is present in both primary and secondary pulmonary hypertension suggesting the important role of NO in the development of the disease (184,185). Systemic inflammation which is found in both COPD and AS, as described in the paragraph on shared risk factors, may also be a key element in the development of pulmonary hypertension in the elderly. Both smokers and COPD patients have increased inflammatory cells numbers in the pulmonary arteriole adventitia, and these are believed to contribute in the remodelling of pulmonary vessels (186). In fact, the severity of the small airway inflammation was associated with the degree of vascular remodelling (187,188). Studies have also linked levels of inflammatory cytokines to increased estimated systolic pulmonary arterial pressures in COPD patients (189,190).

Pulmonary hypertension is important in COPD patients and may affect the RV in AS patients who present lung disease as co-morbidity. COPD and its associated pulmonary hypertension may also contribute to symptoms, exercise intolerance and mortality in AS. The most common screening method to detect pulmonary hypertension is the echocardiographic assessment of the tricuspid regurgitant jet to estimate pulmonary pressures. However, this technique is limited due to the difficulty to adequately visualise the jet, particularly in COPD patients with lung hyperinflation. A previous study in patients with lung disease has demonstrated that pulmonary pressures could not be estimated in over 50% of patients (191). In addition, in those in whom pulmonary pressure were estimated, 48% were misclassified as having pulmonary hypertension. In the National Emphysema Treatment Trial, echocardiography was a poor predictor of pulmonary hypertension with a positive predictive value of 68% and a negative predictive value of 67% (192). Direct CMR imaging of the RV morpho-functional changes driven by increased RV afterload associated with both AS and COPD may prove useful and more effective than detecting increased pulmonary afterload.

1.1.16 Research Hypothesis

Chapter 4 – Cardiac Function in Aortic Stenosis

- RV systolic function in AS with normal LV ejection fraction is unknown but given the commonly increased pulmonary afterload induced by progressive valve obstruction, the RV is likely involved in its compensatory response.
- RV compensation is associated with clinical decompensation in AS and normalises when LV afterload is relieved after AVR, if the right afterload increase has not reached a more advanced permanent stage.
- RV systolic function impacts on outcome in AS.

1.1.17 Research Aim

The first aim of this branch of research was to assess early RV functional change in AS with normal LVEF, its association with clinical decompensation and reversibility after AVR. The second aim was to evaluate the association of RV systolic function with all-cause mortality in severe AS (Chapter 4 – Cardiac Function in Aortic Stenosis).

CLINICAL RELEVANCE

The accurate diagnosis of COPD in symptomatic AS is extremely challenging: COPD-STS definition can be based on COPD therapy alone and does not require spirometry. Therefore, it may reflect long-standing dyspnoea and advanced heart failure in AS rather than real lung dysfunction. Limited data is available on COPD-GOLD defined by spirometry and further characterised by pulmonary functional testing and advanced imaging for the detection of emphysema. The correct identification of COPD may impact on symptomatic AS patients. The presence, classification and grading of COPD may strongly influence the decision-making process on valve treatment strategy and replacement timing in patients with valve obstruction: COPD may confound symptoms of AS, is part of the most commonly adopted risk score algorithms for predicting cardiac surgery mortality and may be one of the main reasons for surgical valve replacement denial.

Consequently, co-morbid COPD may significantly impact on treatment and prognosis in severe AS. First of all, symptoms and signs of COPD may mimic those of AS, leading to premature or unnecessary invasive AVR. Both open-chest surgery and percutaneous aortic replacement are high-risk in patients with lung disease and, if futile, may expose them to premature mortality. Secondly, AS may lead to exertional dyspnoea and lung congestion clinically simulating exacerbated chronic lung disease. Thus, decompensated AS may be misled with COPD and be denied or delayed treatment with AVR with consequent under treatment of valvular disease and higher mortality.

In addition, cardiovascular imaging may be able to comprehensively quantify RV function in AS and be sensitive to potential early changes in this group of patients. RV changes may result

from either elevated RV afterload increase in severe AS with pulmonary hypertension or may directly derive from the effect of COPD as a common co-morbidity in AS. Both AS and COPD are often associated with pulmonary hypertension and may therefore impact on the pulmonary circulation and on RV function. The RV may prove important in the pathophysiological response to pressure overload and may result a determinant in clinical decompensation and mortality in AS. Thus, the following research in AS and COPD may prove useful in evaluating the cardio-respiratory interaction and their effects on outcome in patients with multi-morbidity.

Chapter 2 - General Methods

In this chapter, general methods are discussed. Each result chapter has an individual methods section for a more detailed explanation.

POPULATION AND ELIGIBILITY

2.1.1 Study Population

The following chapters present similar disease populations affected by AS. However, different study designs have been adopted to appropriately test the specific research hypothesis outlined.

2.1.2 Ethical Approval and Recruitment

The multi-centre retrospective study presented in *Chapter 3 - Respiratory Function in Aortic Stenosis* included participants from the prospective study *Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis (AMICA-AS Study)* discussed in *Chapter 5* approved by the National Research Ethics Service committee South Central - Oxford C Ethics Committee (REC Ref: 15/SC/0574). For the Italian arm, the local ethical committees of each participating institution approved the study. The single-centre study presented in *Chapter 4 - Cardiac Function in Aortic Stenosis* included participants of *the prospective, double-blind, randomised controlled trial of the angiotensin-converting enzyme inhibitor Ramipril in Aortic Stenosis (RIAS trial)* approved by the Oxford C Ethics Committee (REC Ref: 07/H606/139) and *the prospective AS study* approved by the National Research Ethics Service committee South Central – Berkshire. The multi-centre outcome study presented in *Chapter 4 - Cardiac Function in Aortic Stenosis* included participants from the AS study and

the AMICA-AS study described above. The other UK centres all provided ethical approvals. Each participant provided written informed consent to be recruited. Patients were recruited from the outpatient cardiology clinics, cardiology departments and clinical imaging lists. Healthy controls were recruited via poster advertisement.

2.1.3 Eligibility Criteria

Inclusion and exclusion criteria vary from one study population to the other reflecting different study designs. Here below is a summary of the inclusion/exclusion criteria adopted.

2.1.3.a Chapter 3 - Respiratory Function in Aortic Stenosis: Multi-centre Retrospective Study

Inclusion criteria:

1. Severe AS defined by the presence of at least one of the following echocardiographic criteria: aortic maximal velocity ≥ 4 m/s, mean transaortic pressure gradient ≥ 40 mm Hg or aortic valve area (AVA) ≤ 1 cm² (indexed AVA ≤ 0.6 cm²/m²).
2. Presence of symptoms attributed to valve obstruction
3. Having been evaluated for appropriate aortic valve replacement strategy at the participating tertiary centres. Both patients undergoing invasive treatment (surgical or TAVI) and excluded from it due to prohibitive risk (palliative medical therapy) were recruited.

2.1.3.b Chapter 4 - Cardiac Function in Aortic Stenosis: Single-centre Prospective Study

Inclusion criteria:

1. Patients with isolated moderate or severe AS defined by echocardiography: maximal aortic velocity ≥ 3 m/s or AVA ≤ 1.5 cm².
2. Normal left ventricular systolic function as defined by echocardiography (LVEF $>55\%$)

Exclusion criteria:

1. LVEF <55% on CMR
2. Elevated SPAP defined as a peak tricuspid regurgitation velocity of >2.9 m/s on echocardiography.
3. Any other severe valvular disease on echocardiography.
4. Underlying cardiomyopathies detected on CMR.
5. In symptomatic patients, significant coronary artery stenosis (>70% luminal diameter) on angiography.

2.1.3.c Chapter 4 - Cardiac Function in Aortic Stenosis: Multi-centre Outcome Study

Inclusion criteria:

1. Patients >18 years with severe AS (one of: AVA < 1 cm², peak trans-aortic pressure gradient >64 mmHg, mean pressure gradient >40 mmHg, peak trans-aortic velocity >4 m/s).
2. Having been referred and listed for valve intervention at one of the six UK cardio-thoracic participating centres
3. Having undergone CMR imaging for research purposes within 6 months from intervention.

Exclusion criteria:

1. Having been excluded from invasive treatment during the study.

2.1.3.d Chapter 5 - Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis: The AMICA-AS Study

Inclusion criteria:

1. Patients with isolated moderate and severe AS defined by echocardiography: maximal aortic velocity ≥ 3 m/s or AVA ≤ 1.5 cm².
2. Normal left ventricular systolic function on echocardiography (LVEF >55%).
3. Dyspnoea as the primary symptom if symptoms were present.

Exclusion criteria:

1. Having been excluded from invasive treatment during the study.
2. Any other severe valvular disease on echocardiography.
3. Underlying cardiomyopathies detected on CMR.
4. In symptomatic patients, significant untreated coronary artery stenosis (>70% luminal diameter) on angiography. Patients with previous percutaneous coronary interventions were not excluded.

CLINICAL ASSESSMENTS

2.1.4 Clinical Evaluation

All participants underwent clinical assessment. This included medical history assessment to document inclusion and exclusion criteria. A detailed clinical assessment was conducted including the following:

- Medical history: previous hospitalisations, diabetes mellitus, systemic hypertension, previous myocardial infarction or coronary treatment, smoking history with detailed smoking exposition (number of cigarettes and years of smoking), known COPD or emphysema or asthma diagnosis, drug and allergy, AS diagnosis and presence of symptoms, other previous or ongoing pathologies.

- Height (cm) and weight (kg) to calculate body mass index (BMI) and body surface area (BSA)
- Blood tests: full blood count, creatinine and brain natriuretic peptide (BNP).

2.1.5 Cardiovascular Evaluation

A comprehensive cardiovascular examination was conducted including the following:

- Systemic blood pressure
- Questionnaires: EuroQoL for quality of life (193–195) (Appendix 1)
- New York Heart Association (NYHA) functional class (196) (Appendix 2)
- Twelve lead electrocardiogram (ECG)
- Echo colour doppler performed according to standard guidelines and manufacturer's instructions (each study had a specific imaging protocol discussed in chapter 3, 4 and 5 methods section)
- Six-minute walking test to assess functional capacity and exertional symptoms. This was performed for research purposes in the prospective studies or for clinical purposes in the retrospective study. The research test was performed according to guidelines (197) and standardised with same location and similar encouragements following the standard operator procedure (SOP - Appendix 3). In addition, baseline and peak exercise heart rate and oxygen saturation, and distance to onset of symptoms were recorded.

2.1.6 Respiratory Evaluation

All participants of the AMICA-AS study underwent comprehensive assessment for:

- Smoking exposition (smoking status, smoking years, smoking type and quantity)
- Medications with inhaled or oral bronchodilators/steroids for respiratory use
- Known respiratory pathologies including known emphysema, chronic bronchitis or asthma
- Previous spirometry or hospitalisations for respiratory symptoms (any type of dyspnoea)

- Questionnaires for symptoms: COPD assessment tool (CAT) (198,199) (Appendix 1).

Basic spirometry to assess volume, time and flow was performed clinically in the retrospective study and for research purposes in all the participants of the AMICA-AS study. Lung function was performed in accordance with the joint American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (200). Spirometry was performed with recordings obtained pre and post 400µg salbutamol bronchodilatation. Spirometry measures included at least the following:

- Forced expiratory volume in 1 second (FEV₁)
- Forced vital capacity (FVC), the maximum amount of air that can be exhaled when blowing out as fast as possible
- Vital capacity (VC), the maximum amount of air that can be exhaled when blowing out as fast as possible
- FEV₁/FVC ratio
- Peak expiratory flow (PEF), the maximal flow that can be exhaled when blowing out at a steady rate
- Forced expiratory flow (FEF), also known as mid- expiratory flow.

The best out of three consecutive blows to record the FEV₁ and the FVC was then used. In the AMICA-AS study, participants with a reduced FEV₁/FVC ratio (FEV₁/FVC <0.7) performed additional full pulmonary function testing (PFT). The procedure for spirometry, gas transfer and lung volumes followed is detailed in Appendix 7.

SCAN PROTOCOLS AND DATA ANALYSIS

2.1.7 Cardiac Imaging

Participants undergoing cardiovascular magnetic imaging (CMR) were screened for magnet safety and completed an additional safety form for the procedure shown in Appendix 4.

The specific image sequences performed in each study are outlined in the appropriate methods paragraphs. CMR imaging always included the following:

- Left and right ventricular volumes, function and mass
- Aortic valve imaging and flow
- Late gadolinium enhancement imaging
- Additional sequences specific to each study are described in the following chapters

All CMR scanning was performed on Siemens scanners (Siemens Healthcare, Erlangen, Germany). Post-processing and data analyses were performed with commercially available software CMR42 Circle Cardiovascular Imaging Inc, Calgary, Canada, Version 5.3.4.

For the multicentre outcome study BSCMR reported in Chapter 4, prespecified SOPs were used across sites. These are reported in Appendix 5.

2.1.7.a Left and right ventricular volumes, function and mass

Cardiac volumes were acquired with balanced steady state free precession (bSSFP) imaging during breath-hold at end expiration to minimise the respiratory motion. Each slice was 8 mm thick with no gap and was usually retrospectively gated with echo time 1.5 msec; repetition

time 3 msec; flip angle 50 degrees. A prospective ECG gating was adopted only in patients with irregular heart rhythm if image quality with retrospective gating was not adequate.

Biventricular epicardial and endocardial borders were contoured manually at end-diastole and end-systole to determine end-diastolic and end-systolic volumes and stroke volume. Ejection fraction was calculated (ejection fraction = stroke volume/end-diastolic volume). Myocardial mass was calculated based on prior knowledge of myocardial specific gravity (1.05 g/cm³) by subtracting the endocardial volume from the epicardial volume.

2.1.7.b Aortic valve imaging and flow

For the aortic valve morphology, a SSFP slice was acquired at the level of the tips of the aortic cusps. This was planned from the coronal and 3-chamber planes in end-systole to ensure correct valve planimetry measurements. The dedicated aortic valve short axis cine was viewed to determine the anatomic aortic valve orifice by valve planimetry in peak systole when the opening of the aortic valve is widest. This was done by manually tracing the inner leaflet edges of the aortic valve cusps at the time of maximal opening. Aortic flow was acquired with non-breath hold through plane phase contrast imaging with phase and magnitude images acquired at the sino-tubular junction proximal to the aortic valve above the opening cusps. The phase images were examined to ensure the quality was sufficient and that the velocity encoding chosen was appropriate. The value for peak flow velocity, forward flow volume, regurgitant fraction and derived peak and mean trans-aortic gradients were recorded.

2.1.7.c Late gadolinium enhancement imaging

Late gadolinium imaging was acquired starting at 5 minutes from the bolus injection of Gadoterate Meglumine (®Dotarem, Guerbet) at the dose of 0.1 mmol/kg (0.2 mL/kg), followed by a 10 mL saline flush. All late gadolinium images were acquired between 5 to a maximum of 15 minutes from injection. The institutional SOP for the administration of contrast was adopted for the AMICA-AS Study (Appendix 6). Similar SOPs were used for the other research studies with CMR imaging. Three long-axes (horizontal, vertical and left ventricular outflow track views) and multiple short axis at the same position of the cine images were acquired for each participant without contraindications to Dotarem. A breath-hold T1-weighted segmented inversion-recovery turbo fast low-angle shot sequence was used. Patients with extensive and typical late gadolinium enhancement due to significant myocardial infarction were excluded.

2.1.8 Respiratory Imaging

Respiratory imaging with chest CT and Hyperpolarised Xenon MRI was performed in the AMICA-AS study only. Description of CT and MRI protocols are provided in *Chapter 5*.

Chapter 3 - Respiratory Function in Aortic Stenosis

HYPOTHESIS AND AIM

- The prevalence of confirmed respiratory dysfunction (COPD-GOLD) in patients with symptomatic AS is high and different from the known prevalence of apparent lung disease (COPD-STS).
- Both under-diagnosis of COPD leading to unnecessary AVR at higher risk, and over-diagnosis of COPD leading to over-estimate of operative risk and surgical denial, exist in a significant proportion of symptomatic AS patients. The co-existence of AS and COPD in patients with symptoms have important implications for aortic valve replacement management and, thus, indirectly and/or directly affect survival
- The unknown prognostic impact of COPD-GOLD is different from the known COPD-STS prognostic impact in AS.

The aim of this chapter was to evaluate the prevalence of COPD (apparent: -STS and confirmed: -GOLD) and its long-term impact on mortality according to COPD definition, in a large cohort of patients with symptomatic severe AS undergoing various aortic valve treatment options (SAVR, TAVI, palliative).

MATERIAL AND METHODS

3.1.1 Subjects

Patients with symptomatic and severe AS were collected from two tertiary centres (University of Oxford, Oxford University Hospitals NHS Foundation Trust and University of Brescia,

Spedali Civili Hospital) between 2013 to 2017. All the patients were clinically referred to the heart team for the assessment of the most appropriate aortic valve therapeutic strategy. The patients were either clinical and consecutively collected or simultaneously taking part in the prospective research AMICA-AS study. The Institutional Ethics Committee approved the study protocol.

3.1.2 Study Measures

3.1.2.a Clinical data collection

Detailed medical history, physical examination, blood samples, electrocardiogram, and a comprehensive echocardiographic-Doppler evaluation were collected on admission. The following co-morbidities were diagnosed according to established diagnostic criteria: *diabetes mellitus* if overnight fasting serum glucose > 7 mmol/l (126 mg/dl) on at least two samples or ongoing treatment; *systemic arterial hypertension* if blood pressure measurements were $> 140/90$ mmHg or on medical treatment with antihypertensive drugs; *hypercholesterolemia* if total serum cholesterol > 200 mg/dl or on statin therapy; *renal dysfunction* by the assessment of the absolute value of serum creatinine and the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation to estimate the glomerular filtration rate (eGFR) during hospitalisation; *coronary artery disease* was defined by the presence of a previous myocardial infarction, previous percutaneous or surgical revascularisation or coronary artery stenosis $> 50\%$ on angiography.

3.1.2.b Cardiovascular assessment: AS definition and management

Severe AS was confirmed by a comprehensive echocardiographic-doppler evaluation. Aortic valve obstruction was considered severe in the presence of at least one of the following criteria:

aortic maximal velocity ≥ 4 m/s, mean transaortic pressure gradient ≥ 40 mm Hg or aortic valve area (AVA) ≤ 1 cm² (indexed AVA ≤ 0.6 cm²/m²), as defined by current guidelines (9). LV diameters, volumes, wall thickness and diastology were measured according to recommendations (201). LV volumes and LVEF were measured with the biplane Simpson's method. LV mass was calculated using a necropsy validated formula and a value of LV mass > 115 g/m² in men and 95 g/m² women was defined LV hypertrophy (202). Pulmonary arterial pressure was assessed using the tricuspid peak systolic regurgitant jet velocity.

Patients were treated according to their clinician choice. Invasive treatment options were either open-heart SAVR or TAVI. Those excluded from invasive AVR treatment were managed conservatively (palliative treatment with valvuloplasty or medical therapy).

3.1.2.c Respiratory assessment: COPD definition and management

A known clinical diagnosis of COPD was recorded if present in the medical notes or electronic records. COPD-STS was established during hospitalisation according to STS criteria: a history of dyspnoea AND long-term use of bronchodilators/steroids OR previous confirmation of persistent airflow limitation on spirometry; a cut-off value of the ratio between forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) of 0.7 was adopted (FEV1/FVC ≤ 0.7) (203).

Simple spirometry or full standard pulmonary function testing with spirometry, body plethysmography and the single breath test of carbon monoxide uptake (Jaeger MasterScope Body, Carefusion) were performed if deemed necessary by the clinician during aortic valve disease management evaluation. COPD-GOLD was diagnosed in the subgroup of patients with

available spirometry results: COPD was defined in the presence of symptoms (dyspnoea) AND evidence of airway obstruction ($FEV_1/FVC < 0.7$) as per GOLD guidelines: “COPD should be considered in any patient with dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors. Spirometry is required to make the diagnosis; a post-bronchodilator FEV_1/FVC less than 0.70 confirms the presence of persistent airflow limitation.” (90) COPD grading was retrospectively assessed based on FEV_1 values: Gold 1 Mild $FEV_1 \geq 80\%$ predicted, Gold 2 Moderate $50\% \leq FEV_1 \leq 80\%$ predicted, Gold 3 Severe $30\% \leq FEV_1 \leq 50\%$ predicted, Gold 4 Very Severe $FEV_1 < 30\%$ predicted. Medical therapy for COPD with bronchodilators, steroids or oxygen was recorded.

3.1.3 Study Endpoints

The primary endpoint was all-cause mortality occurring after index hospitalisation. All-cause mortality was chosen as the primary endpoint over cardiovascular death to avoid inappropriate interpretation of data, even in the case cardiac death was accurately distinguished from non-cardiac (204,205). Information on outcomes was obtained after discharge at regular time points from digital medical records.

3.1.4 Post-hoc power calculation

Post-hoc power calculation for the primary endpoint mortality were conducted to assess the ability of the retrospective study to detect the difference in the dichotomous outcome between the two different groups of AS patients with and without COPD. Power calculations were performed for both COPD definitions (COPD-STS and COPD-GOLD).

3.1.4.a COPD-STs power calculation

The power to detect a difference in mortality between COPD-STs and no COPD patients with symptomatic AS at an alpha of 0.05 was 94%. Below the detailed power calculations:

$$\text{Power} = \Phi \{ [\Delta / \sqrt{(p_1 q_1 / n_1 + p_2 q_2 / n_2)}] - z_{1-\alpha/2} * [\sqrt{pq (1/n_1 + 1/n_2)} / \sqrt{(p_1 q_1 / n_1 + p_2 q_2 / n_2)}] \}$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$p = (p_1 + kp_2) / (1 + K)$$

$$q = 1 - p$$

$$\text{Power} = \Phi \{ [0.13 / \sqrt{(0.18 * 0.82 / 472 + 0.31 * 0.69 / 184)}] - 1.96 * [\sqrt{0.216 * 0.784 (1/472 + 1/184)}] / \sqrt{(0.18 * 0.82 / 472 + 0.31 * 0.69 / 184)} \}$$

$$\text{Power} = \Phi (1.558) = 0.94 = 94\% \text{ power}$$

p_1, p_2 = proportion (incidence) of groups 1 and 2

$\Delta = |p_2 - p_1|$ = absolute difference between two proportions

n_1 = sample size for group 1

n_2 = sample size for group 2

α = probability of type I error (0.05)

z = critical Z value for a given α or β

K = ratio of sample size for group 2 to group 1

$\Phi()$ = function converting a critical Z value to power

Equations from Rosner B. *Fundamentals of Biostatistics*. (2006)

3.1.4.b COPD-GOLD power calculation

The power to detect a difference in mortality between COPD-GOLD and no COPD patients with symptomatic AS at an alpha of 0.05 was 5.4%. Below the detailed power calculations:

$$\text{Power} = \Phi \{ [\Delta / \sqrt{(p_1 q_1 / n_1 + p_2 q_2 / n_2)}] - z_{1-\alpha/2} * [\sqrt{pq (1/n_1 + 1/n_2)} / \sqrt{(p_1 q_1 / n_1 + p_2 q_2 / n_2)}] \}$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$p = (p_1 + K p_2) / (1 + K)$$

$$q = 1 - p$$

$$\text{Power} = \Phi \{ [0.02 / \sqrt{(0.17 * 0.83 / 151 + 0.15 * 0.85 / 73)}] - 1.96 * [\sqrt{[0.163 * 0.837 (1/151 + 1/73)]} / \sqrt{(0.17 * 0.83 / 151 + 0.15 * 0.85 / 73)}] \}$$

$$\text{Power} = \Phi (-1.609) = 0.054 = 5.4\% \text{ power}$$

p_1, p_2 = proportion (incidence) of groups 1 and 2

$\Delta = |p_2 - p_1|$ = absolute difference between two proportions

n_1 = sample size for group 1

n_2 = sample size for group 2

α = probability of type I error (0.05)

z = critical Z value for a given α or β

K = ratio of sample size for group 2 to group 1

$\Phi()$ = function converting a critical Z value to power

Equations from Rosner B. *Fundamentals of Biostatistics*. (2006)

3.1.5 Statistical Analyses

Continuous variables are presented as mean $\pm$ standard deviation if normally distributed, as median $\pm$ interquartile range if not; categorical variables are described as percentages. Baseline characteristics were compared using the unpaired Student *t*-test, Mann-Whitney-Wilcoxon test and Chi-square (χ^2), as appropriate. χ^2 of homogeneity with post-hoc multiple z-tests and Bonferroni correction or χ^2 for independence were used between categorical multinomial variables (COPD, COPD grade and AV treatment) to assess differences and associations.

Kaplan-Meier curves were adopted to assess survival; log-rank test and number at risk tables were presented for comparison between groups. Predictors of all-cause mortality were assessed with Cox proportional hazards models and presented as hazard ratios and confidence intervals (HR 95% CI). Significant variables at the univariable Cox analysis were included in the multivariable Cox analysis to determine the adjusted HR of all-cause mortality.

RESULTS

3.1.6 Baseline Characteristics of the Study Population

Baseline demographic, clinical and echocardiographic characteristics of the study population stratified according to type of COPD diagnosis are shown in

Table 3-1 and Table 3-2. A total of 656 patients with symptomatic AS were included. Of these, 184 (28%) were classified by their clinician as presenting with COPD-STS. A subgroup of 224 patients (34% of the total symptomatic AS population) were able or selected to perform a spirometry during their aortic valve treatment assessment period. Of these, 73 (33%) had a degree of COPD-GOLD.

3.1.6.a Baseline characteristics of symptomatic AS according to COPD-STS diagnosis

Patients with symptomatic AS and COPD-STS had similar age, body habitus, co-morbidities, aortic valve disease hemodynamic and symptomatic burden, compared to those without COPD (Table 3.2, Figure 3-1). COPD-STS patients were more males (57%, $p=0.005$), with higher cardiac risk scores (EuroSCORE $p<0.0001$), less medically treated for cardiac disease although presenting with higher prevalence of heart failure (81%, vs 72%, $p=0.026$), compared to AS only patients.

3.1.6.b Baseline characteristics of symptomatic AS according to COPD-GOLD diagnosis

COPD-GOLD AS patients had similar age, body habitus, co-morbidities, aortic valve disease hemodynamic and symptomatic burden, compared to those without COPD (Table 3-2). Most of them had a low degree of airway obstruction (85% in stage 1-2) and were often not treated for their lung disease (only 37% on inhaled therapy). Only 40% of COPD-GOLD AS patients presented with a clinically known COPD diagnosis.

Table 3-1. **Baseline characteristics in aortic stenosis stratified according to COPD-STS diagnosis.**

	COPD-STS		
	No COPD (n=472)	COPD (n=184)	P-value
Clinical characteristics			
Age, yrs	81 11	81 9	0.6
Gender, Male	210 (45%)	104 (57%)	0.005
BMI (kg/m²) [n/a 30%]	26 ± 4	26 ± 5	0.4
Co-morbidities			
Hypertension	354 (75%)	132 (72%)	0.4
Diabetes	134 (28%)	43 (24%)	0.2
Atrial Fibrillation	152 (32%)	58 (32%)	0.9
Previous cancer [n/a 9%]	73 (17%)	31 (20%)	0.3
Hb, g/dL [n/a 10%]	12 ± 2	12 ± 2	0.8
eGFR [n/a 36%]	49 35	45 40	0.8
Logistic EuroSCORE	15 23	24 28	<0.0001
Medical therapy			
ACE-inhibitor	281 (64%)	100 (56%)	0.07
Beta-blockers	174 (40%)	54 (30%)	0.029
Diuretics	321 (73%)	121 (68%)	0.2
COPD Inhalers* [n/a 12%]	6 (5%)	30 (41%)	<0.0001
Symptomatic burden			
Heart Failure	320 (72%)	126 (81%)	0.026
NYHA class 3-4	161 (53%)	64 (54%)	0.8
Angina	147 (33%)	46 (30%)	0.5
Syncope	77 (17%)	20 (13%)	0.2
Echocardiographic parameters			
AVA, cm² [n/a 10%]	0.7 ± 0.2	0.7 ± 0.2	0.4
Mean aortic gradient, mmHg [n/a 12%]	50 ± 17	50 ± 14	0.9
Peak aortic gradient, mmHg [n/a 10%]	79 ± 25	79 ± 22	0.9
LV Mass, g [n/a 45%]	216 ± 67	214 ± 61	0.8
LVEF, % [n/a 10%]	50 ± 13	50 ± 13	0.4
SPAP, mmHg [n/a 10%]	41 ± 14	43 ± 13	0.09

Continuous variables as mean ± standard deviation or median | interquartile range; categorical as counts (percent). P-values for independent Student T, Mann-Whitney-Wilcoxon and χ^2 test. *COPD therapy was recorded only in subgroup with spirometry. [n/a] percentage of missing values for variables with more than 5% missing data. BMI: body mass index; Hb: haemoglobin;

eGFR: estimated glomerular filtration rate by Cockcroft; NYHA: New York Heart association; AVA: aortic valve area; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure.

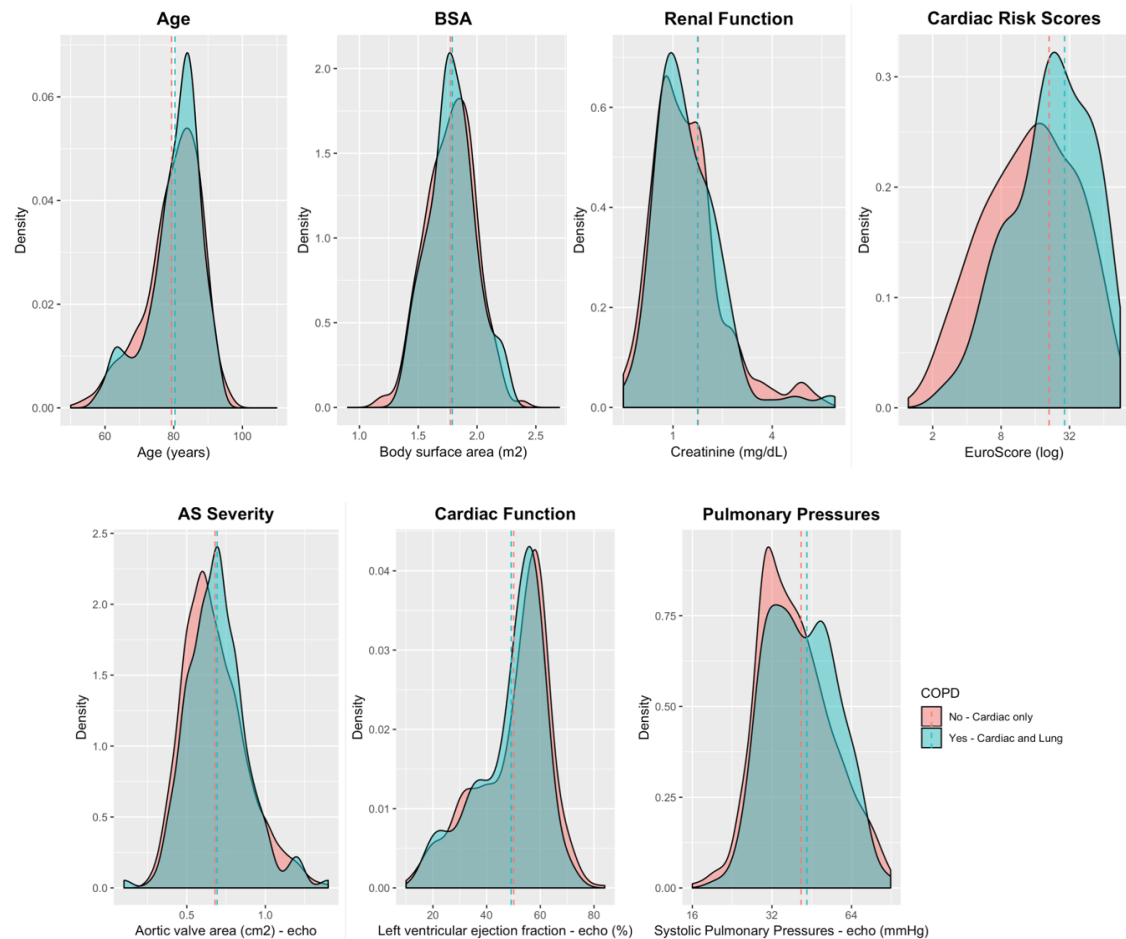


Figure 3-1. Baseline clinical and echocardiographic characteristics in aortic stenosis according to COPD-STS diagnosis.

Similar baseline characteristics between isolated AS patients and COPD-AS patients, with the exception of cardiac risk scores which were higher in COPD-STS patients, and almost significant pulmonary pressures differences.

Table 3-2. Baseline characteristics of the aortic stenosis subgroup with spirometry, according to COPD-GOLD diagnosis.

	COPD-GOLD		
	No COPD (n=151)	COPD (n=73)	P-value
Clinical characteristics			
Age, yrs	80 10	80 10	0.5
Gender, Male	68 (45%)	42 (57%)	0.08
BMI, kg/m ² [n/a 9%]	27 ± 5	27 ± 5	0.9
Known COPD diagnosis [n/a 9%]	26 (19%)	25 (40%)	<0.0001
COPD-STS diagnosis	21 (14%)	68 (93%)	<0.0001
Co-morbidities			
Hypertension	113 (75%)	49 (67%)	0.2
Diabetes	43 (29%)	16 (22%)	0.3
Atrial Fibrillation	56 (38%)	19 (26%)	0.09
Previous cancer [n/a 26%]	18 (15%)	7 (14%)	0.8
Hb, g/dL	12 ± 2	12 ± 2	0.6
eGFR [n/a 23%]	49 35	45 40	0.9
Logistic EuroSCORE	15 23	24 28	0.07
Medical therapy			
ACE-inhibitor	98 (68%)	38 (58%)	0.1
Beta-blockers	49 (34%)	19 (29%)	0.5
Diuretics	96 (66%)	35 (53%)	0.06
COPD Inhalers [n/a 12%]	14 (10%)	22 (37%)	<0.0001
Symptomatic burden			
Heart Failure	84 (72%)	33 (67%)	0.6
NYHA class 3-4	75 (51%)	34 (47%)	0.6
Angina	39 (33%)	18 (37%)	0.7
Syncope	15 (13%)	5 (10%)	0.6
Spirometry parameters			
GOLD 1-2 (mild/moderate)	-	62 (85%)	-
GOLD 3-4 (severe/very severe)	-	11 (15%)	-
FEV ₁ /FVC ratio	0.8 ± 0.1	0.6 ± 0.1	<0.0001
FEV ₁ , L	1.9 ± 0.8	1.6 ± 0.6	0.002
FVC, L	2.4 ± 0.9	2.6 ± 0.6	0.1
FEV ₁ % pred	97 ± 26	76 ± 22	<0.0001
FVC % pred	95 ± 26	95 ± 21	0.9
PEF % pred	82 ± 22	68 ± 26	0.001
FEF % pred [n/a 27%]	71 ± 27	29 ± 12	<0.0001
VC % pred [n/a 8%]	101 ± 27	99 ± 23	0.5
Echocardiographic parameters			
AVA, cm ² [n/a 22%]	0.7 ± 0.2	0.7 ± 0.2	0.3
Mean aortic gradient, mmHg [n/a 23%]	51 ± 16	51 ± 15	0.9
Peak aortic gradient, mmHg [n/a 26%]	79 ± 25	80 ± 21	0.9
LV Mass, g [n/a 42%]	216 ± 72	198 ± 62	0.2
LVEF, % [n/a 26%]	51 ± 13	50 ± 11	0.5
SPAP, mmHg [n/a 26%]	41 ± 13	46 ± 15	0.026

Continuous variables as mean $\pm$ standard deviation or median | interquartile range; categorical as counts (percent). P-values for independent Student T, Mann-Whitney-Wilcoxon and χ^2 test. [n/a] percentage of missing values for variables with more than 5% missing data. BMI: body mass index; Hb: haemoglobin; eGFR: estimated glomerular filtration rate by Cockcroft; NYHA: New York Heart association; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; FEF: forced expiratory flow; VC: vital capacity; pred: of predicted; AVA: aortic valve area; LV: left ventricular; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure.

3.1.6.c COPD prevalence and classification in symptomatic AS

There was a relevant discrepancy between COPD diagnosis according to -STS and -GOLD criteria, as shown in Figure 3-2. The overall population of symptomatic AS undergoing various aortic valve disease treatment options had a COPD prevalence of 28% if the diagnosis was defined by the assessing clinician following the STS scoring. The prevalence was even higher (33%) if spirometry criteria were applied and, thus, GOLD guidelines were followed.

In the subgroup with available spirometry data, COPD was classified by the degree of airflow limitation. Most of the COPD patients (85%) had a low stage (1-2) of COPD with mild-moderate airflow limitation. Only 11 participants with AS and COPD-GOLD had a FEV₁ % of predicted $\leq$ 50.

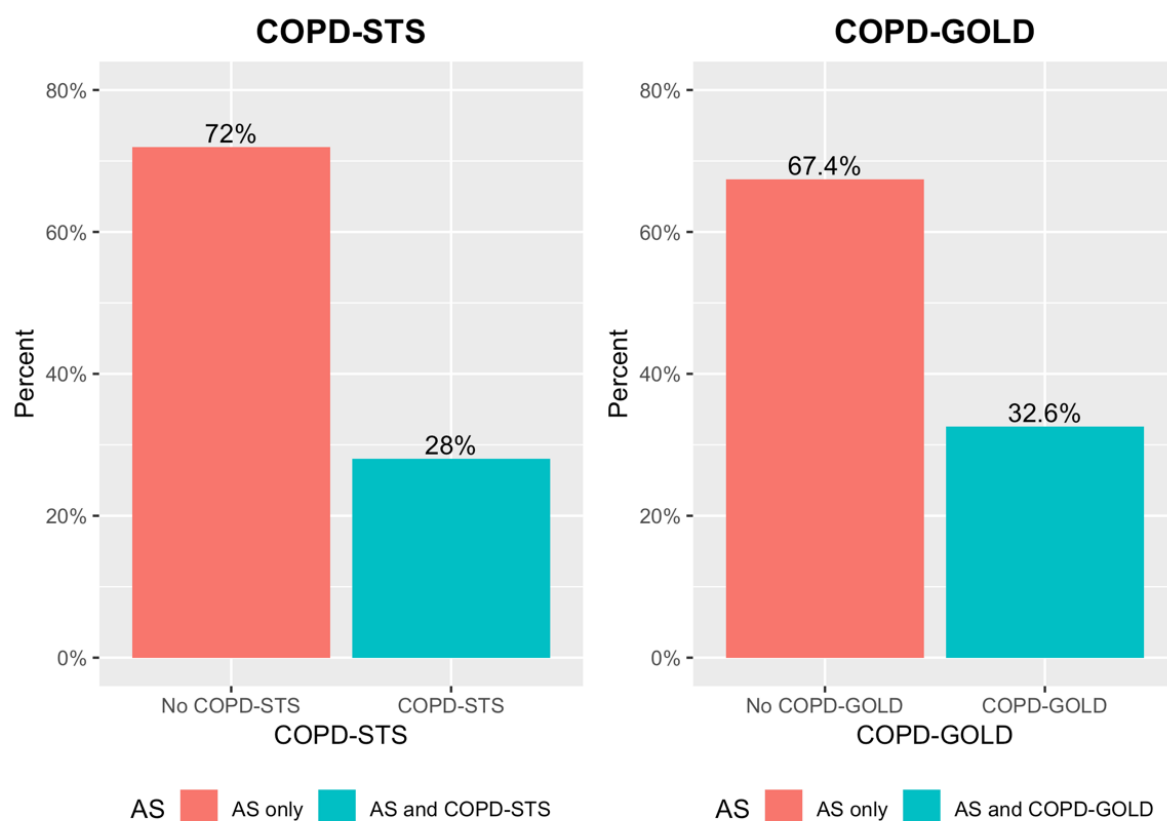


Figure 3-2. **COPD discrepancy in aortic stenosis.**

Discrepancy between COPD prevalence according to COPD definition (COPD-STS and COPD-GOLD) in symptomatic AS. Fewer patients were classified with COPD-STS (28%) compared to those retrospectively classified using COPD-GOLD criteria (33%).

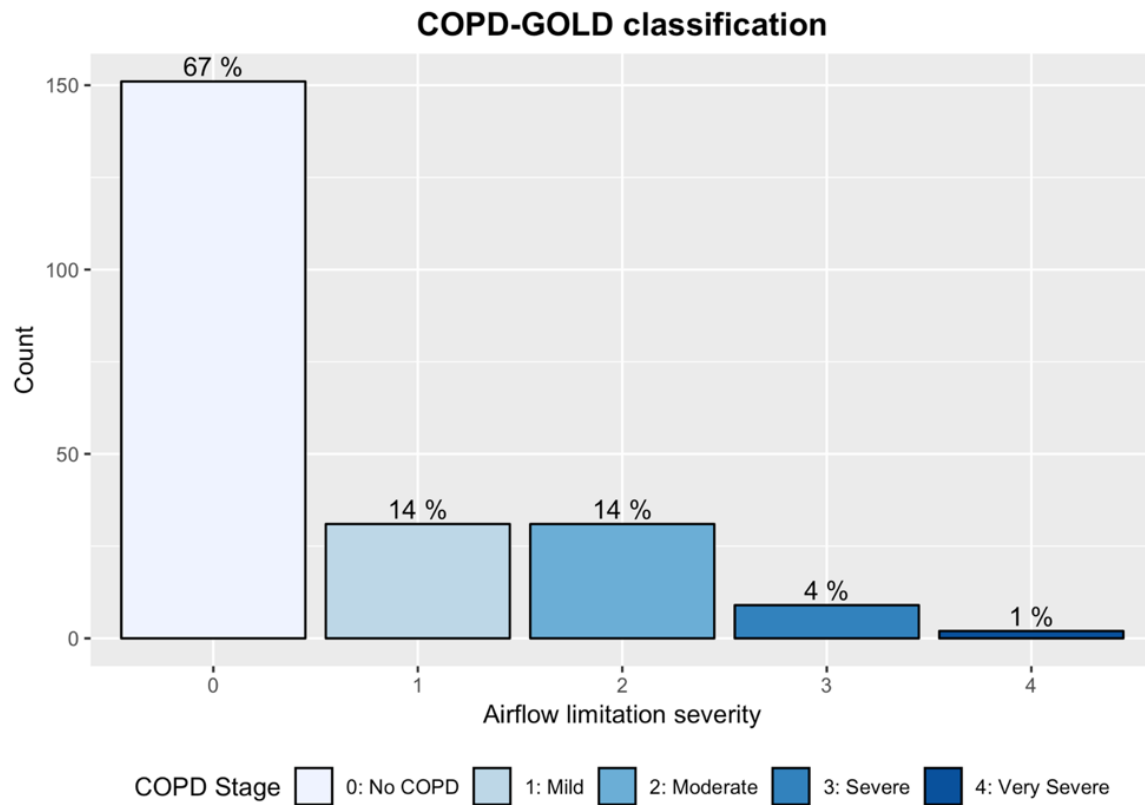


Figure 3-3. **COPD-GOLD stage in aortic stenosis.**

Classification of COPD-GOLD stages based on airway limitation severity in symptomatic AS with available spirometry. Most of the COPD patients had mild-moderate airflow limitation only. Mild $FEV_1 \geq 80\%$ predicted, moderate $50\% \leq FEV_1 \leq 80\%$ predicted, severe $30\% \leq FEV_1 \leq 50\%$ predicted, very severe $FEV_1 < 30\%$ predicted.

The discrepancy between COPD definitions was also assessed in the subgroups divided according to aortic valve treatment strategies (Figure 3-4 and Figure 3-5). COPD-STS prevalence in surgical patients was significantly lower than in higher-risk groups (TAVI and palliative AS), with those who were excluded from any invasive treatment manifesting the highest COPD-STS prevalence (30%). However, if COPD was reclassified according to GOLD guidelines, the prevalence was the highest in TAVI patients with almost 1 out of 2 patients having a degree of COPD but the lowest in the palliative group (19%). The discrepancy in the palliative AS group was the most striking (COPD-STS 30% vs COPD-GOLD 19%).

Of those AS patients who were classified as having COPD by their clinician, a quarter had no COPD when spirometry was retrospectively assessed (Figure 3-6). The most relevant misclassification was again in the palliative group: when assessed more accurately more than half of these patients were misclassified as having COPD but had normal spirometry.

The contrasting prevalence of COPD may be better explained by the evaluation of spirometry performance, stratified by aortic valve treatment group. As seen in Figure 3-7, missing spirometry data and patient selection may explain the diagnostic discrepancy. Only 1 out of 3 of the high-risk patients performed a spirometry. Moreover, the AS subgroup with spirometry data may have been selected for presenting with a less severe clinical burden. The large proportion of patients with symptomatic AS and missing spirometry (61%) who have been excluded from any invasive treatment, may have been too fragile and unable to perform a respiratory assessment. In addition, the clinician assessing their operative risk may have considered futile to perform a lung function test in those who had already been excluded based on other factors and/or comorbidities.

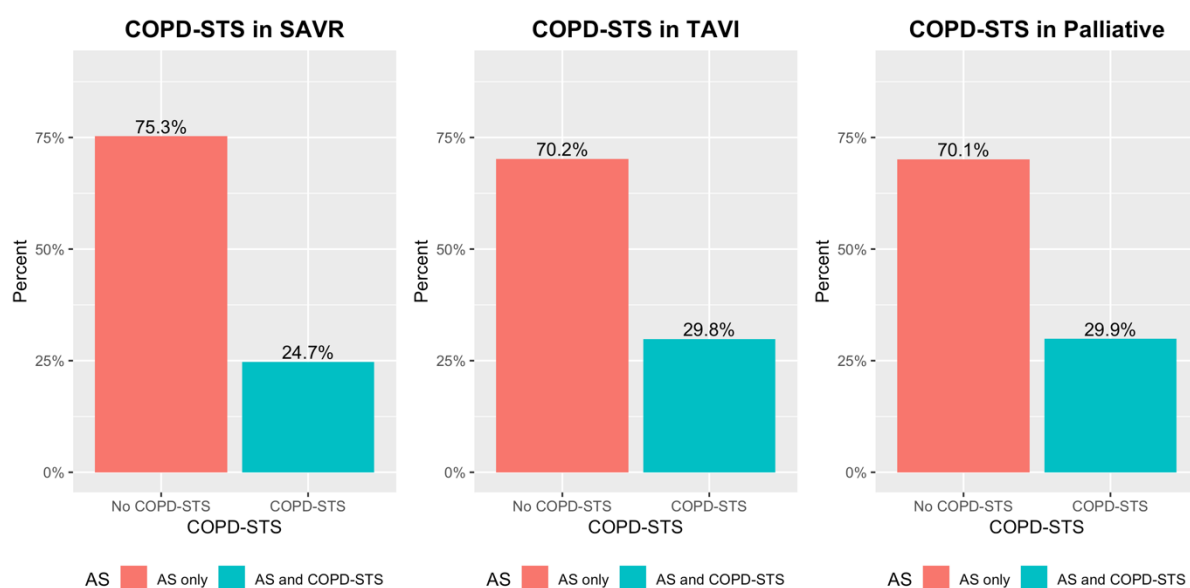


Figure 3-4. COPD-STs prevalence in aortic treatment groups.

COPD-STs prevalence in surgical patients is significantly lower than TAVI and palliative AS, the latter group manifesting the highest prevalence.

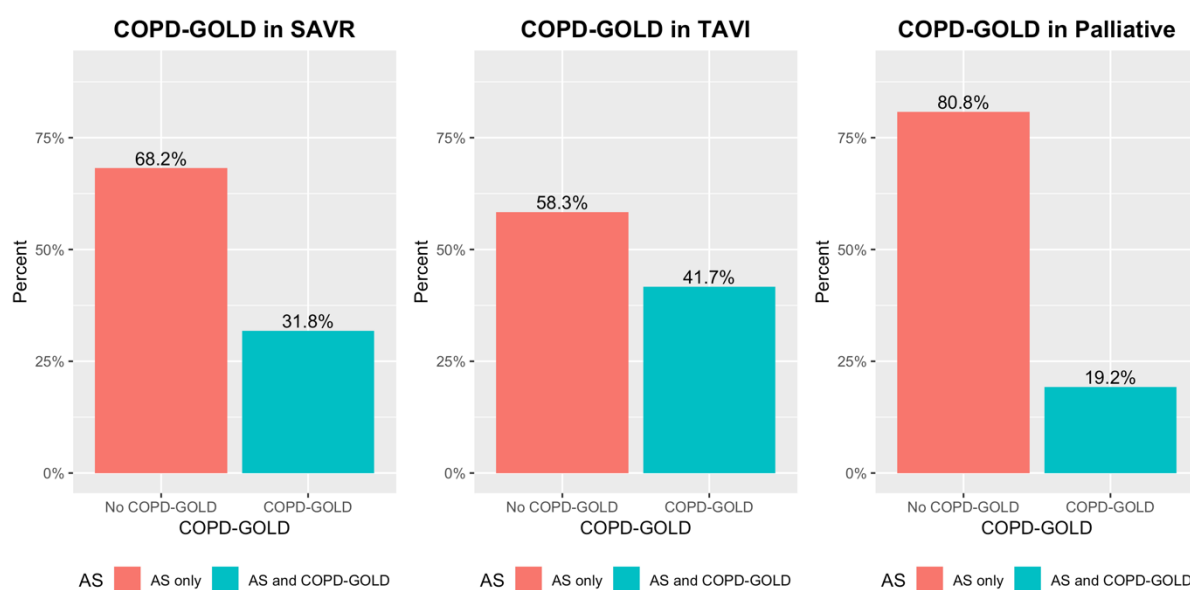


Figure 3-5. COPD-GOLD prevalence in aortic treatment groups.

COPD-GOLD prevalence in surgical patients is lower compared to TAVI, as expected. Interestingly, palliative AS had the lowest prevalence of COPD-GOLD as assessed by spirometry. This is in contrast with COPD-STs prevalence which was the highest in the palliative AS group.

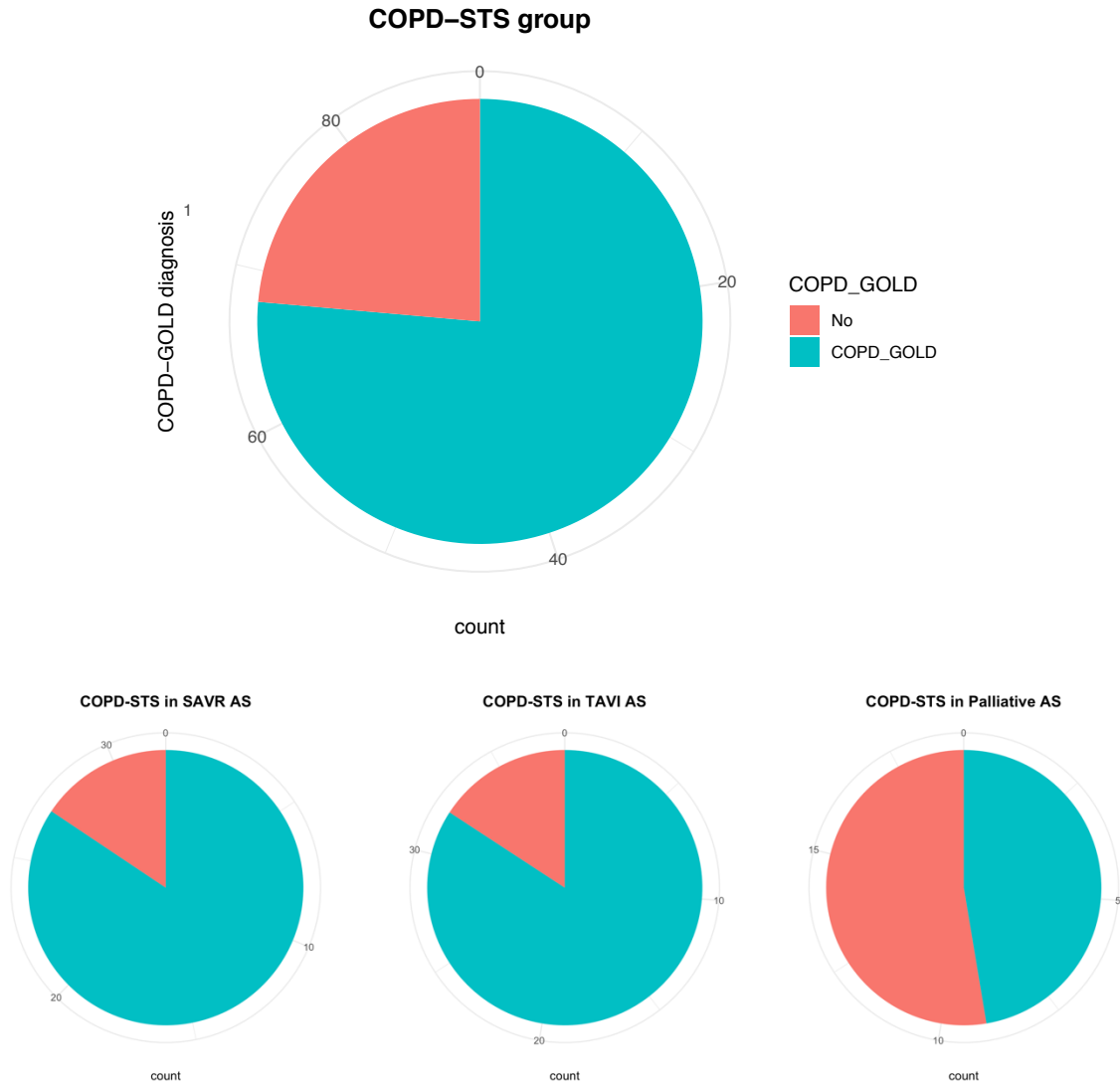


Figure 3-6. Discrepancy between COPD-STS and COPD-GOLD diagnosis in aortic stenosis.

Top panel: in the overall symptomatic AS population, 24% of patients diagnosed with COPD by STS criteria had no COPD-GOLD. *Bottom panel:* the discrepancy between COPD diagnosis was lower in surgical and TAVI patients (16% misclassified in both treatment subgroups). However, palliative AS patients had a severe COPD diagnostic inconsistency with most patients (53%) classified as COPD-STS not having any spirometry evidence of airway obstruction.

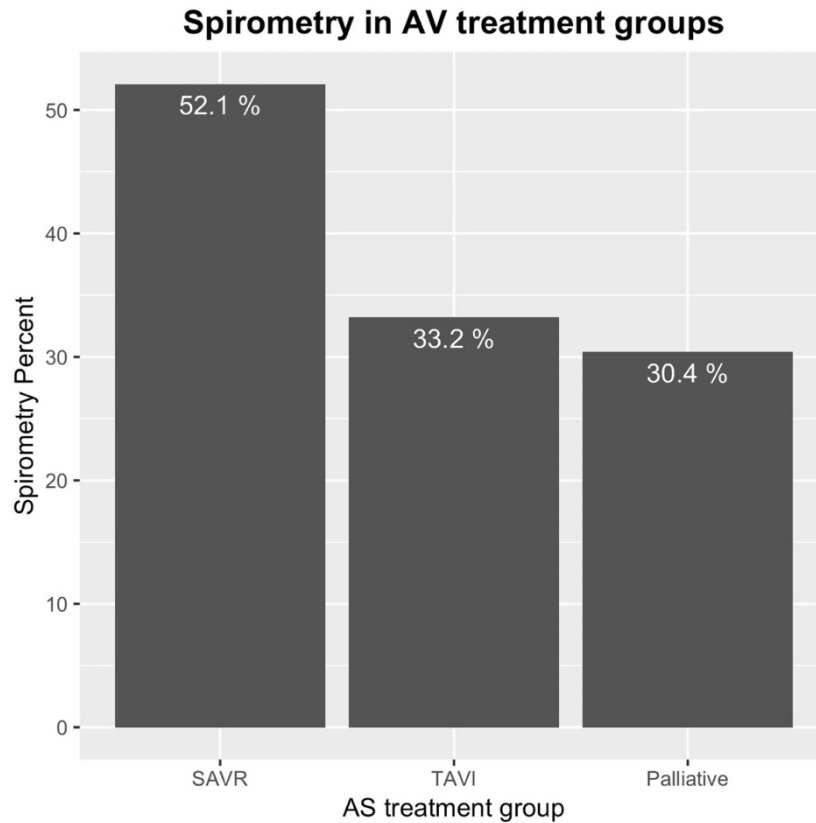


Figure 3-7. **Spirometry in aortic stenosis according to valve management.**

Missing spirometry data and patient selection may explain the COPD diagnostic discrepancy. Only approximately 30% of the TAVI and palliative care patients performed a spirometry. Moreover, the AS subgroup with spirometry data may have been selected for presenting with a less severe clinical burden. The large proportion of patients with missing spirometry who have been excluded from any invasive treatment, may have been too fragile to perform a respiratory assessment. In addition, the clinician assessing their operative risk may have considered futile to perform a spirometry in those who had already been excluded from the invasive aortic valve treatment due to other reasons.

3.1.6.d COPD associations in symptomatic AS

Simple linear regressions were conducted to assess the relationship between FEV₁/FVC and baseline clinical and functional characteristics of the study population. In this particular cohort of patients who were symptomatic for dyspnoea, FEV₁/FVC measured on spirometry determined the diagnosis of COPD-GOLD. Assumptions of independence, linearity, collinearity, homoscedasticity and normality of residuals were met. Gender, peak expiratory flow (PEF) and forced expiratory flow (FEF) were associated to FEV₁/FVC ratio and could explain a 3, 4 and 48% of variation, respectively.

A multiple linear regression was run adopting a stepwise progression from the maximal model to the minimal adequate model to explain the variation in FEV₁/FVC in symptomatic AS. The multiple linear regression was tested for assumptions: there was independence of residuals (Durbin-Watson statistic); the independent variables collectively were linearly related to the dependent variable; and each independent continuous variable was linearly related to the dependent variable; there was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values; no collinearity between variables; the standardized residuals were approximately normally distributed by Q-Q plot and histogram inspection.

The minimal (simplest) adequate model could predict 70% of the variation of FEV₁/FVC in symptomatic AS, a very large effect size by Cohen (207), and accounted for gender, NYHA functional class, PEF and FEF.

Table 3-3. FEV₁/FVC associations with baseline characteristics in aortic stenosis.

<i>Simple linear regression analysis</i>			
	r	r²	sig.
Age, yrs	0.02	0.001	0.73
Gender, male	0.16	0.03	0.015
BMI, kg/m ²	0.003	0	0.97
Peak aortic gradient, mmHg	0.09	0.01	0.2
AVA, cm ²	0.07	0.005	0.35
NYHA functional class	0.003	0	0.96
LVEF, %	0.01	0	0.89
LV mass index, g/m ²	0.13	0.02	0.13
PEF % pred	0.20	0.04	0.002
FEF % pred	0.69	0.48	<0.0001
<i>Multiple linear regression analysis</i>			
Maximal model: r 0.84, r² 0.70, p<0.0001	B	SE	sig
Age, yrs	0	0.08	0.97
Gender	6.15	1.35	<0.0001
BMI, kg/m ²	-0.2	0.15	0.19
Peak aortic gradient, mmHg	0.003	0.03	0.93
AVA, cm ²	5.08	3.5	0.15
NYHA functional class	2.12	0.95	0.02
LVEF, %	0.03	0.06	0.64
LV mass index, g/m ²	0.01	0.01	0.39
PEF % pred	-0.12	0.03	<0.0001
FEF % pred	0.32	0.02	<0.0001
Minimal model: r 0.80, r² 0.70, p<0.0001			
Gender, male	5.88	1.04	<0.0001
NYHA functional class	2.76	1.04	0.001
PEF % pred	-0.10	0.02	<0.0001
FEF % pred	0.31	0.02	<0.0001

BMI: body mass index; AVA: aortic valve area; NYHA: New York Heart association; LVEF: left ventricular ejection fraction, PEF: peak expiratory flow; FEF: forced expiratory flow.

3.1.7 Follow-up Characteristics of the Study Population

Short-term follow-up with aortic valve treatment information was collected in 643 patients (98%). Longer term follow-up with outcome assessment was available in 502 (77%). During an overall median follow-up of 15 months (range 1- 46 months), there were 110 (22%) all-cause deaths in the overall symptomatic AS population. Of these, 66 (71%) were cardiovascular deaths, while 27 (29%) patients died from non-cardiovascular causes. Of the patients who died due to a cardiovascular event, half of them (34, 51%) had a sudden death. In 17 patients (15% of total deaths), the physician who retrospectively evaluated the cause of death was not able to discriminate between cardiovascular and non-cardiovascular cause. Follow-up characteristics of the study population stratified by type of COPD definition (COPD-STs, COPD-GOLD) are summarised in Table 3.5.

Table 3-4. Follow-up characteristics stratified according to COPD-STS and COPD-GOLD.

	No COPD	COPD-STS	P-value
AV Treatment			0.42
AVR	146 (32%)	48 (26%)	
TAVI	186 (40%)	79 (43%)	
Palliative	129 (28%)	55 (30%)	
Follow-up, months	17 ± 10	15 ± 10	0.04
Mortality	65 (18%)	45 (31%)	0.002
CV mortality	41 (76%)	25 (64%)	0.2
	No COPD	COPD-GOLD	P-value
AV Treatment			0.025
AVR	60 (40%)	28 (38%)	
TAVI	49 (32%) *	35 (48%) *	
Palliative	42 (28%) *	10 (14%) *	
Follow-up, months	16 ± 11	15 ± 9	0.9
Mortality	26 (17%)	11 (15%)	0.7
CV mortality	4 (22%)	3 (37%)	0.4

P-values for chi-squared tests of homogeneity. *Significant post-hoc analyses with pairwise comparison by z-tests and Bonferroni correction ($p < 0.016667$). AV: aortic valve; AVR: aortic valve replacement; TAVI: transaortic valve implantation; CV cardiovascular.

3.1.7.a COPD impact on aortic valve treatment in symptomatic AS

Is there a difference in aortic valve treatment according to the presence of COPD?

A χ^2 test of homogeneity was conducted between COPD-STS diagnosis and type of aortic valve treatment performed. All expected cell counts were greater than or equal to five with the lowest expected cell count equal to 52. The two multinomial probability distributions were equal in the population, $\chi^2(2) = 1.74$, $p = 0.42$. Observed frequencies and percentages of aortic valve treatment type for each type of COPD-STS diagnosis are presented in Table 3.5. The multinomial probability distributions between the two groups were not statistically significantly different ($p > .05$). The null hypothesis “there is no difference in aortic valve treatment according to COPD-STS presence” cannot be rejected.

A χ^2 test of homogeneity was conducted between COPD-GOLD diagnosis) and type of aortic valve treatment performed. All expected cell counts were greater than or equal to five with the lowest expected cell count equal to 17. The two multinomial probability distributions were not equal in the population, $\chi^2(2) = 7.40$, $p = 0.025$. Observed frequencies and percentages of aortic valve treatment type for each type of COPD-GOLD diagnosis are presented in Table 3.5. There was a statistically significant difference in the multinomial probability distributions between the two groups (no COPD-GOLD diagnosis and COPD-GOLD diagnosis, $p=0.025$). Therefore, the null hypothesis can be rejected, and the alternative hypothesis accepted: there is a difference in aortic valve treatment according to COPD-GOLD diagnosis. Post hoc analysis involved pairwise comparisons using multiple z-tests of two proportions with a Bonferroni correction. Statistical significance was accepted at $p < 0.016667$. There were differences in the proportion of COPD-GOLD AS patients treated with TAVI and not treated compared to AS patients with no COPD-GOLD diagnosis. There were no statistically significant differences in the proportion of patients with and without COPD-GOLD who underwent surgery.

Is there an association between aortic valve treatment and the degree of COPD?

A χ^2 test for independence was used to determine whether there was an association between COPD-GOLD grade and type of aortic valve treatment in the subgroup of symptomatic AS with PFT results. The COPD-GOLD grade categories were as follows: No COPD-GOLD, mild COPD diagnosis (GOLD stage 1), moderate or severe COPD (GOLD stages 2, 3, 4). Treatment types were AVR, TAVI and palliative medical therapy. All expected cell counts were greater than five. There was a trend to a significant association between COPD-GOLD grade and aortic valve treatment type $\chi^2(4) = 8.57$, $p = 0.07$. The strength of the almost significant association was moderately strong $\phi = 0.2$. This association resulted statistically significant if COPD-GOLD grade categories were grouped as: absence of COPD-GOLD diagnosis, mild-moderate COPD diagnosis (GOLD stage 1-2), and severe/very severe COPD (GOLD stages 3-4) with $\chi^2(4) = 11.63$, $p = 0.02$, $\phi = 0.2$. The strength of the association was also confirmed as moderately strong. However, given the low number of the very severe COPD patients (stage 4) in palliative care being able to perform a spirometry, the assumption for expected cell count $> five$ was not met (minimum count 3).

Is COPD associated to aortic valve treatment type in symptomatic AS?

A multinomial logistic regression was run to evaluate the likelihood of a particular type of treatment (AVR, TAVI or palliative treatment) according to COPD-STS and other baseline characteristics (Table 3-5). COPD-STS was not a significant predictor of type of treatment. Other clinical and echocardiographic characteristics were significant predictors: age ($p < 0.0001$), renal function (eGFR Cockcroft $p = 0.028$) and AVA ($p = 0.032$) with an overall good model fitting (Goodness-of-fit Deviance χ^2 $p = 0.995$, pseudo $r^2 = 0.48$).

The same type of model adopting a COPD definition based on FEV₁/FVC applied to the subgroup of patients with available spirometry data, had a better fit compared to the above (Goodness-of-fit Deviance χ^2 p=0.995, pseudo r²=0.66). FEV₁/FVC was a significant predictor of type of aortic valve treatment (p=0.02), together with age (p= 0.02), peak trans-aortic gradient on echo (p= 0.002) and estimated pulmonary pressures (p=0.03).

Table 3-5. **Multinomial logistic regression evaluating the likelihood of aortic treatment type according to baseline characteristics in aortic stenosis.**

AV Treatment Type	Likelihood Ratio Test	
	χ^2	P-value
AVR, TAVI or Palliative		
<i>Overall Model: pseudo $r^2=0.48$</i>	452.76	<0.0001
Clinical characteristics		
COPD-STs	2.50	0.29
Age, yrs	19.96	<0.0001
Gender, male	0.20	0.91
BMI, kg/m ²	2.39	0.30
NYHA functional class	4.51	0.11
Diabetes Mellitus	0.81	0.66
Systemic Hypertension	2.93	0.23
eGFR, Cockcroft	7.18	0.028
Logistic EuroSCORE	0.01	0.99
Hospital Centre	0.34	0.87
Atrial Fibrillation	3.51	0.17
Medical Therapy		
ACE inhibitors	1.66	0.44
Beta blockers	0.52	0.77
Diuretics	0.15	0.92
Echocardiographic parameters		
AVA, cm ²	6.90	0.032
Peak aortic gradient, mmHg	3.04	0.22
LVEF, %	1.40	0.50
SPAP, mmHg	1.91	0.38

AV: aortic valve; AVR: aortic valve replacement; TAVI: transaortic valve implantation; BMI: body mass index; NYHA: New York Heart association; eGFR: estimated glomerular filtration rate; AVA: aortic valve area; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure.

Table 3-6. **Multinomial logistic regression evaluating the likelihood of aortic treatment type according to baseline characteristics in aortic stenosis with spirometry.**

AV Treatment Type	Likelihood Ratio Test	
	χ^2	P-value
AVR, TAVI or Palliative		
<i>Overall Model: pseudo $r^2=0.66$</i>	94.8	<0.0001
Spirometry parameters		
FEV ₁ /FVC	7.82	0.02
PEF % pred	0.05	0.98
FEF % pred	3.65	0.16
Clinical characteristics		
Age, yrs	8.04	0.018
Gender, male	5.35	0.069
BMI, kg/m ²	1.15	0.56
NYHA functional class	4.73	0.09
Diabetes Mellitus	0.76	0.68
Systemic Hypertension	2.08	0.35
eGFR, Cockcroft	3.48	0.21
Logistic EuroSCORE	4.25	0.12
Hospital Centre	2.12	0.31
Atrial Fibrillation	0.60	0.18
Medical Therapy		
ACE inhibitors	1.17	0.56
Beta blockers	2.15	0.34
Diuretics	0.12	0.94
Echocardiographic parameters		
AVA, cm ²	0.86	0.65
Peak aortic gradient, mmHg	12.73	0.002
LVEF, %	5.38	0.068
SPAP, mmHg	6.76	0.034

AV: aortic valve; AVR: aortic valve replacement; TAVI: transaortic valve implantation; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; FEF: forced expiratory flow; pred: of predicted; BMI: body mass index; NYHA: New York Heart association; eGFR: estimated glomerular filtration rate; AVA: aortic valve area; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure.

3.1.7.b Prognostic impact of COPD in symptomatic AS

A significantly reduced survival was observed in COPD-STS patients, as shown by the Kaplan Meier survival analyses curves in Figure 3-8. A similar percentage of censored cases was present in those without COPD by STS criteria (84%) and those with COPD (74%). AS only patients had a survival of 36 months (95% C.I. 34 – 38). This was longer than COPD-STS AS patients' survival of 28 months (95% C.I. 24 – 32). A log rank test was conducted, and survival distributions resulted statistically significantly different, $\chi^2(2) = 15.14, p < 0.0001$. This survival difference was confirmed in the high-risk groups (TAVI and Palliative) while was not present in those undergoing SAVR.

However, when COPD was more accurately assessed in the subgroup of AS patients with spirometry data available, a COPD-GOLD diagnosis was not associated with mortality: there were no differences in survival distributions between AS patients with a diagnosis of COPD and those without (Figure 3-9). No statistically significant differences were present also when only moderate/severe or very severe COPD-GOLD grades were considered. However, the power of the study to assess this association was limited.

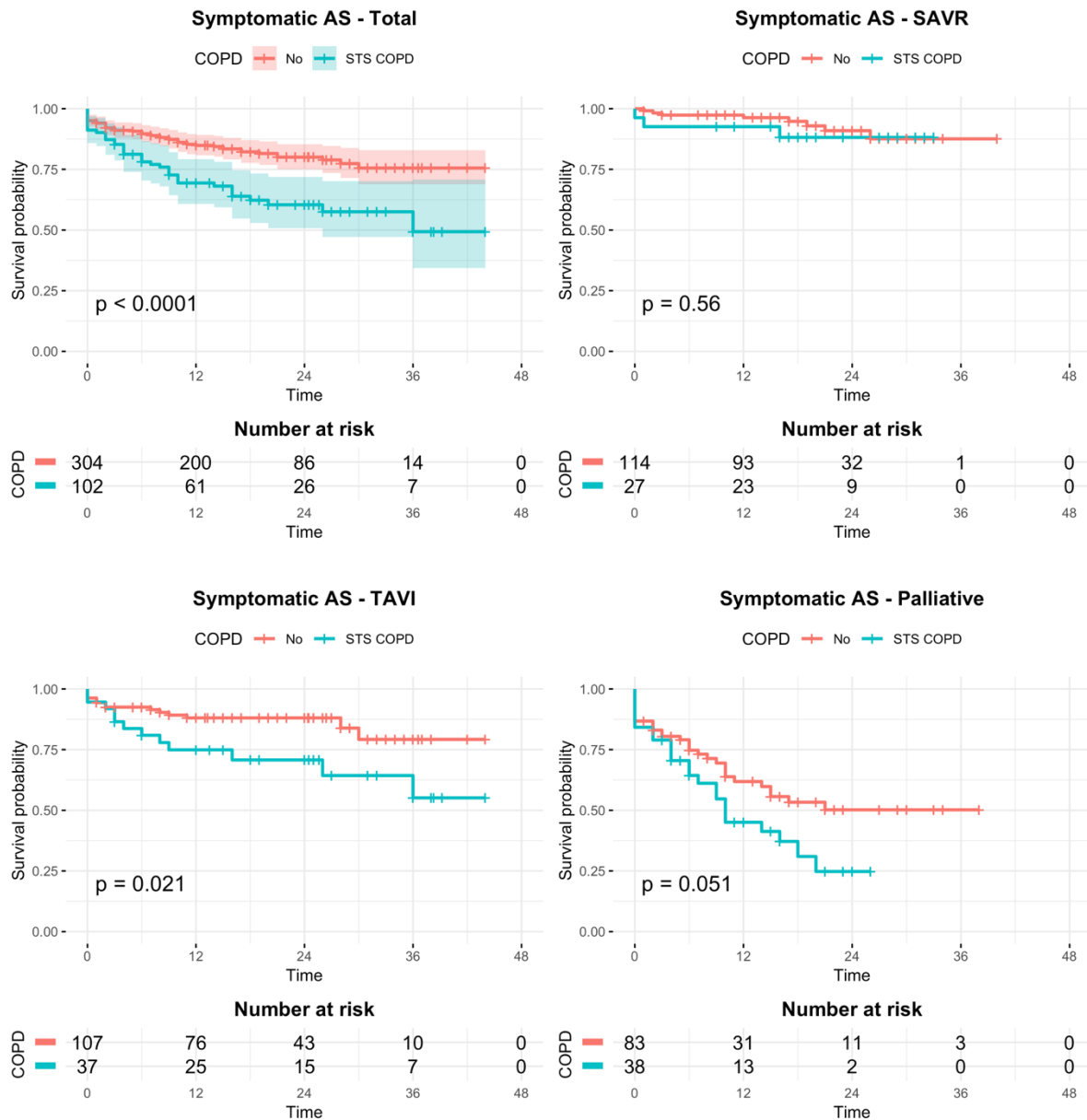


Figure 3-8. Kaplan-Meier survival curves for COPD-STS in aortic stenosis according to valve management.

COPD-STS patients had a significantly reduced survival in the overall symptomatic AS population compared to no COPD-STS (log rank $p < 0.0001$). The prognostic impact of COPD-STS was confirmed in the higher-risk subgroups (patients excluded from surgical aortic valve treatment) but not in those who underwent surgical aortic valve replacement.

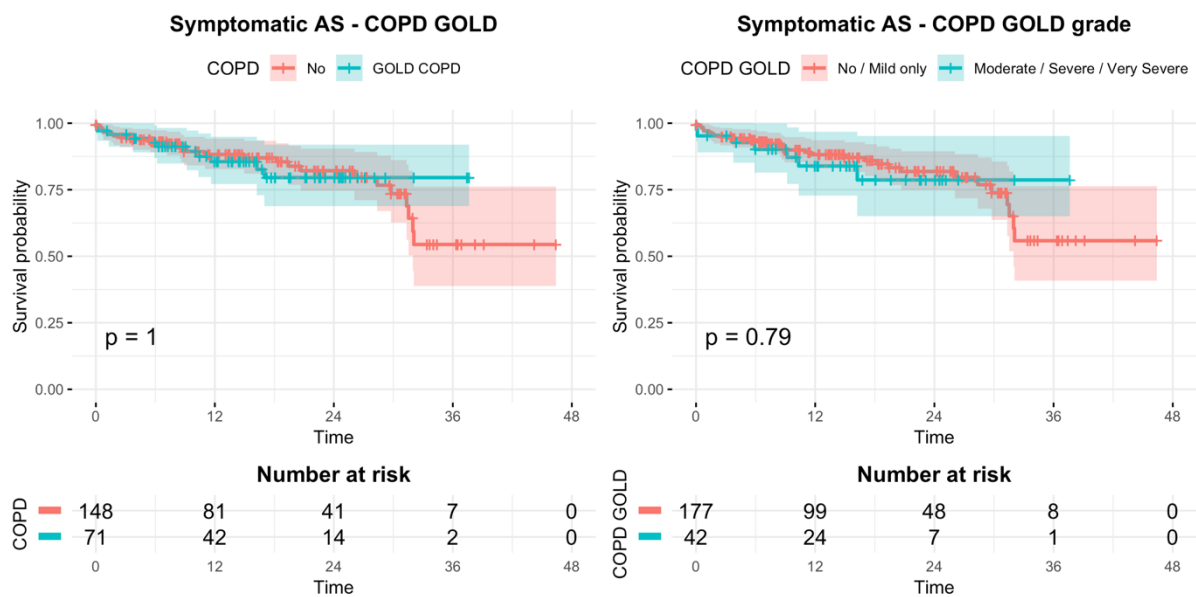


Figure 3-9. Kaplan-Meier survival curves for COPD-GOLD in aortic stenosis with spirometry.

In the overall symptomatic AS population with spirometry data available, COPD-GOLD diagnosis was not prognostic. Even when only significant stages of airway obstruction (GOLD grade 2-4) were considered, AS patients with at least moderate COPD-GOLD did not have a survival distribution significantly different from those without relevant COPD-GOLD.

The results of the univariable Cox analysis for the prediction of the primary endpoint all-cause death in the symptomatic AS population are shown in Table 3-7. COPD-STs patients had almost a 2-fold increased risk of all-cause mortality ($p=0.004$) compared to no COPD-STs. This was the most significant hazard ratio (HR) after measures of heart failure (NYHA functional class and diuretics use) and aortic valve treatment type (invasive AVR/TAVI vs palliative medical therapy). Other significant clinical predictors were: age, BMI, renal function, logistic EuroSCORE, use of medical therapy. Significant echocardiographic predictors were: AS severity (AVA), cardiac function (LVEF), and pulmonary pressures.

Unadjusted HR were also reported in the subgroup with spirometry data (Table 3-8). COPD-GOLD diagnosis was not a prognostic factor. Other clinical parameters were confirmed prognostic with the highest HR (2.1 95% C.I. 1.07-4.13) being palliative AS treatment compared to invasive AVR (TAVI or surgical). Two objective spirometry measures (PEF and FVC) potentially linked to heart failure, were significant prognostic factors.

The independence of the above prognostic factors was assessed with multivariable Cox regressions. The adjusted HR are reported in the Forrest plots (Figure 3-10 and Figure 3-11). COPD-STs was a significant and powerful independent prognostic factor in all the three models explored, with adjusted HR ranging from 1.7 to 2. COPD-STs prognostic impact was independent from other significant clinical, echocardiographic and cardiac treatment parameters. PEF% of predicted, a measure of large airway disease, was also independently associated to all-cause death.

Table 3-7. Cox proportional hazard model for all-cause mortality in the total aortic stenosis population.

All-cause Mortality		
<u>Total AS population:</u> n = 502, Events = 110		
Univariable Cox Regression		
	HR (95% CI)	P-value
Clinical characteristics		
COPD-STS	1.90 (1.22 – 2.95)	0.004
Age, yrs	1.09 (1.06-1.13)	<0.0001
Gender, male	1.06 (0.69-1.63)	0.78
BMI, kg/m ²	0.87 (0.82-0.92)	<0.0001
NYHA functional class	2.09 (1.51-2.89)	<0.0001
Diabetes Mellitus	1.19 (0.743-1.9)	0.47
Hypertension	0.98 (0.59-1.6)	0.94
eGFR, Cockcroft	0.96 (0.95-0.98)	<0.0001
Logistic EuroSCORE	1.02 (1.01-1.03)	<0.0001
Hospital Centre	0.96 (0.43 – 1.52)	0.81
Atrial Fibrillation	1.46 (0.936-2.28)	0.1
Cardiac treatment		
ACE inhibitors	0.56 (0.35-0.89)	0.014
Beta blockers	0.54 (0.31-0.94)	0.028
Diuretics	1.96 (1.08-3.58)	0.028
AV treatment, palliative	5.2 (3.35-8.07)	<0.0001
Echocardiographic parameters		
AVA, cm ²	0.13 (0.03-0.46)	0.002
Peak aortic gradient, mmHg	0.99 (0.98-1.00)	0.21
LV mass index, g/m ²	1 (1.00-1.01)	0.18
LVEF, %	0.96 (0.95-0.98)	<0.0001
SPAP, mmHg	1.03 (1.01-1.04)	0.0004

BMI: body mass index; NYHA: New York Heart association; eGFR: estimated glomerular filtration rate; AV: aortic valve; AVA: aortic valve area; LV: left ventricular; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary arterial pressure.

Table 3-8. Cox proportional hazard model for all-cause mortality in the subgroup of aortic stenosis with spirometry.

All-cause Mortality		
<u>AS patients with spirometry:</u> n = 224, events = 37		
Univariable Cox Regression	HR (95% CI)	P-value
Clinical characteristics		
COPD-GOLD	1 (0.49-2.04)	1
Age, yrs	1.05 (0.99-1.1)	0.054
Gender, male	0.55 (0.28-1.07)	0.077
BMI, kg/m ²	0.81 (0.73-0.90)	0.0002
NYHA functional class	1.39 (0.85-2.25)	0.19
Diabetes Mellitus	1.48 (0.75-2.91)	0.26
Hypertension	0.85 (0.39-1.84)	0.69
eGFR, Cockcroft	0.97 (0.95-0.99)	0.007
Logistic EuroSCORE	1 (0.98-1.3)	0.98
Hospital Centre	1.1 (0.92-1.38)	0.78
Atrial Fibrillation	1.46 (0.76-2.8)	0.25
Cardiac treatment		
ACE inhibitors	1.36 (0.667-2.78)	0.4
Beta blockers	0.97 (0.48-1.98)	0.94
Diuretics	1.52 (0.71-3.24)	0.28
AV treatment, palliative	2.1 (1.07-4.13)	0.032
Echocardiographic parameters		
AVA, cm ²	0.46 (0.07-3.06)	0.43
Peak aortic gradient, mmHg	0.99 (0.97-1)	0.08
LV mass index, g/m ²	1.0 (0.99-1.01)	0.61
LVEF, %	0.98 (0.96-1.01)	0.17
SPAP, mmHg	0.99 (0.97-1.02)	0.54
Spirometry parameters		
FEV ₁ /FVC	0.99 (0.97-1.02)	0.75
FEV ₁ (L)	0.71 (0.43-1.19)	0.2
FVC (L)	0.78 (0.53-1.15)	0.21
FEV ₁ % pred	0.99 (0.97-1)	0.064
FVC % pred	0.98 (0.97-0.99)	0.031
PEF % pred	0.98 (0.97-0.99)	0.0023
FEF % pred	0.76 (0.48-1.19)	0.23

BMI: body mass index; NYHA: New York Heart association; eGFR: estimated glomerular filtration rate; SPAP: systolic pulmonary arterial pressure; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; PEF: peak expiratory flow; FEF: forced expiratory flow.

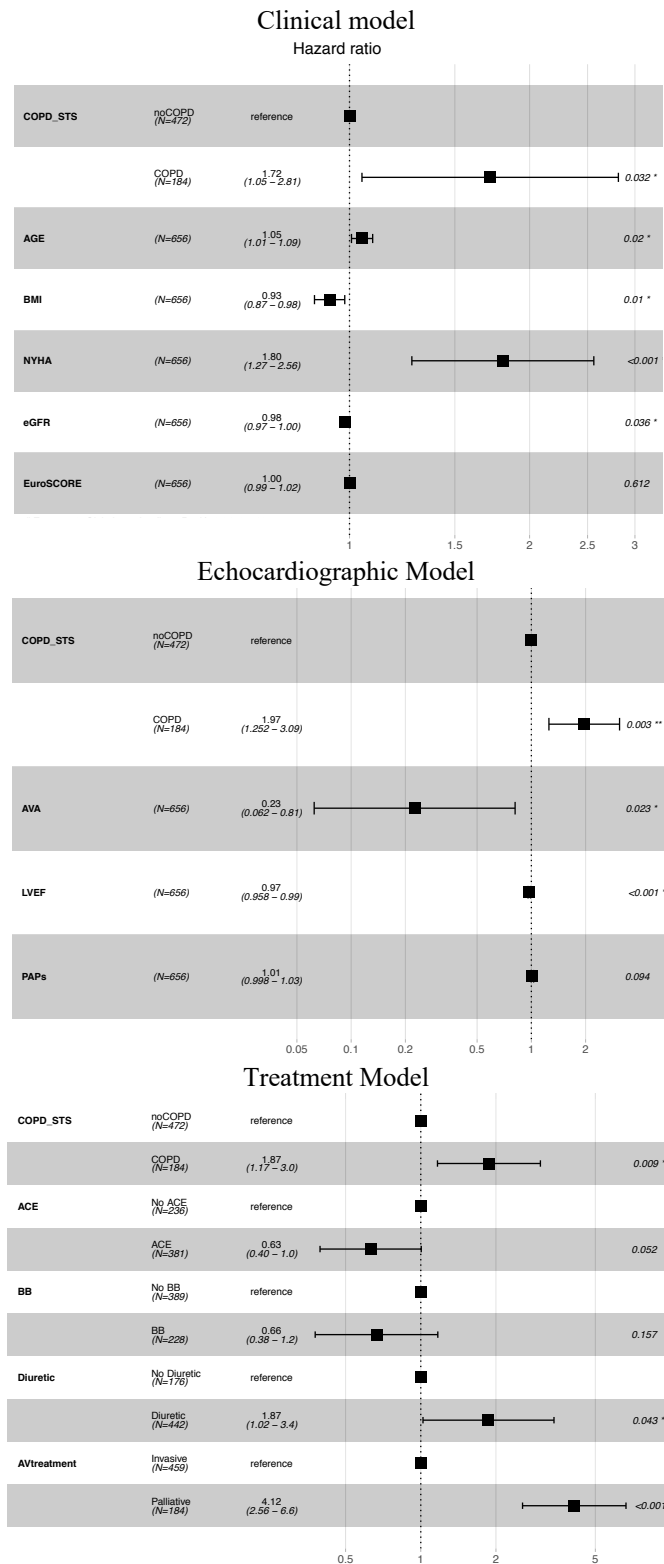


Figure 3-10. **Forrest plots for all-cause mortality in aortic stenosis.**

In all the multi-variable Cox proportional hazards models explores (clinical, echocardiographic and treatment), COPD-STs was a powerful and independent predictor of mortality.

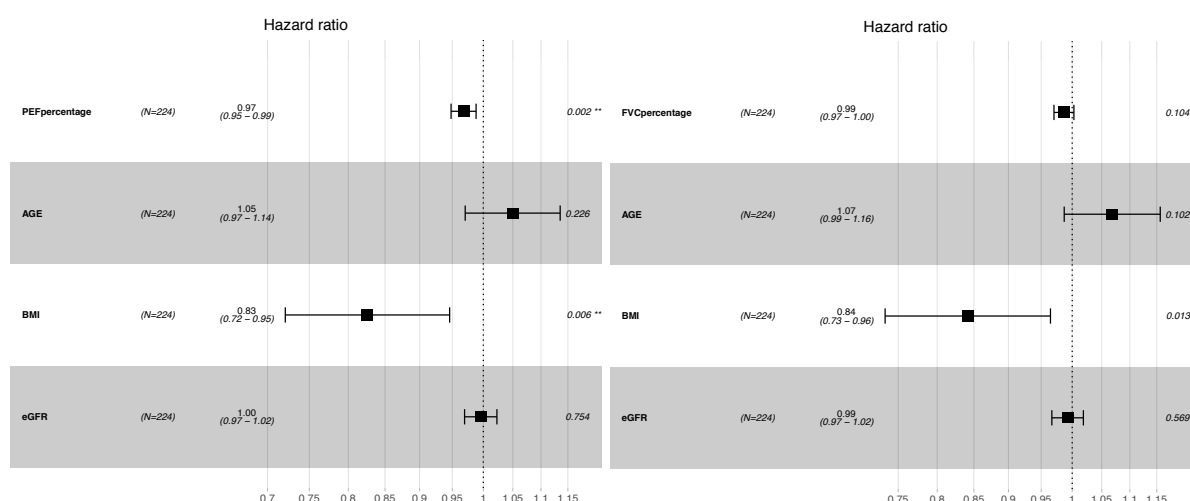


Figure 3-11. Forrest plots for all-cause mortality in aortic stenosis with spirometry.

The left multivariable Cox proportional hazard model shows that PEF% of predicted remained significant also when adjusted for other significant clinical characteristics. On the contrary, FVC % of predicted was not an independent predictor of all-cause mortality (right model).

DISCUSSION

3.1.8 A Multidisciplinary Approach to the Multi-morbid Patient

Current clinical practice and research do not embrace the new challenges imposed by the growing elderly and multimorbid population (208). Randomised and prospective studies still target single disease-specific population by stringent inclusion and exclusion criteria and do not offer solutions for the most common and complex cases affected by multiple underlying diseases (209). Therefore, there is a compelling need for a multidisciplinary approach incorporating multimorbidity and integration between specialities into clinical decision making.

This chapter presents the results of a large multi-centre retrospective cohort of patients affected by severe AS and referred for different aortic valve treatments (SAVR, TAVI and palliative medical therapy), with the aim to assess the prevalence and prognostic impact of COPD, according to its definition and classification. A large cohort of AS patients with adequate follow-up was needed to explore the above points. The chapter discussion will follow the hypothesis formulated in the previous paragraph 0 “Hypothesis and Aim”.

3.1.9 Discrepancy in COPD Prevalence and Diagnosis in Aortic Stenosis

The first hypothesis stated that *“The prevalence of confirmed respiratory dysfunction (COPD-GOLD) in patients with symptomatic AS is unknown but likely to be high and different from apparent lung disease (COPD-STs) prevalence.”*

In the AS literature and, more generally, in cardiac disease undergoing invasive treatment, what is currently defined as COPD is often not a gold-standard diagnosis of lung disease based on

the evidence of respiratory symptoms and airflow limitation, but an extrapolation from cardiac risk scores parameters often collected at the time of aortic management and easily accessible for retrospective sub-analyses of larger cardiac trials. For example, in the sub-analysis from the Partner Trial evaluating the prognostic impact of chronic lung disease in AS (83), lung disease was defined by STS classification and was severely limited by the lack of data on the degree of airflow obstruction at baseline. Therefore, only the “COPD-STS” diagnosis was assessed. No data was reported on the available spirometry measures nor on the percentage of COPD patients with confirmed respiratory dysfunction. Another large study assessing COPD impact in TAVI patients (82) defined COPD according to -STS criteria only, and no data on spirometry was available. Smaller studies in AS reporting spirometry data (94,210) were limited to a particular aortic valve treatment group (TAVI only) and were underpowered to assess associations with mortality (only 5 deaths in the COPD/AS patients recorded from the Swedish registry). The prevalence of confirmed airway dysfunction in AS is unknown.

As hypothesised, the prevalence of spirometry defined COPD was high (COPD-GOLD 33% vs COPD-STS 28%) even when analyses were conducted only in the subgroup of patients selected for or able to perform a spirometry who were likely not including the most severe cases. This clinically preselected subgroup who performed a spirometry assessment showed a significant discrepancy compared to the overall AS population. This discrepancy was obvious when the differences between apparent and confirmed lung dysfunction were assessed in the palliative groups composed by those patients who were later excluded from any invasive treatment (Figure 3-4, Figure 3-5). In this group, the COPD-STS prevalence was the highest (30%) when compared to the surgery and TAVI subgroups, as expected in a fragile comorbid and high-risk group. However, when airway dysfunction was more accurately assessed with spirometry, the palliative group had the lowest COPD-GOLD prevalence (19%). Moreover, of those palliative

patients who performed a spirometry, 53% were misclassified as having a diagnosis of COPD (COPD-STs) but not actually showing any sign of airflow limitation (normal FEV₁/FVC ratio on spirometry, Figure 3-6).

This striking discrepancy between COPD-STs and COPD-GOLD may be explained by two main reasons. First of all, the overwhelming missing data in the higher-risk patients with only approximately 30% of them having spirometry results available (Figure 3-7). Secondly, by the fact that if lung disease is assessed through a simple risk scoring system such as the STs, the clinician may be biased by the overall patient evaluation and may not apply a rigorous objective COPD diagnosis, even if spirometry is available. The large proportion of patients with missing spirometry (70% of the palliative group and 67% of the TAVI group) may either have been too fragile to perform a simple spirometry or it may have been considered futile for them to perform a spirometry if they already had been excluded due to other morbidities. Therefore, there may have been a significant preselection bias explaining why the highest-risk AV treatment group (palliative medical therapy) displayed the lowest prevalence of COPD-GOLD. On the contrary, a diagnosis of COPD-STs is an easier to perform which does not require spirometric confirmation and can be based only on the presence of symptoms and long-term use of bronchodilators/steroids or oxygen therapy.

COPD-STs is wider adopted in the elderly AS population but is severely biased by the confounding effect of heart failure and by the clinician subjective judgment. COPD-STs may reflect a long-standing and progressive dyspnoea under the treatment with common respiratory medications which may have been started to help symptomatic patients with decompensated AS. Thus, COPD-STs is a general risk assessment tool rather than a proper lung disease diagnosis and, as such, performs well for prognostic stratification. It should not be confounded

with true lung disease or airflow obstruction since most patients were misclassified when objective spirometry measures were assessed.

Up to date, it is still unclear whether different COPD assessment approaches commonly adopted in cardiology are comparable. These COPD diagnostic discrepancies are extremely important: the presence of apparent (COPD-STS) or confirmed (COPD-GOLD) lung dysfunction may directly and indirectly impact on outcomes of patients with dyspnoea needing invasive treatment. On the basis of the current limited literature that defines COPD-STS as COPD, patients with spirometry data may be wrongly excluded from aortic valve treatment only due to their spirometric impairment. In our cohort, COPD-GOLD was only mild-moderate (GOLD grade 1 and 2) in most patients (85%). These early airflow limitation stages should not directly impact on outcome (76).

In an unpublished study from the University of Miami conducted in a TAVI population to assess discrepancies in COPD prevalence (211), the researchers found a comparable high prevalence of COPD defined by STS criteria (55% vs 42% in the present research), despite only 26% of them presented formal airflow obstruction on spirometry. This is in keeping with the above hypothesis that COPD prevalence is high and that there is a wide discrepancy between COPD-STS and -GOLD diagnosis which is most prominent in the high-risk severe AS group. The selection of patients who performed spirometry may differ in the various clinical context not being regulated by strict guidelines and may explain why COPD-GOLD prevalence was lower than in our subgroup undergoing TAVI. Our results underlie the importance of defining the better suited diagnostic approach to assess preoperative respiratory function in AS.

3.1.10 Is Respiratory Dysfunction in Aortic Stenosis a Measure of Lung Disease?

COPD-GOLD was defined by the FEV₁/FVC ratio in a typically symptomatic for dyspnoea AS population. This ratio was strongly and independently associated with male gender, symptoms (NYHA functional class), and objective spirometry measures of airway resistance in large and small airways (Table 3-3). The most significant variation of FEV₁/FVC was explained by FEF, a measure of small airway disease . In patients with symptomatic AS, an increased FEF may be due to interstitial oedema which compresses the small airways at the level of their peribronchial cuffs and isolates them from the normal traction of the surrounding parenchyma (215). The second most important relationship was with PEF, a measure of large airway disease which may be affected by alveolar oedema and, therefore, be associated to more advanced stages of heart failure with lung congestion. Airway resistance is typically increased when large airways are full of fluid and, in addition, the bronchoconstrictor reflex may be activated (215). Therefore, a diagnosis of COPD-GOLD in AS may be significantly confounded by the presence of lung congestion.

3.1.11 Does Respiratory Dysfunction in Aortic Stenosis Affect Aortic Valve Management?

The second hypothesis stated that *“The co-existence of AS and COPD in patients with symptoms may have important implications for aortic valve replacement management and thus may indirectly and/or directly affect survival.”*

To assess this, I explored the associations between COPD definitions and aortic treatment choice (Table 3-4). AS patients affected by COPD-GOLD were more likely to undergo TAVI compared to other treatment options, with a significant difference in TAVI and palliative treatment prevalence when compared to patients with similar aortic disease burden but without COPD-GOLD. Interestingly, there were no differences in aortic valve treatment between the

COPD-STS/AS patients and those without COPD-STS. However, the prevalence of exclusion from any invasive treatment in the COPD-STS group (30%) was considerably higher than in the COPD-GOLD group (14%).

These results are clinically important as they confirm the significant association between COPD-GOLD diagnosis, even if only mild-moderate, and the cardiac treatment choice. This relationship was not seen between COPD-STS and treatment choice. This may have been related to the fact that the highest-risk fragile subgroup who was unable to perform a spirometry was excluded from invasive treatment based on other reasons. Therefore, a COPD-STS diagnosis may not have impacted aortic treatment choice by itself but was likely associated with other comorbidities. On the contrary, the FEV₁/FVC ratio was also confirmed a significant and independent predictor of cardiac treatment type, together with age and other widely adopted measures of aortic valve disease severity (peak trans-aortic gradient and estimated pulmonary pressures on echo).

3.1.12 The Importance of COPD Assessment for Defining Prognosis in Aortic Stenosis

As hypothesised, “*The prognostic impact of COPD-GOLD is likely to be different from COPD-STS’ impact in AS*”. Although COPD-GOLD and measures of airway flow limitation were associated to aortic valve treatment choice, the study was not able to assess whether a COPD-GOLD diagnosis when assessed more accurately in this subgroup with spirometry data was prognostic. This may be due to the loss to follow-up: although short-term follow-up was collected 98% of patients, longer term follow-up with outcome assessment was available in 502 (77%). In addition, only a limited number of patients underwent formal airflow limitation assessment with spirometry due to a selection bias: patients who were excluded from treatment due to other causes or who were too unfit to perform a spirometry had no assessment of airflow

limitation. The post-hoc analysis performed showed that the power to detect a difference in mortality was only 5.4%, in contrast to the higher power of 94% for COPD-STS assessment of mortality association. Therefore, the clinician should be aware that the current literature is limited for assessing the prognostic impact of respiratory dysfunction (absolute FEV₁/FVC ratio) and degree of COPD-GOLD (assessed by FEV₁). In this study, COPD-GOLD was not significantly associated with all-cause mortality, but power was lacking due to the above limitation.

COPD-GOLD may either be not associated with mortality or the study may be inadequate to assess this association. The lack of prognostic impact of COPD-GOLD would be pathophysiologically in keeping with previous research in other cardiac diseases showing that although heart failure affects spirometric results, mainly FEV₁ and FVC, the absolute ratio between the two does not change and, therefore, the FEV₁/FVC diagnostic criterion for COPD-GOLD may results independent from heart failure and cardiac impairment (216–219). A reasonable explanation of the above findings is that most patients with severe AS have mild degrees of COPD, and therefore their more severe cardiac disease is a greater determinant of their prognosis.

However, no conclusion can be drawn from the COPD-GOLD evaluation of mortality association due to the low power mainly driven by the limited number of patients who were referred for spirometry assessment and the long-term loss to follow-up. Thus, COPD-GOLD should not be regarded as the same as other cardiac risk scoring assessments (COPD-STS) which have been previously proven (and here confirmed) to affect prognosis. When assessing for lung disease in symptomatic AS, the clinician may instead be selecting for high-risk patients with heart failure rather than real COPD. These patients are at higher mortality risk but would

also most benefit from AVR and heart failure treatment. Thus, it is important to recognise the differences, limitations and discrepancy between COPD diagnosis and classifications when evaluating symptomatic patients in need of cardiac treatment.

Other objective measures on spirometry (PEF and FVC % of predicted) were independent predictors of mortality in the subgroup of patients who performed spirometry, although their HR did not result clinically relevant in our subgroup. PEF is a measure of large airway disease and may be better associated with heart failure and lung congestion rather than with COPD. Also FVC is a measure of lung compliance and its reduction is typical of restrictive disease (77,220), such as expected in heart failure rather than COPD.

On the contrary, COPD-STS resulted a powerful and independent predictor of all-cause mortality. As seen previously, COPD-STS was not associated with aortic valve treatment choice but still resulted an important and independent predictor of mortality with an unadjusted HR of 1.90 (1.22 – 2.95) and an adjusted HR ranging from 1.7 to 2. The prognostic impact of COPD-STS was seen in the TAVI and palliative medical therapy groups, but not in the surgical group. These results confirm that COPD-STS is a marker of high-risk patients irrespective of aortic valve treatment (TAVI or palliative). Patients with COPD-STS who were selected for surgery were likely fitter than those who underwent TAVI or were excluded and, therefore, COPD-STS did not have the same risk stratification ability in the SAVR subgroup.

3.1.13 Possible Mechanisms of COPD Interactions and Impact in Aortic Stenosis

COPD may impact on prognosis of patients affected by AS through a direct and/or an indirect pathway, or both. COPD may be directly linked to AS by sharing common risk factors, similar management concerns and underlying common pathophysiological mechanisms. Pathologies

that interact through a direct pathway have been defined “concordant” (221,222). This type of *concordant* interaction is easier to study and may be addressed by specialty guidelines.

On the contrary, conditions that interact in a “discordant” way are less related by pathogenesis but can affect one another in an indirect way. In AS, the presence, classification and grading of COPD may strongly influence the decision-making process on aortic valve treatment strategy and timing: COPD may confound symptoms of valve obstruction, is part of the most commonly adopted risk score algorithms for predicting cardiac surgery mortality and one of the reasons for valve replacement denial. This type of *discordant* interaction is subtle, often overlooked and difficult to recognise. Co-morbidities which are not pertinent to the specialist are often not formally recorded in the medical records, or not correctly diagnosed and graded despite their relevance for patient care. Therefore, COPD may be over or under-estimated due to an unconscious simplified diagnosis performed by the cardiologist who selects AS patients for aortic treatment.

The complexity of the discordant heart-lung interaction is well shown by the discrepancy between COPD diagnosed (discussed in paragraph 3.1.9) and by the lack of spirometry data in different aortic treatment groups.

The spirometry selection strategy performed by the cardiologist may have resulted in an overall minor burden of airway obstruction in the palliative COPD-GOLD group compared to the palliative COPD-STS. This was likely due to the missing spirometry data (the sickest patients did not perform a spirometry). The lower prevalence of COPD-GOLD diagnosis in the higher-risk patients may explain why a COPD-GOLD diagnosis was not prognostic in severe AS. In addition, the findings seem to favour a more direct prognostic pathway of COPD-STS as a

measure of heart failure and risk. Thus, it is not surprising that it holds a powerful prognostic impact in AS which appeared not to be determined by an aortic treatment choice effect.

3.1.14 Limitations

The limited number of patients with confirmed severe airflow obstruction (11 with COPD-GOLD stage 3-4) renders it difficult to relate the above findings to this particular group. In addition, the low number of overall COPD-GOLD patients with consequent low study power does not allow to assess differences in mortality compared to the no-COPD group. This limitation may be due to a pre-aortic valve treatment natural selection: patients with COPD may not reach the severe symptomatic stages of AS due to their higher mortality at younger age compared to those without COPD. Another possible explanation is that patients with COPD-GOLD and AS presenting with cardiac symptoms might be misdiagnosed and not referred to the cardiologist for their cardiac management. In addition, patients with concomitant true severe COPD and symptomatic AS may be too unwell and fragile to perform a spirometry and, therefore, would be unable to be selected in the COPD-GOLD group. These patients might be classified as COPD-STs and this might be one of the reasons for the prognostic impact of COPD-STs over COPD-GOLD. Large prospective studies with standardised spirometry and risk factors data collection are needed to assess whether COPD-GOLD is prognostic.

However, the severe multi-morbidity group (severe AS with COPD 3-4) resulted uncommon and would be functionally limited with low quality of life and expectancy. In these patients, aortic treatment would be too risky and likely futile. On the contrary, the research findings should be further evaluated in those patients with milder stages of COPD-GOLD who represent the 85% of the COPD-GOLD population and may be wrongly excluded or delayed from cardiac treatment. They would also be the ones who may most benefit from the correct

management of their culprit aortic disease. COPD-STG should be adopted for risk stratification, as confirmed by our results, but should not be mistaken for COPD-GOLD. Further research in confirmed airflow obstruction is needed to assess its impact in symptomatic AS.

Smoking status was not considered due to the incomplete data collection which was performed from the clinical notes on medical history collected at the time of the cardiological admission. Tobacco smoking is the main risk factor for COPD but other environmental exposures, air pollution, shared risk factors and pathophysiological pathways (discussed in the Chapter 1 – Introduction: Shared Risk Factors and Pathophysiology in Aortic Stenosis and COPD) may contribute. In addition, the smoking prevalence in the elderly population is known to be extremely low (approximately 8% in Europeans aged >75 (223)). However, active and previous exposure to smoking is important and needs to be further investigated with appropriate data collection. This will be partially addressed in the prospective study AMICA-AS which better evaluates association between smoking and AS.

Causes of death were analysed by a single physician who assigned the outcome type on the basis of the information acquired from medical records. Long-term follow-up with outcome definition was available in 77% of the population due to either loss of follow-up or inability to adjudicate the primary endpoint. To reduce possible confounders on outcome definition, all-cause mortality was chosen as the primary endpoint being the most objective hard endpoint available.

Formal lung function assessment may still be limited in patients with symptomatic AS due to heart failure and elderly age which may confound the spirometry results. The simple spirometric fixed ratio of FEV₁/FVC less than 0.70 used in the GOLD guidelines to diagnose

COPD may result in a more frequent diagnosis in the elderly and less frequent diagnosis in younger adults, especially in mild disease, compared with a cut-off based on the lower limit of normal (LLN) values for FEV₁/FVC (97,224). However, there are several limitations to the LLN criteria: it is dependent on the choice of reference standard, there are no longitudinal studies to validate it yet and no confirmation in populations where smoking is not the major cause of COPD (225). A novel approach from the Global Lung Initiative (GLI) has also been adopted suggesting that in adults with GLI-defined normal spirometry, the use of a fixed ratio may misclassify individuals as having respiratory impairment (226,227). However, these findings await additional research before clinical translation.

Regardless of the adopted criteria to define COPD, spirometry is an objective measurement of respiratory function and GOLD guidelines favour using the fixed ratio for diagnostic simplicity and consistency. However, novel methods to discriminate COPD from heart failure are urgently needed and will be discussed in *Chapter 5: Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis: The AMICA-AS Study* and in *Chapter 6: Conclusions and Future Work*.

3.1.15 Conclusion

Apparent respiratory dysfunction (COPD-STs) was common and a powerful independent predictor of all-cause mortality in symptomatic severe AS considered for AVR. However, when assessed more accurately in the subgroup selected to perform a spirometry, confirmed respiratory dysfunction (COPD-GOLD) was mild-moderate only, associated with aortic valve treatment choice favouring TAVI, but did not show any prognostic impact in AS. Other spirometry measures linked to heart failure were independent prognostic factors.

In symptomatic AS, COPD-STS and COPD-GOLD are two distinct entities with different prevalence and prognostic impact. COPD-STS has been confirmed useful to risk stratify symptomatic AS but is not a measure of lung disease and is likely associated with heart failure. On the contrary, patients should not be undertreated based on a mild-moderate COPD-GOLD diagnosis which was not prognostic. This discrepancy between apparent and confirmed respiratory dysfunction should be recognised for the optimal evaluation and treatment of symptomatic patients needing cardiac management.

Chapter 4 - Cardiac Function in Aortic Stenosis

HYPOTHESIS AND AIM

- Right ventricular function in aortic stenosis with normal left ventricular ejection fraction is likely involved in the compensatory response to severe AS, given the frequent increased pulmonary afterload induced by the progressive aortic valve obstruction.
- Right ventricular compensation is associated with clinical decompensation in aortic stenosis and normalises when left ventricular afterload is relieved after aortic valve replacement, if the right afterload increase has not reached a permanent stage.
- Right ventricular function impacts on outcome in aortic stenosis at early stages of systolic dysfunction.

The first aim of this chapter was to assess early RV functional change in AS with normal LVEF, its association with clinical decompensation and its reversibility after AVR.

The second aim was to evaluate the association of RV systolic function with all-cause mortality in severe AS.

MATERIALS AND METHODS

This chapter presents two studies designed to answer the above questions: a single-centre cross-sectional/longitudinal study and a multi-centre longitudinal outcome study.

4.1.1 Single-Centre Cross-Sectional and Longitudinal Study

4.1.1.a Study population

Patients with isolated moderate and severe AS were prospectively recruited from the Oxford University Hospitals between January 2013 and January 2016. Eligibility was defined by echocardiography: maximal aortic velocity ≥ 3 m/s or AVA ≤ 1.5 cm² (228). Exclusion criteria were: LVEF $< 55\%$, elevated estimated systolic pulmonary artery pressures (SPAP) defined as a peak tricuspid regurgitation velocity of > 2.9 m/s or any other severe valvular disease. Underlying cardiomyopathies and LV dysfunction were also excluded by CMR. Symptomatic patients with significant coronary artery stenosis ($> 70\%$ luminal diameter) on angiography were excluded.

Twenty-eight age- and sex-matched subjects with no cardiovascular disease were recruited via poster advertisement and served as controls. They had a normal ECG, echocardiography and CMR assessment. Of these, hypertensive controls were defined as those under specific medical treatment for systemic hypertension or with elevated systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) at baseline visit.

The study complied with the Declaration of Helsinki and ethical approval was obtained from the National Research Ethics Service Committee. All subjects gave written informed consent.

4.1.1.b Study protocol

Asymptomatic AS and controls underwent a single baseline research visit. Symptomatic AS patients had a baseline visit plus a follow-up visit at 6 to 12 months after AVR. Each visit

included medical evaluation, blood tests, ECG, a 6MWT, echocardiography and CMR. Symptoms were confirmed on the research 6MWT.

4.1.1.c Cardiac magnetic resonance

CMR imaging was performed with a 1.5 Tesla Siemens Avanto or a 3 Tesla Siemens Trio (Siemens Healthcare, Erlangen, Germany). Cines were recorded using steady-state free precession sequences (229) and used to evaluate biventricular volumes, function, mass according to society of CMR guidelines (230). CMR-tagging ECG-segmented k-space fast gradient echo sequence by spatial modulation of magnetisation was used for LV strain acquisition (231). LGE imaging was acquired after contrast to exclude underlying cardiomyopathies.

Post-processing CMR-TT for RV strain was performed using CVI42 software (Circle Cardiovascular Imaging; version 5.3.4; Calgary, Alberta, Canada). RV tracing excluded slices lacking full myocardium coverage and was checked visually. The most reliable strain parameters were analysed (232). RV circumferential strain was reported since transverse shortening is the least influenced by directional motion, which mostly occurs in the RV longitudinal plane, and by cardiac surgery. Two blinded observers analysed the images. Intra and inter-observer agreement was assessed in 20 random AS and controls. LV mass regression was calculated as a percentage of baseline LV mass: $[(LV \text{ mass pre-AVR} - LV \text{ mass post-AVR}) / LV \text{ mass pre-AVR}] \times 100$.

4.1.1.d Echocardiography

Transthoracic echocardiography was performed using IE33 (Philips Medical Systems, Best, Netherlands) to evaluate AS grading parameters, LV diastology, and right-side parameters according to recent guidelines (148,233,234).

4.1.1.e Statistical analysis

Data are expressed as mean $\pm$ standard deviation for continuous variables, or numbers and percentages for categorical variables. Comparisons between groups for continuous normally distributed variables were performed using one-way ANOVA with post-hoc Bonferroni test. The Fisher exact test was used to compare proportions. Comparisons between pre- and post-AVR were obtained by paired Student T-tests. The relationships between variables were investigated using simple Pearson's linear regressions and standard multiple regression models. Receiver operating characteristic (ROC) curves were used to assess diagnostic accuracy.

4.1.2 Multi-Centre Longitudinal Outcome Study

4.1.2.a Study population

Patients with severe AS referred and listed for valve intervention at six cardiothoracic surgical centres (John Radcliffe Hospital, Oxford; Brompton Hospital and Barts Heart Centre, London; Edinburgh Heart Centre, Edinburgh; Glenfield Hospital, Leicester; Leeds Teaching Hospitals NHS Trust, Leeds), constituted the study population of the multi-centre longitudinal, observational outcome study. Patients were prospectively recruited between January 2003 and May 2015 after evaluation by the multi-disciplinary heart team. Patients from the Oxford single-centre study were included in the multi-centre study. The study was approved by the

UK National Research Ethics Service (13/NW/0832), conformed to the principles of the Helsinki Declaration, and patients gave written informed consent. The primary endpoint was all-cause mortality. Cardiovascular disease-related mortality, as defined by diagnosis on the death certificate, was also assessed. Inclusion criteria were patients >18 years with severe AS (one of: AVA < 1cm², peak trans-aortic pressure gradient >64mmHg, mean pressure gradient >40 mmHg, peak trans-aortic velocity >4m/s). All patients had undergone CMR imaging for research purposes. Study design is summarised in

Figure 4-1.

4.1.2.b Echocardiography and Cardiac Magnetic Resonance Image Acquisition

Echocardiographic parameters were acquired clinically following the guidelines for assessment of AS severity recommended by the American and European Societies of Echocardiography (228). CMR was performed on 1.5 T and 3T scanners using standardised protocols. In brief, cine images were acquired in long-axis planes and contiguous short-axis slices for ventricular volumes, mass and function. Phase-contrast velocity-encoded images were acquired for valve parameters and the LGE technique was used to identify myocardial scar, as previously described (235).

4.1.2.c Data Management and Outcomes

Anonymised clinical and imaging DICOM data were collected and managed using REDCap (Research Electronic Data Capture) software (236). All deaths were identified through the UK National Health Service National Spine Database. Cardiovascular mortality was established from the official death certificates, which listed up to three causes of death, and were adjudicated by two readers blinded to clinical data. Cardiovascular death was defined when

attributable to myocardial ischaemia and infarction, heart failure, cardiac arrest due to arrhythmia or unknown cause, or cerebrovascular accident.

4.1.2.d Data Analysis

All CMR scans were centralised and re-reported using CVI42 software (Circle Calgary, Alberta, Canada) in core-lab fashion by experienced readers blinded to clinical parameters. Each centre analysed a single component of the CMR scan, according to standard operating procedure (SOP, reported in Appendix) after a period of training and reproducibility evaluation. LV volumes and mass analyses were performed by manual contouring of the endo- and epicardial borders at end-diastole and end-systole (237). Left atrial area and length at end-systole were measured in the horizontal and vertical long axis views for left atrial volumes by the biplane area length method and indexed. Aortic flow for regurgitant volume and fraction was quantified from phase-contrast velocity-encoded images (238). LGE was categorised by two observers into three patterns (none, infarct or non-infarct patterns) and quantified with the full-width-at-half-maximum method as LV percentage (235).

4.1.2.e Statistical Analysis

Distribution of data was visualised with histograms and assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean $\pm$ standard deviation or as median and interquartile range; categorical variables, as counts and percent. Baseline characteristics of participants were compared using the unpaired Student *t*-test, Mann-Whitney-Wilcoxon test, χ^2 or Fisher exact tests, as appropriate. Survival in patients according to RV systolic function was evaluated using the Kaplan-Meier method and compared among groups using the log-rank test. HR were expressed as mean $\pm$ 95% CI. All clinical parameters were proposed for inclusion in a

univariate Cox proportional hazards model. The relevant univariable predictors with a p value <0.10 were entered in the multivariable models with a forward stepwise procedure.

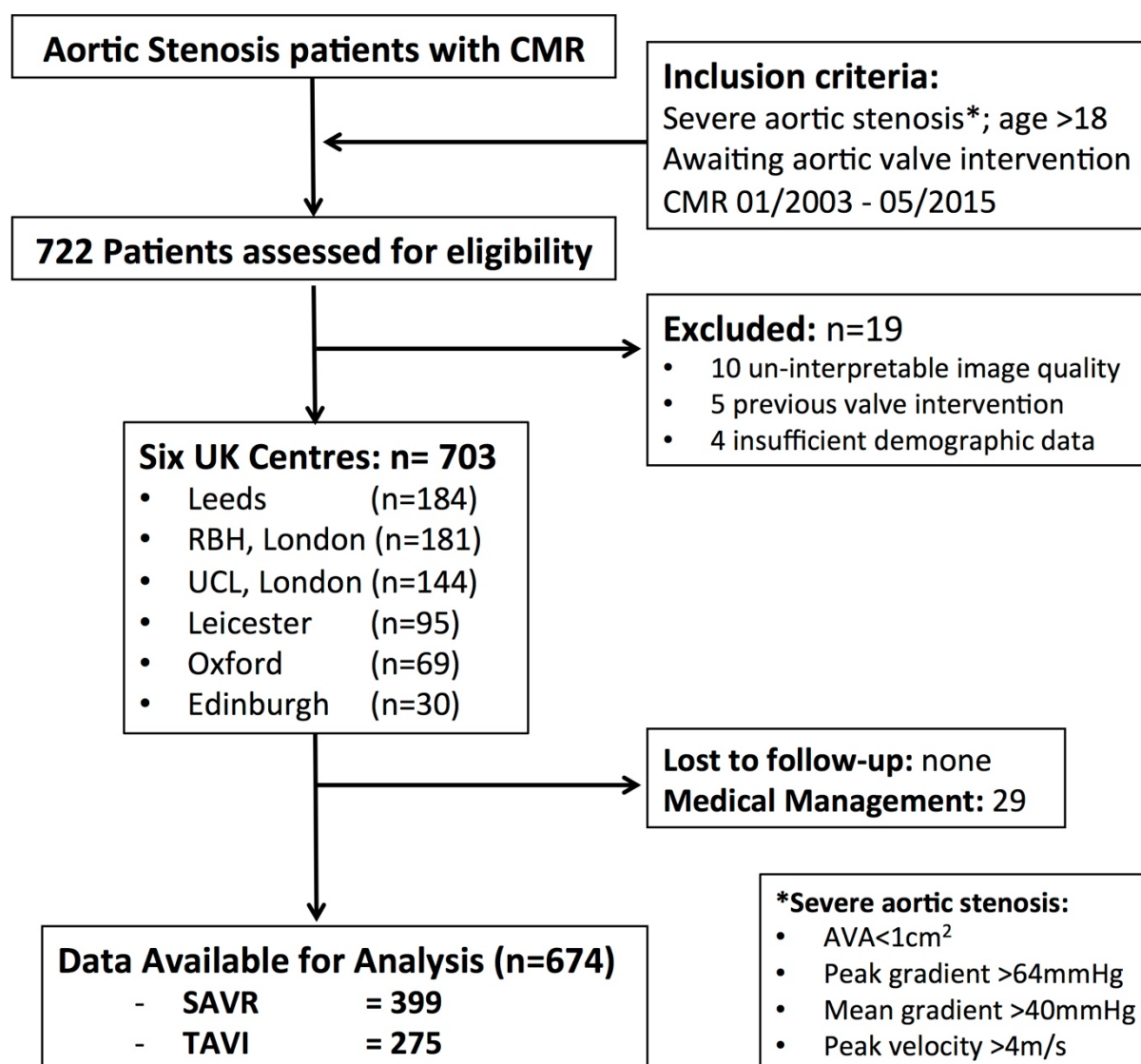


Figure 4-1. Multi-centre observational longitudinal outcome study diagram.

Patients were prospectively recruited after evaluation by the multi-disciplinary heart team. Inclusion criteria were patients >18 years with *severe AS (one of: aortic valve area [AVA]<1cm², peak pressure gradient >64mmHg, mean pressure gradient >40mmHg, peak velocity >4m/s) who had undergone CMR imaging for clinical or research purposes. AVA: aortic valve area; CMR: cardiovascular magnetic resonance; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; RBH: Royal Brompton Hospital; UCL: University College London.

Reproduced from Musa TA et al. Circulation Nov 2018 (239), Rigolli M. co-authored the article.

RESULTS

4.1.3 Single-Centre Cross-Sectional Study

4.1.3.a Baseline Clinical and Imaging Characteristics of the Study Population

A total of 121 participants were identified: 93 AS and 28 controls of similar age and gender. Of these, 2 did not complete the visit due to claustrophobia and 11 were excluded: 3 had suboptimal CMR images due to poor breath-holding, 3 discordant aortic valve parameters, 4 underlying ischemic disease and/or LV dysfunction, one mild AS only. Baseline clinical and imaging characteristics are summarised in Table 4-1. CMR parameters for cross-sectional groups affected by worsening AS are displayed in Table 4-2.

Table 4-1. Single-centre baseline clinical and imaging characteristics.

	Aortic Stenosis (n=80)			Controls (n=28)	P-value
	Symptomatic	Asymptomatic			
	Severe (n=33)	Severe (n=24)	Moderate (n=23)		
Age, years	69 ± 8	69 ± 8	69 ± 7	66 ± 5	0.29
Male, n (%)	22 (67)	15 (62)	18 (78)	15 (54)	0.32
Body surface area, m²	2.0 ± 0.2	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.10
Heart rate, bpm	66 ± 9	63 ± 10	71 ± 13*	62 ± 9	0.02
Systolic BP, mmHg	135 ± 17	132 ± 13	140 ± 21	141 ± 19	0.34
Diastolic BP, mmHg	75 ± 10	75 ± 10	77 ± 8	81 ± 9	0.18
Peak aortic velocity - echo, m/s	4.6 ± 0.6§	4.2 ± 0.5§	3.3 ± 0.4	1.2 ± 0.1	<0.001
Mean aortic gradient - echo, mmHg	54 ± 14#	54 ± 20#	36 ± 10	- (<20)	<0.001
AVA - CMR, cm²	0.8 ± 0.1#	0.8 ± 0.1#	1.3 ± 0.2	- (≥2)	<0.001
E/E’ ratio - echo	14 ± 5§	13 ± 5**	12 ± 5**	8 ± 2	<0.001
TAPSE, mm - echo	24 ± 6	25 ± 4	23 ± 4	22 ± 3	0.44
Estimated sPAP, mmHg - echo	26 ± 11	27 ± 7	29 ± 7	25 ± 5	0.72
Diuretic use	4 (12)	2 (8)	2 (9)	0	0.33
<i>Symptomatic status, n (%)</i>					
Exertional dyspnoea	23 (70)	-	-	-	-
Angina	9 (27)	-	-	-	-
Syncope	1 (33)	-	-	-	-
NYHA functional class 1-2	27 (82)	-	-	-	-

Note: Values are expressed as mean ± standard deviation, or percentages. P-values for continuous variables are for one-way ANOVA with post hoc Bonferroni correction for differences between groups: * p<0.05 vs controls; † p<0.001 vs controls and p<0.01 vs moderate; ‡ p<0.05 vs asymptomatic severe; § p<0.001 vs controls and vs moderate; ||p<0.001 vs controls, # p<0.001 vs moderate; ** p<0.01 vs controls. AS: aortic stenosis; AVA: aortic valve area; CMR: cardiovascular magnetic resonance; NYHA: New York Heart Association functional class; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure.

Table 4-2. Single-centre cardiovascular magnetic imaging parameters.

	Aortic Stenosis			Controls	P-value
	Symptomatic Severe	Asymptomatic Severe	Moderate		
<i>Left-side parameters</i>					
LV EDV, mL	146 ± 47	149 ± 29	144 ± 33	143 ± 30	0.95
LV ESV, mL	43 ± 20	48 ± 15	51 ± 17	46 ± 14	0.38
LV SV, mL	103 ± 32	98 ± 19	93 ± 23	97 ± 20	0.50
LV EF, %	71 ± 7*	67 ± 8	65 ± 6	68 ± 6	0.02
LV mass index, g/m ²	92 ± 30 ^{†*}	91 ± 26 [†]	74 ± 18 [‡]	55 ± 11	<0.001
IVS max, mm	16 ± 2 ^{**}	16 ± 3 [†]	14 ± 2 [†]	10 ± 2	<0.001
LV strain, circ %	-17 ± 2 [‡]	-17 ± 4	-17 ± 1	-19 ± 3	0.04
LA volume, mL	88 ± 28	86 ± 24	88 ± 22	79 ± 23	0.49
<i>Right-side parameters</i>					
RV EDV, mL	127 ± 36 [‡]	130 ± 29	139 ± 35	151 ± 35	0.04
RV ESV, mL	32 ± 10 ^{†§}	42 ± 15 [‡]	53 ± 14 [#]	54 ± 19	<0.001
RV SV, mL	95 ± 28	88 ± 19	87 ± 23	97 ± 20	0.31
RV EF, %	75 ± 4 ^{†§}	68 ± 7 ^{§#}	62 ± 4 [#]	65 ± 6	<0.001
RV mass, g	29 ± 5 [§]	27 ± 5	28 ± 7 ^{†#}	22 ± 5	<0.001
RV strain, circ %	-17 ± 4 [‡]	-16 ± 4	-15 ± 4	-14 ± 3	0.04
RA volume, mL	75 ± 22	72 ± 24	76 ± 23	67 ± 23	0.49

Note: Values are expressed as mean ± standard deviation, or percentages. P-values are for one-way ANOVA with post hoc Bonferroni correction for differences between groups: * p<0.05 vs moderate; † p<0.001 vs controls; ‡ p<0.05 vs controls; § p<0.001 vs moderate; ||p<0.001 vs severe asymptomatic, # p<0.001 vs severe symptomatic. LV: left ventricular; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; IVS: interventricular septum, circ: circumferential; LA: left atrium; RV: right ventricle; RA: right atrium.

4.1.3.b Right Ventricular Systolic Function in Aortic Stenosis

With worsening AS categories, RVEF significantly increased (Figure 4-2). Symptomatic AS had the highest RVEF ($75 \pm 4\%$, $p < 0.001$ compared to all other groups), with almost no overlap in values with less significant afterload categories, including asymptomatic but equally severe aortic stenosis (Table 4-3). RVEF in moderate AS was similar to hypertensive controls ($62 \pm 4\%$ and $61 \pm 4\%$ respectively).

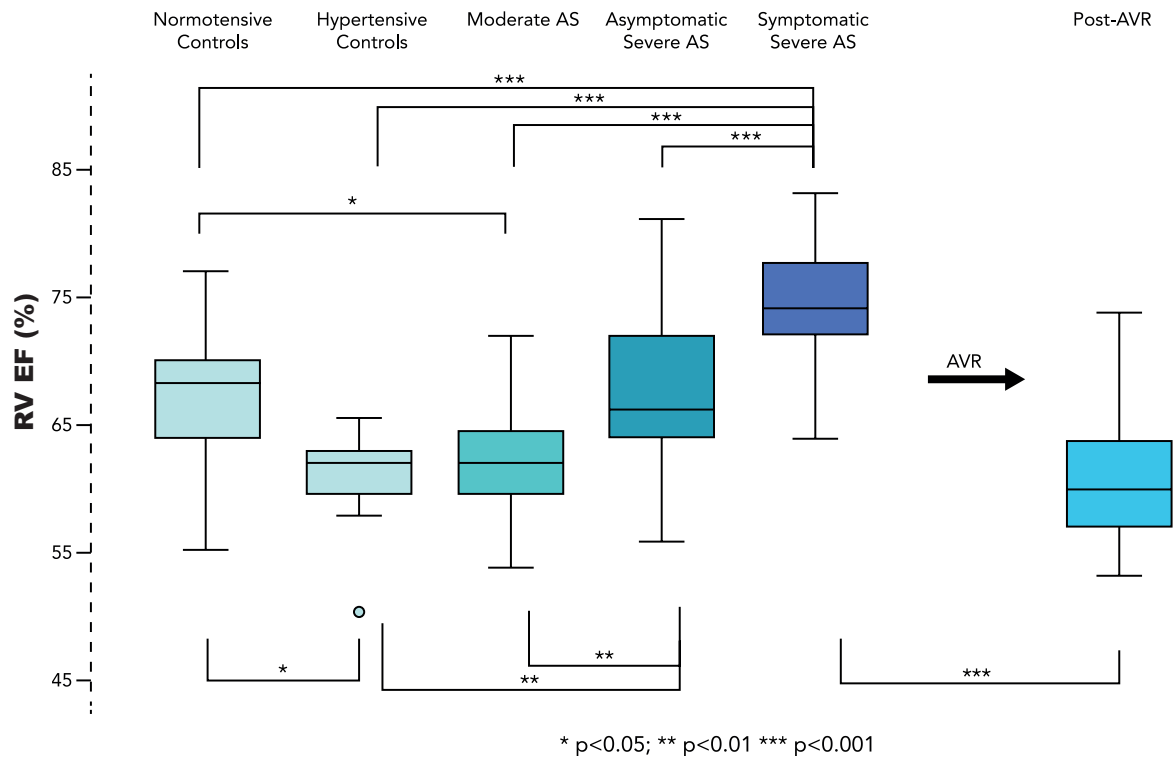


Figure 4-2. RVEF differences in the study groups.

RVEF differences between normotensive controls, hypertensive controls (higher systemic afterload), worsening degrees of AS (moderate, severe asymptomatic and severe symptomatic), and follow-up patients after AVR with afterload relief. Worsening LV afterload categories showed significant RV systolic function increases across the groups. Following afterload relief, the RVEF reversal towards normal supports the hypothesis of a compensatory hyperdynamic RV, which is no longer required post-surgery. P-values are for one-way ANOVA with post hoc Bonferroni correction for differences between groups.

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Table 4-3. Differences in severe aortic stenosis according to symptoms.

	Severe AS		
	Symptomatic	Asymptomatic	P-value
Age	69 ± 8	69 ± 8	0.98
AVA – CMR, cm ²	0.8 ± 0.1	0.8 ± 0.1	0.96
Mean aortic gradient – echo, mmHg	54 ± 14	54 ± 20	0.36
E/E' ratio - echo	14 ± 5	13 ± 5	0.35
LV SV – CMR, mL	103 ± 32	98 ± 19	0.49
LV EF – CMR, %	71 ± 7	67 ± 8	0.08
<i>Right-side parameters, CMR</i>			
RV EDV, mL	127 ± 36	130 ± 29	0.67
RV ESV, mL	32 ± 10	42 ± 15	0.004
RV SV, mL	95 ± 28	88 ± 19	0.2
RV EF, %	75 ± 4	68 ± 7	<0.001
RV strain, circ %	-17 ± 4	-16 ± 4	0.05

Note: Values are expressed as mean ± standard deviation, or percentages. P-values for continuous variables are for unpaired Student T-tests. AVA: aortic valve area; CMR: cardiovascular magnetic resonance; E/E': septal e/e' ratio; LV: left ventricular; RV: right ventricle EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; circ: circumferential.

RV end systolic volume (RVESV) gradually decreased with increasing LV afterload groups (Figure 4-3, Table 4-2). RV strain was assessed in terms of longitudinal, circumferential and radial component. The most significant differences between groups were noted in RV circumferential strain (Figure 4-3, Table 4-2). RV strain was also significantly different between symptomatic and asymptomatic patients with same degree of valve narrowing (Table 4-3). CMR-TT demonstrated a good intra and inter-observer agreement in all three components, as shown by the intra-class coefficients for intra and inter-observer: longitudinal: 0.91, 0.78; circumferential: 0.87, 0.78; radial: 0.79, 0.73.

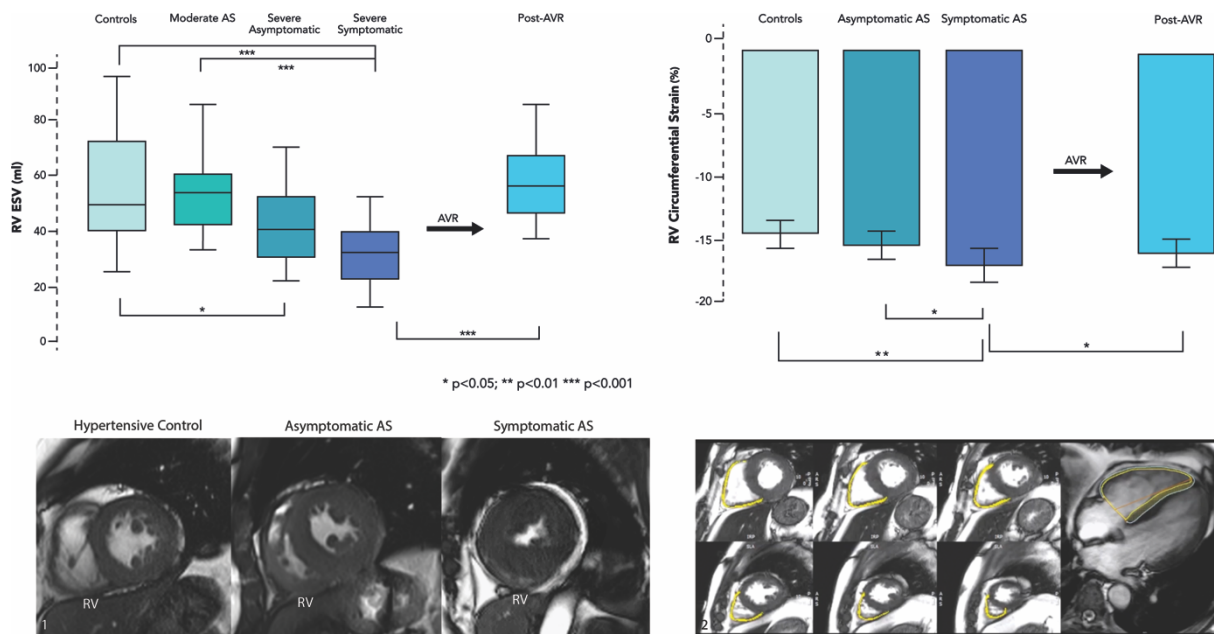


Figure 4-3. Differences in RVESV and RV strain between controls, worsening aortic stenosis degrees and follow-up after AVR.

Worsening LV afterload by progressive AV obstruction was associated with a hyperactive RV with increasingly smaller end-systolic cavity and higher strain values. This was reversed towards normal following AVR. *Superior panel:* RVESV and RV strain differences between groups. P-values are for one-way ANOVA with post hoc Bonferroni correction. *Left inferior panel:* CMR end-systolic mid short-axis slices in three subjects with different systemic afterloads. Smaller RV end-systolic cavity are present with worsening degrees of LV afterload. *Right inferior panel:* RV strain assessment by tissue-tracking with automatic RV wall recognition.

4.1.3.c Association between Right Ventricular Systolic Function and Aortic Valve Obstruction

RVEF was associated with the degree of aortic valve obstruction (

Figure 4-4). RVEF was also associated with symptoms of valve obstruction in AS. The relationship between RVEF and symptoms was the strongest ($r=0.66$, $p<0.001$) by point-biserial correlation. Preliminary analyses showed that there were no outliers; RVEF was normally distributed (Shapiro-Wilk's test $p > 0.05$); and there was homogeneity of variances (Levene's test for equality of variances $p > 0.05$). RVEF accounted for 44% of the variability in symptomatic status (coefficient of determination $r_{pb}^2 = 0.436$). In addition, a binomial logistic regression was performed to ascertain the effects of RVEF on the likelihood that participants with AS had symptoms of valve obstruction. The logistic regression was statistically significant, $\chi^2(4) = 41.884$, $p < .0005$. The variable explained 57% (Nagelkerke R^2) of the variance in symptoms and correctly classified 81.6% of cases. Sensitivity was 78.1%, specificity was 84.1%. Increasing values of RVEF were associated with an increased likelihood of exhibiting symptoms: each RVEF increase of one percentage point incremented the odds of being symptomatic by 1.35. A linear regression was performed to evaluate the relationship between RVEF and symptomatic status (NYHA functional class). RVEF accounted for 24% of the variation in symptomatic status with $r = 0.49$, adjusted $r^2 = 0.24$, a medium size effect. RVEF statistically significantly correlated with symptomatic status, $F(1, 74) = 23.238$, $p < .0005$.

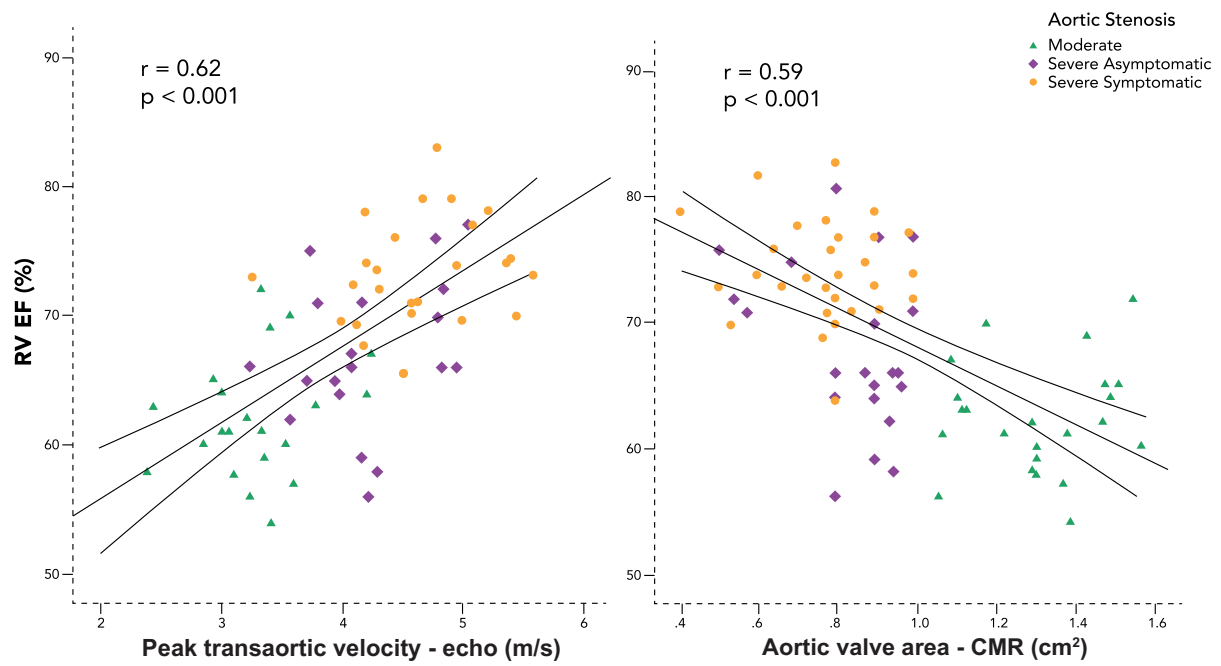


Figure 4-4. RVEF association with aortic stenosis degree.

RVEF was strongly correlated to multi-imaging parameters of AS severity. These associations suggest a RV compensatory role as part of the physiological response to aortic valve disease.

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RVEF was positively correlated with trans-aortic peak velocity on echo ($r=0.62$, $p<0.001$), circulating BNP values ($r=0.51$, $p=0.01$), functional class (NYHA $r=0.49$, $p<0.001$), and inversely with aortic valve area on CMR planimetry ($r=-0.59$, $p<0.001$). In addition, RV function was associated with LV parameters of increased afterload response: RVEF correlated with LV systolic function (LVEF: $r=0.42$, $p<0.001$, LV strain: $r=0.33$, $p<0.003$) and LV hypertrophy (LV mass index: $r=0.39$, $p=0.001$; septal thickness: $r=0.31$, $p=0.006$).

ROC analysis indicated an optimal cut-off of RVEF $\geq 71\%$ to identify symptoms (area under the curve 0.89, CI 0.81-0.96, $p<0.001$) (Figure 4-5). This threshold showed the best balance between negative predictive value (NPV) and positive predictive values (PPV): NPV 90% (95% CI, 78 – 96%), PPV 76% (95% CI, 63 – 85%). A lower threshold ($\geq 63\%$) reached NPV of 100%, with all symptomatic patients presenting a RVEF over or equal to 63%.

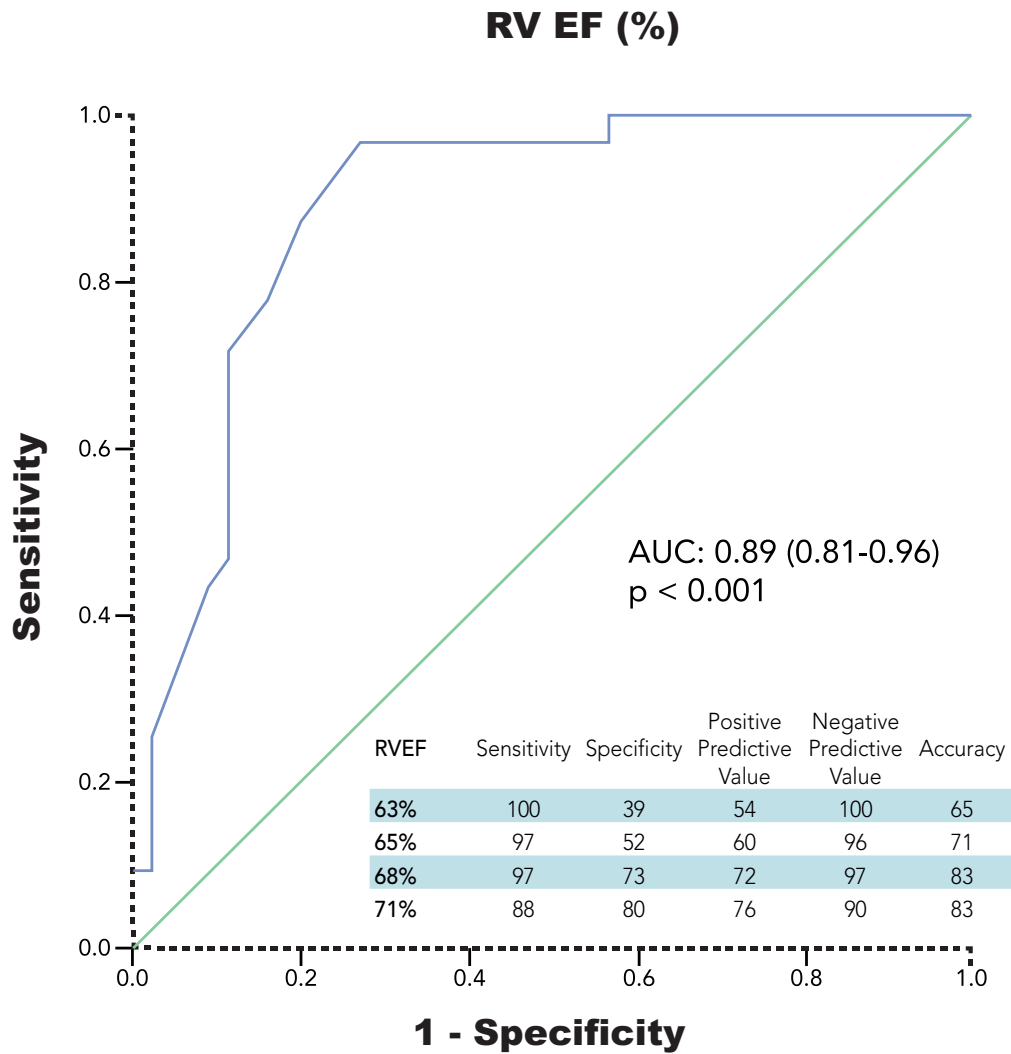


Figure 4-5. RVEF thresholds to detect symptoms in aortic stenosis.

Receiver operator curve (ROC) analyses in participants affected by severe AS indicated an optimal cut-off of RVEF $\geq$ 71% to identify symptoms of valve obstruction with an area under the curve (AUC) of 0.89, $p < 0.001$. Other RVEF thresholds for symptoms are also shown with corresponding sensitivity, specificity, positive and negative predictive values, and accuracy.

4.1.3.d Right Ventricular Systolic Function in Aortic Stenosis

On multivariate linear regression analysis, aortic valve obstruction degree, symptomatic status, LV mass and function were all independent predictors of RVEF (Table 4-4). The strongest independent predictors of RVEF were symptoms of valve obstruction, AVA and LVEF. The best predictive model for RVEF accounted for both AS degree and LV afterload response ($r=0.82$, $p<0.001$).

Table 4-4. RVEF associations with other characteristics in aortic stenosis.

<i>Univariable linear regression analysis</i>			
	r	r²	sig.
Age, years	0.004	0	0.97
Gender, male (%)	0.14	0.18	0.17
Body surface area, m ²	0.13	0.18	0.18
Peak aortic velocity, m/s (echo)	0.62	0.39	<0.001
AVA, cm ² (CMR)	-0.59	0.35	<0.001
Symptomatic status	0.66	0.43	<0.001
NYHA functional class	0.49	0.24	<0.001
BNP, pg/mL	0.51	0.26	<0.01
LV EF, % (CMR)	0.42	0.18	<0.001
LV GLS, % (CMR)	0.33	0.11	0.035
LV E/E' (echo)	0.18	0.03	0.16
LV mass index, g/m ² (CMR)	0.40	0.16	0.001
IVS max, mm (CMR)	0.31	0.10	0.006
<i>Multivariable standard regression analysis</i>			
<i>Model 1, AV and LV: r= 0.82, r²=0.68, p<0.001</i>	B	SE	sig
AVA, cm ²	-8.5	2.3	<0.001
Symptomatic status	4.7	1.3	0.001
LV EF, %	0.3	0.08	<0.001
LV mass index, g/m ²	0.07	0.02	0.001
<i>Model 2, AV: r= 0.77, r²=0.59, p<0.001</i>			
Peak aortic velocity, m/s	2.3	1.2	0.06
AVA, cm ²	-4.4	3.1	0.16
Symptomatic status	7.8	1.8	<0.001
<i>Model 3, LV: r= 0.65, r²=0.42, p<0.001</i>			
LV EF, %	0.4	0.09	<0.001
LV E/E'	0.3	0.1	0.05
LV mass index, g/m ²	0.04	0.01	0.001

AVA: aortic valve area; NYHA: New York Heart association; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; LVGLD: left ventricular global longitudinal strain; CMR: cardiovascular magnetic resonance; IVS: interventricular septum; AV: aortic valve

4.1.4 Single-centre Longitudinal Study

4.1.4.a Follow-Up After Aortic Valve Replacement

Of the symptomatic AS participants, 21 (64%) underwent CMR imaging 8 ± 2 months after AVR. There was a significant tendency to restore RV volumes and function values similar to non-obstructive AS and controls (Table 4-5, Figure 4-2, Figure 4-3). In particular, RVESV increased meaningfully after AVR ($p=0.001$), resulting in a restored lower RVEF with values similar to non-significant AS.

Baseline RVEF was the strongest statistical predictor of LV mass regression degree after SAVR ($r=0.61$, $p=0.01$), as shown in Figure 4-6. RVEF was also the only significant independent predictor of LV mass recovery in the multivariable regression accounting for other significant univariable predictor. RVEF remained independent in all models. The strongest predictive model of left mass regression accounted for RVEF and LV mass pre-AVR ($r=0.76$, $p=0.002$). Univariable and multivariable linear regressions are presented in Table 4-6.

Table 4-5. CMR imaging parameters pre- and post-AVR.

	Follow-up (n = 21)		P-value
	Pre-AVR	Post-AVR	
<i>Left-side</i>			
LV EDV, mL	138 ± 46	136 ± 28	0.79
LV ESV, mL	38 ± 15	52 ± 16	<0.001
LV SV, mL	101 ± 33	85 ± 18	0.008
LV EF, %	73 ± 5	62 ± 7	<0.001
LV mass, g	184 ± 72	132 ± 43	<0.001
LA volume, mL	83 ± 28	68 ± 23	0.001
<i>Right-side</i>			
RV EDV, mL	123 ± 36	135 ± 30	0.06
RV ESV, mL	32 ± 12	54 ± 18	<0.001
RV SV, mL	92 ± 26	81 ± 16	0.07
RV EF, %	75 ± 4	61 ± 7	<0.001
RV strain, circ %	-17 ± 4	-16 ± 4	0.05
RV mass, g	28 ± 5	29 ± 5	0.68
RA volume, mL	75 ± 21	62 ± 13	0.004

Note: Values are expressed as mean ± standard deviation, or percentages. P-values are for paired Student T-tests. AS: aortic stenosis; AVR: aortic valve replacement; LV: left ventricular; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; circ: circumferential; LA: left atrium; RV: right ventricle; RA: right atrium.

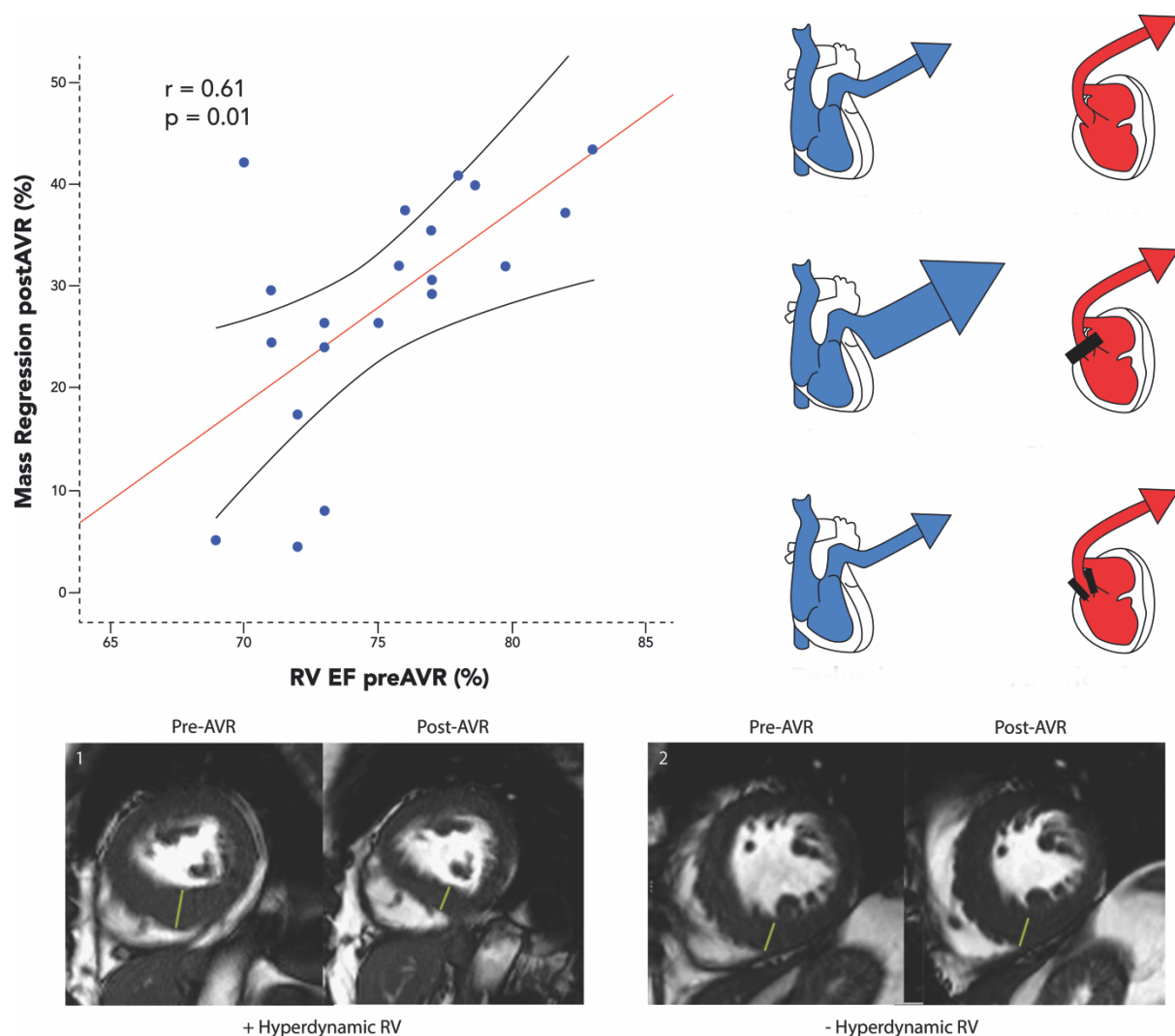


Figure 4-6. RVEF association with LV mass recovery and proposed mechanism.

Baseline RVEF was strongly associated with post-operative LV mass recovery degree. The LV may be aided by compensatory increased RV contractility to augment LV filling and maintain stroke volume across the valve obstruction (graphic). *Lower panel 1:* an example of symptomatic AS patient with highly hyperdynamic RV (RVEF>75%) manifesting a good LV mass regression (over 50%) post-AVR. *Lower panel 2:* Another participant with a less hyperdynamic RV not showing any significant LV mass regression after LV afterload relief.

Table 4-6. Predictors of LV mass regression post-AVR.

<i>Univariable linear regression analysis</i>			
	r	r²	sig.
Age, years	-0.47	0.22	0.05
Gender, male	0.34	0.12	0.16
Body surface area, m ²	0.30	0.09	0.22
Diuretic use	0.11	0.01	0.81
Beta-blocker use	0.49	0.24	0.04
Statin use	0.51	0.26	0.03
Peak aortic velocity, m/s (echo)	0.16	0.03	0.73
Mean aortic gradient, mmHg (echo)	0.18	0.03	0.69
Aortic valve area, cm ² (CMR)	0.14	0.02	0.59
LV EF, % (CMR)	0.18	0.03	0.48
LV E/E' (echo)	0.13	0.02	0.63
LV mass index, g/m ² (CMR)	0.54	0.30	0.02
RV EF, % (CMR)	0.61	0.37	0.01
<i>Multivariable standard regression analysis</i>			
<i>Model 1: r = 0.84, r² = 0.71, p = 0.003</i>	B	SE	sig
Age, years	-0.5	0.2	0.11
Beta-blockers use	-0.7	5.6	0.90
Statin use	-4.2	4.4	0.36
LV mass pre-AVR, g	0.04	0.03	0.31
RV EF, %	1.9	0.6	0.01
<i>Model 2: r = 0.83, r² = 0.68, p = 0.001</i>			
Age, years	-0.7	0.2	0.003
Beta-blocker use	-2.8	5.4	0.61
RV EF, %	2.0	0.6	0.007
<i>Model 3: r = 0.76, r² = 0.58, p = 0.002</i>			
LV mass pre-AVR, g	0.08	0.03	0.02
RV EF, %	1.8	0.5	0.004

CMR: cardiovascular magnetic resonance; LVEF: left ventricular ejection fraction; RVEF: right ventricular ejection fraction; AVR: aortic valve replacement.

4.1.5 Multi-centre Longitudinal Outcome Study

4.1.5.a Baseline Clinical and Imaging Characteristics of the Study Population

Baseline characteristics of the 674 patients included are shown in Table 4-7. Median age was 75 years, 63% were male, mean AVA $0.72 \pm 0.24 \text{ cm}^2$. LV myocardial scar, as assessed by LGE, was present in 51% of patients, in a 2:1 ratio between non-infarct (33%) and infarct pattern scar (18%). RV systolic dysfunction (RVSD) was present in 16% of AS patients undergoing AVR and 16% of patients had at least moderately elevated SPAP (30-55mmHg by echocardiography).

Patients with RVSD were older, more treated with TAVI and showing an overall higher burden of co-morbidities (atrial fibrillation, lower BMI) and risk scores. Of these, almost half (48%) had increased SPAP, 65% had LGE and most patients manifested a degree of LV systolic dysfunction (median LVEF 40%). In Table 4-8, right side imaging characteristics are stratified according to LVEF and SPAP.

Table 4-7. Multi-centre baseline clinical and imaging characteristics.

		All patients (n=674)	No RVSD* (n=559) §	RVSD* (n=107) §	P-value
Clinical characteristics					
Age, years		75 (66 - 80)	74 (65 – 80)	76 (69 – 82)	0.028
Intervention (%)	SAVR†	399 (59.2)	346 (61.9)	46 (43.0)	<0.001
	TAVR	275 (40.8)	213 (38.1)	61 (57.0)	
Male, No. (%)		425 (63)	346 (61.9)	74 (69.1)	0.19
BMI, Kg/m²		27.6 ± 5.1	27.8 ± 5.0	26.3 ± 5.1	0.008
Atrial Fibrillation, No. (%)		84 (12.5)	50 (8.9)	34 (31.8)	<0.001
Diabetes Mellitus, No. (%)		146 (21.7)	115 (20.1)	28 (26.2)	0.25
Hypertension, No. (%)		358 (53.1)	302 (54.0)	49 (45.8)	0.14
Bicuspid Aortic Valve, No. (%)§		149 (22.1)	125 (22.3)	22 (20.6)	0.78
Previous PCI/CABG, No. (%)		115 (17.1)	89 (15.9)	25 (23.4)	0.15
History of MI, No. (%)§		73 (10.8)	56 (10.0)	16 (15.0)	0.18
STS Mortality Risk score, %		1.75 (1.09 - 2.97)	1.65 (1.02 – 2.92)	2.05 (1.34 – 3.19)	0.01
EuroSCORE II, %		1.81 (1.01 - 3.38)	1.60 (0.96 – 3.06)	3.00 (1.54 – 5.43)	<0.001
NYHA Functional Class, No. (%)§					
	I/II	339 (50.3)	297 (53.1)	38 (35.5)	0.01
	III/IV	270 (40.1)	214 (38.3)	53 (49.5)	
Medications, No. (%)§					
	ACE or ARB	262 (38.9)	210 (37.5)	46 (43.0)	0.37
	β-blocker	240 (35.6)	191 (34.2)	46 (43.0)	0.10
	Aldosterone	36 (5.3)	23 (4.1)	13 (12.1)	0.002
	Statin	406 (60.2)	339 (60.1)	61 (57.0)	0.39
Echo data					
Mean aortic valve gradient, mmHg		46 (38 – 56)	47 (39 - 58)	42 (32 - 52)	<0.001
Peak aortic valve gradient, mmHg		78 (66 – 96)	79 (67 - 98)	70 (57 - 89)	<0.001
AVA, cm²		0.72 ± 0.24	0.73 ± 0.24	0.69 ± 0.23	0.17
SPAP, No. (%)§ Normal ≤ 30mmHg		316 (46.9)	284 (50.8)	29 (27.1)	<0.001
	Moderate 31-55mmHg	80 (11.9)	55 (9.8)	22 (20.6)	
	Severe >55mmHg	30 (4.5)	21 (3.7)	9 (8.4)	
CMR data					
LV EDV indexed, mL/m²		80 (67 – 96)	78 (66 - 92)	95 (74 - 118)	<0.001
LV ESV indexed, mL/m²		30 (22 – 45)	29 (21 - 39)	56 (34 - 81)	<0.001
LV SV indexed, mL/m²		47 ± 11	48 ± 11	39 ± 12	<0.001
LV EF, %		61 (52 – 68)	63 (56 - 69)	40 (29 - 53)	<0.001
LV mass index, g/m²		42 (35.3 – 52.1)	42 (35 - 51)	45 (37 - 56)	0.12
LA volume indexed, mL/m²		53 (41 – 67)	52 (41 - 65)	62 (49 - 83)	<0.001
LGE present, No. (%)		341 (50.6)	270 (48.3)	70 (65.4)	<0.001
	Non-infarct-pattern, No. (%)	222 (32.9)	189 (33.8)	33 (30.8)	
	Infarct-pattern, No. (%)	119 (17.7)	81 (14.5)	37 (34.6)	
RV EDV indexed, mL/m²		67 (59 – 81)	66 (58 - 77)	79 (63 - 96)	<0.001
RV ESV indexed, mL/m²		24 (18 – 31)	22 (17 - 28)	40 (32 - 50)	<0.001
RV SV indexed, mL/m²		44 ± 11	45 ± 10	37 ± 10	<0.001
RV EF, %		65 (58 – 71)	66 (62 - 72)	48 (43 - 52)	<0.001

Note: normally distributed continuous variables are expressed as mean $\pm$ standard deviation; nonparametric continuous variables are expressed as median | interquartile range; categorical variables are expressed as counts (percent). *RVSD defined as RVEF on CMR $<55\%$. § denotes that this variable of counts contains missing data, † refers to all SAVR: of these 69 patients (17.3%) underwent SAVR+CABG. p-values are for unpaired Student t-test for normally distributed continuous variables, Mann-Whitney-Wilcoxon test for nonparametric continuous variables, and Pearson's Chi-squared test for categorical variables. ARB, angiotensin receptor blocker; AVA, aortic valve area; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LA: left atrium; LGE, late gadolinium enhancement; LV, left ventricle; MI, myocardial infarction; No., numbers; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; RV, right ventricle; SAVR, surgical aortic valve replacement; SV: stroke volume, TAVR, transcatheter aortic valve replacement.

Table 4-8. **Right heart parameters according to LVEF and pulmonary pressures.**

	Normal	Reduced*	<i>p</i> -	Normal	Increased [#]	<i>p</i> -
	LVEF	LVEF	value	SPAP	SPAP	value
	(n=467)	(n=200)		(n=317)	(n=110)	
Right heart parameters						
RV EDV, mL/m ²	67 (58 – 77)	71 (60 – 75)	0.001	67 (59 – 77)	71 (58 – 85)	0.08
RV ESV, mL/m ²	22 (17 – 28)	29 (21 – 41)	<0.001	23 (18 – 29)	27 (19 – 38)	0.001
RV SV indexed, mL/m ²	45 ± 11	41 ± 11	0.001	44 ± 10	44 ± 13	0.49
RV EF, %	66 (61 – 72)	58 (48 – 66)	<0.001	65 (60 – 72)	62 (53 – 70)	<0.001
RV/LV afterload coupling	1.41 ± 0.55	1.03 ± 0.45	<0.001	1.41 ± 0.55	1.01 ± 0.59	<0.001
RV/PA coupling	57 (18 – 67)	27 (16 – 59)	<0.001	65 (60 – 72)	27 (22 – 33)	<0.001

Note: *Reduced LVEF defined as LVEF on CMR <55%; [#]Increased PASP defined as PASP on echo > 30 mmHg. RV/LV afterload coupling: new index of RV coupling to the degree of LV afterload measured as RVEF on CMR divided by LA volume indexed. RV/PA coupling: new index of RV coupling to pulmonary artery afterload measured as RVEF on CMR divided by SPAP class on echo (1 for normal SPAP, 2 for moderate pulmonary hypertension, 3 for severe pulmonary hypertension). P-values are for unpaired Student t-test for normally distributed continuous variables, Mann-Whitney-Wilcoxon test for nonparametric continuous variables.

4.1.5.b RV systolic function associations in severe aortic stenosis

Simple linear regressions were run to assess RVEF variations according to baseline clinical and imaging characteristics. Measure of aortic valve disease and LV systolic and diastolic function were significant at the univariable regression analyses (Table 4-9).

A multiple linear regression was then run. The maximal model statistically significantly predicted RVEF ($r=0.59$, $r^2=0.34$, $p<0.0001$). From this model, a minimal model was acquired with backward deletion following a stepwise procedure. The simplest multiple regression model to explain variation of RVEF in severe AS accounted for only 4 independent variables: diastolic blood pressure, LVEF, LA volume and LGE ($r=0.51$, $r^2=0.26$, $p<0.0001$). All four variables added statistically significantly to the prediction with $p<0.01$ for each. Regression coefficients and standard errors can be found in Table 4-9.

RVEF relationship with other variables is also presented in the tree model showed in Figure 4-7. The strongest associations of RVEF are seen with LVEF and LGE, which mostly explain RVEF in the patients with severe AS and a low LV systolic function. In patients with higher LVEF, other variables need to be considered and the association is more complex involving measures of diastolic dysfunction and AS disease.

The strong linear relationship between RVEF and LVEF is shown in Figure 4-8. This association resulted stronger in patients with severe AS and increased estimated SPAP ($r=0.49$, $p<0.0001$) compared to those with non-detectable pulmonary hypertension on echocardiography ($r=0.35$, $p<0.0001$).

Table 4-9. RVEF associations with baseline parameters in severe aortic stenosis.

<i>Univariable linear regression analysis</i>			
	r	r²	sig.
Age, years	0.048	0.002	0.22
Gender, male	0.071	0.005	0.068
Body mass index, kg/m ²	0.074	0.006	0.055
Systolic blood pressure, mmHg	0.086	0.007	0.045
Diastolic blood pressure, mmHg	0.075	0.006	0.082
NYHA functional class	0.128	0.016	0.001
STS score	0.076	0.006	0.051
Hospital centre	0.062	0.004	0.121
Peak trans-aortic gradient, mmHg (echo)	0.155	0.024	<0.001
Mean trans-aortic gradient, mmHg (echo)	0.136	0.018	0.002
Aortic valve area, cm ² (CMR)	0.109	0.012	0.016
LV EF, % (CMR)	0.512	0.262	<0.001
LV mass, g (CMR)	0.027	0.001	0.49
LA volume, mL (CMR)	0.195	0.038	<0.001
LGE mass (CMR)	0.028	0.001	0.609
<i>Multivariable standard regression analysis</i>			
	B	SE	sig
<i>Maximal model: $r=0.58$, $r^2=0.33$, $p<0.0001$</i>			
Age, years	0.04	0.09	0.68
Gender, male	1.52	1.82	0.41
Body mass index, kg/m ²	0.22	0.15	0.14
Systolic blood pressure, mmHg	0.04	0.04	0.37
Diastolic blood pressure, mmHg	-0.22	0.07	0.002
NYHA functional class	-1.89	1.25	0.13
STS score	-0.73	0.79	0.36
Hospital centre	0.33	0.57	0.56
Peak trans-aortic gradient, mmHg (echo)	-0.01	0.10	0.94
Mean trans-aortic gradient, mmHg (echo)	0.03	0.14	0.86
Aortic valve area, cm ² (CMR)	-9.17	3.79	0.017
LV EF, % (CMR)	0.27	0.06	<0.0001
LV mass, g (CMR)	0.04	0.03	0.22
LA volume, mL (CMR)	-0.09	0.04	0.02
LGE mass (CMR)	0.49	0.18	0.006
<i>Minimal model: $r=0.51$, $r^2=0.26$, $p<0.0001$</i>			
Diastolic blood pressure, mmHg	-0.15	0.05	0.001
LV EF, % (CMR)	0.32	0.04	<0.001
LA volume, mL/m ² (CMR)	-0.04	0.01	0.002
LGE mass (CMR)	0.35	0.07	<0.001

Note: minimal regression model obtained via stepwise backward deletion of the least significant covariate. CMR: cardiovascular magnetic resonance; LVEF: left ventricular ejection fraction; LGE: late gadolinium enhancement; LA: left atrium.

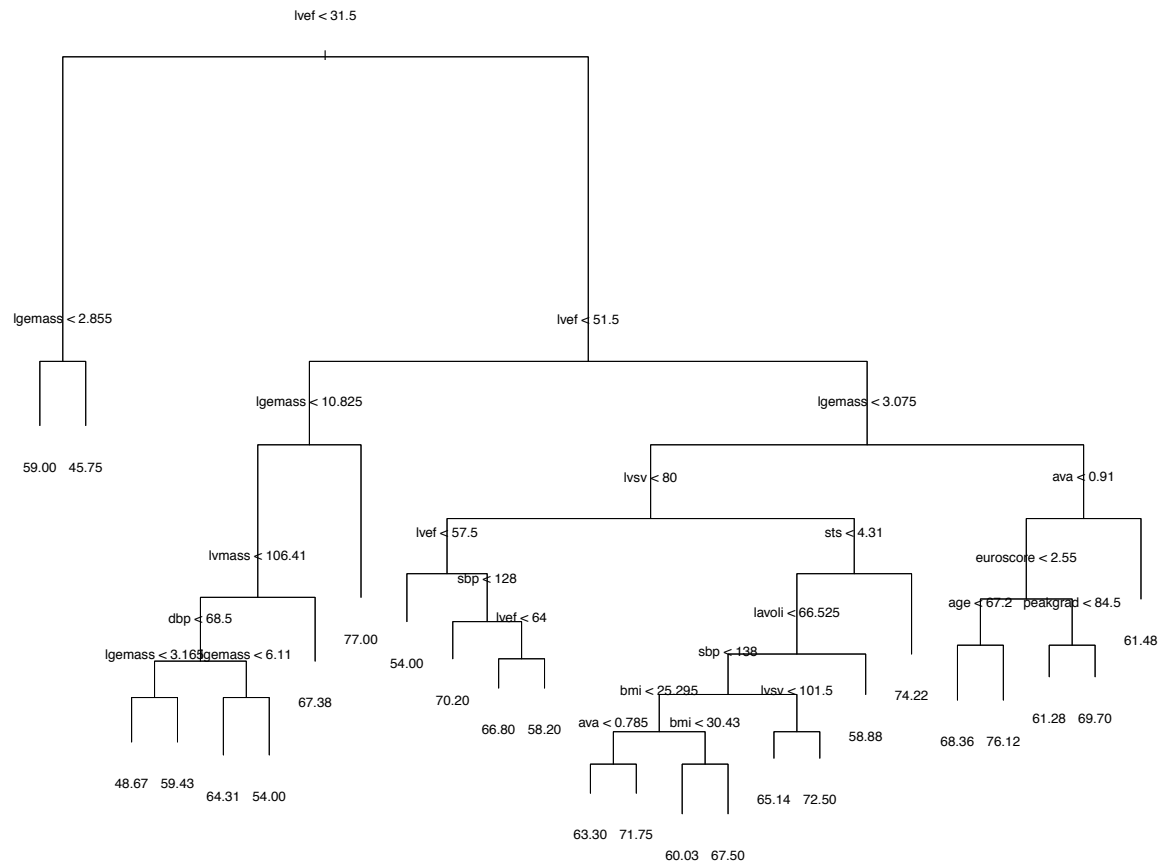


Figure 4-7. Tree model of RVEF relationships with baseline parameters in aortic stenosis.

Most of the RVEF variability is explained by LVEF and LGE mass. These variables have the longest branches and, therefore, are the most important explaining factors of RVEF in severe AS. In patients with low LVEF ($\text{LVEF} < 31.5\%$), the variation in RVEF is completely explained by LGE mass. In patients with higher values of LVEF ($\text{LVEF} > 31.5\%$), RVEF has a more complex interaction with other variables. Note: in this model, only interactions between continuous variables have been explored, SPAP was recorded as a categorical variable and thus was not included.

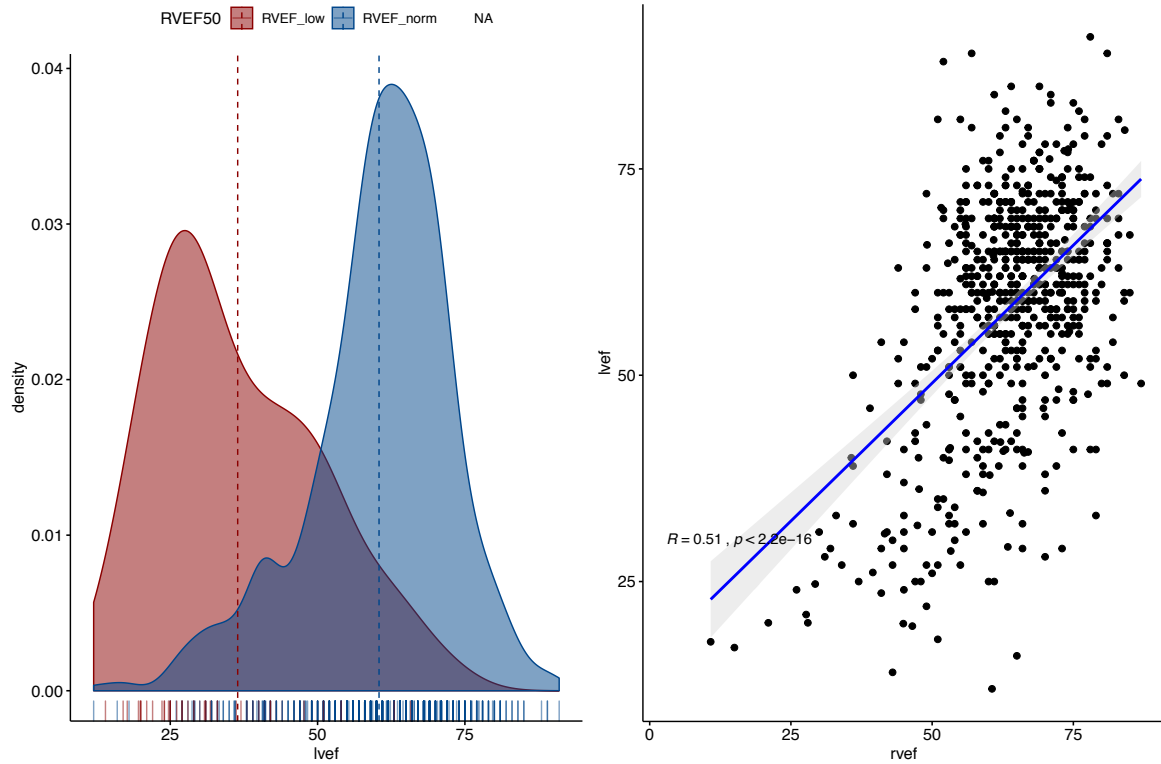


Figure 4-8. RVEF association with LVEF in aortic stenosis.

Left panel: Density plot for population distribution according to RV systolic function. Most patients with RVEF<50% had a degree of LVEF reduction (dotted lines express mean values of LVEF). Right panel: Strong linear association between RVEF and LVEF in severe AS ($r=0.51$, $p<0.0001$), especially at lower and higher values of ventricular function.

4.1.5.c Prognostic impact of the Right Ventricle in Aortic Stenosis

During a median 3.6 years follow-up (IQR 2.6-5.9 years), 145 (21.5%) patients died (52 post-SAVR and 93 post-TAVI). This corresponded to 52 deaths/1,000 patient years (27 and 104 for SAVR and TAVI groups, respectively). A cardiovascular cause of death was present in 70 patients (10.4% of whole cohort; 19 post-SAVR [4.8%], 51 post-TAVI [18.5%]). At 1-year, overall mortality was 6.2% (n=42), with 3.0% (n=12) in SAVR patients and 10.9% (n=30) in TAVR patients.

RVSD was a significant prognostic factor, showing a better discrimination than LV systolic function when survival distributions were assessed (Figure 4-9). The prognostic impact was especially seen in TAVI patients, while a non-significant tendency was present in the SAVR subgroup (Figure 4-10).

Patients with early stages of RVSD (RVEF between 45 to 50%) had a significantly worse survival than those with preserved RVEF, as shown in Figure 4-11. Their survival distribution was similar to those AS patients with more advanced RVSD (RVEF < 45%).

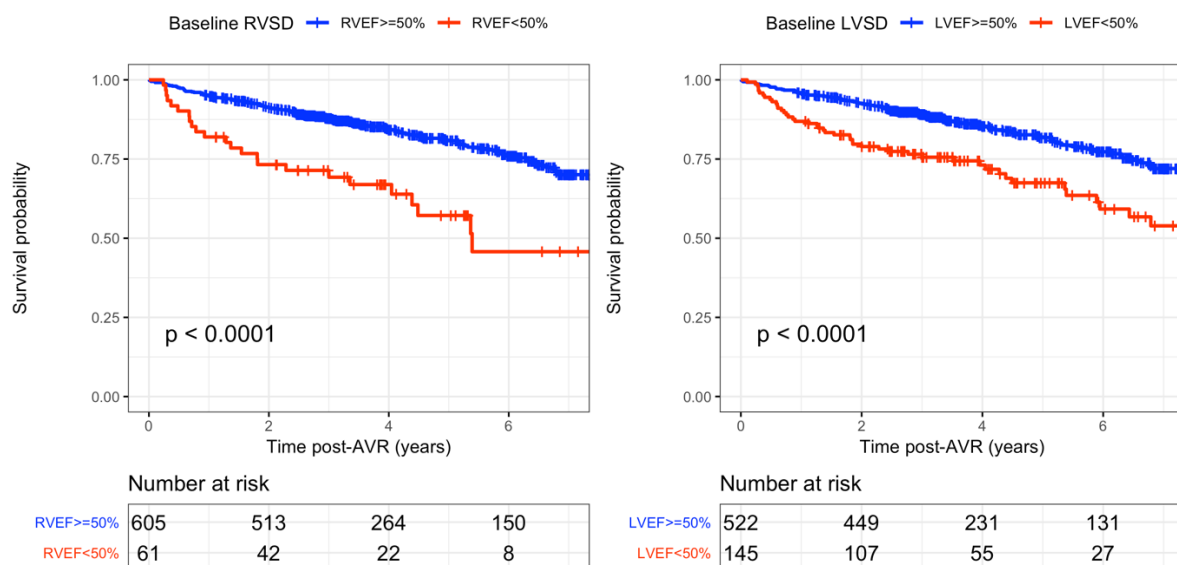


Figure 4-9. Kaplan-Meier survival curves stratified by pre-AVR biventricular systolic dysfunction on CMR.

Both pre-AVR RVEF and LVEF were significant prognostic factors for all-cause mortality in severe AS. A threshold of baseline ejection fraction of 50% for the RV (RVEF 50%) better separated survival curves than the same threshold applied to the LV (LVEF 50%).

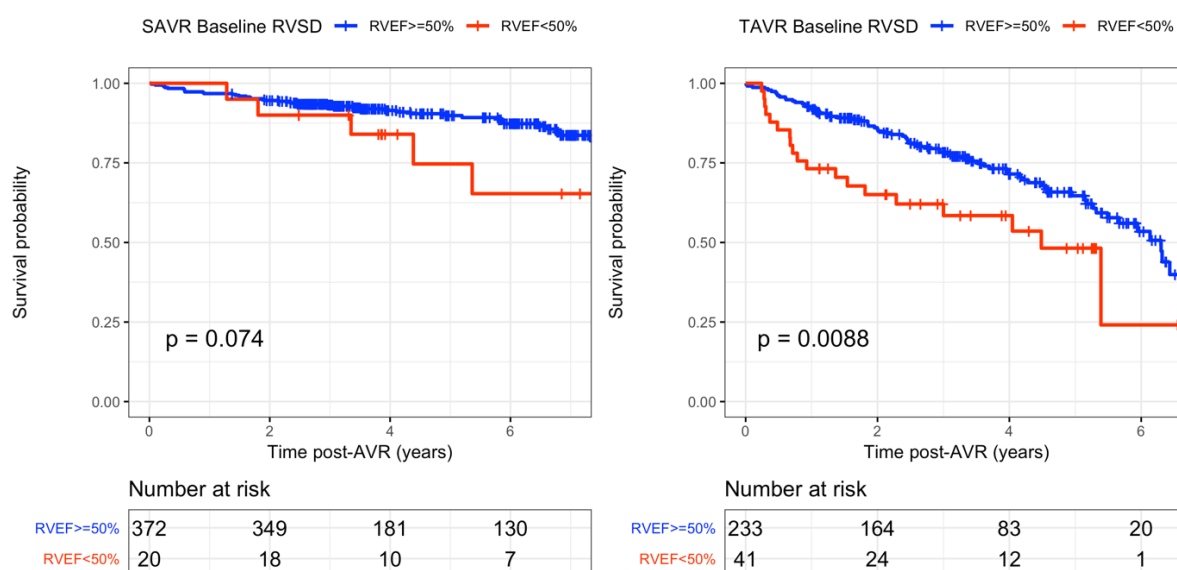


Figure 4-10. Kaplan-Meier survival curves stratified by RV systolic dysfunction in invasive valve treatment groups (SAVR and TAVI).

Patients undergoing TAVI with RVEF under 50% had a worst survival than TAVI AS patients with preserved RVEF. There was a similar but not significant tendency in SAVR patients.

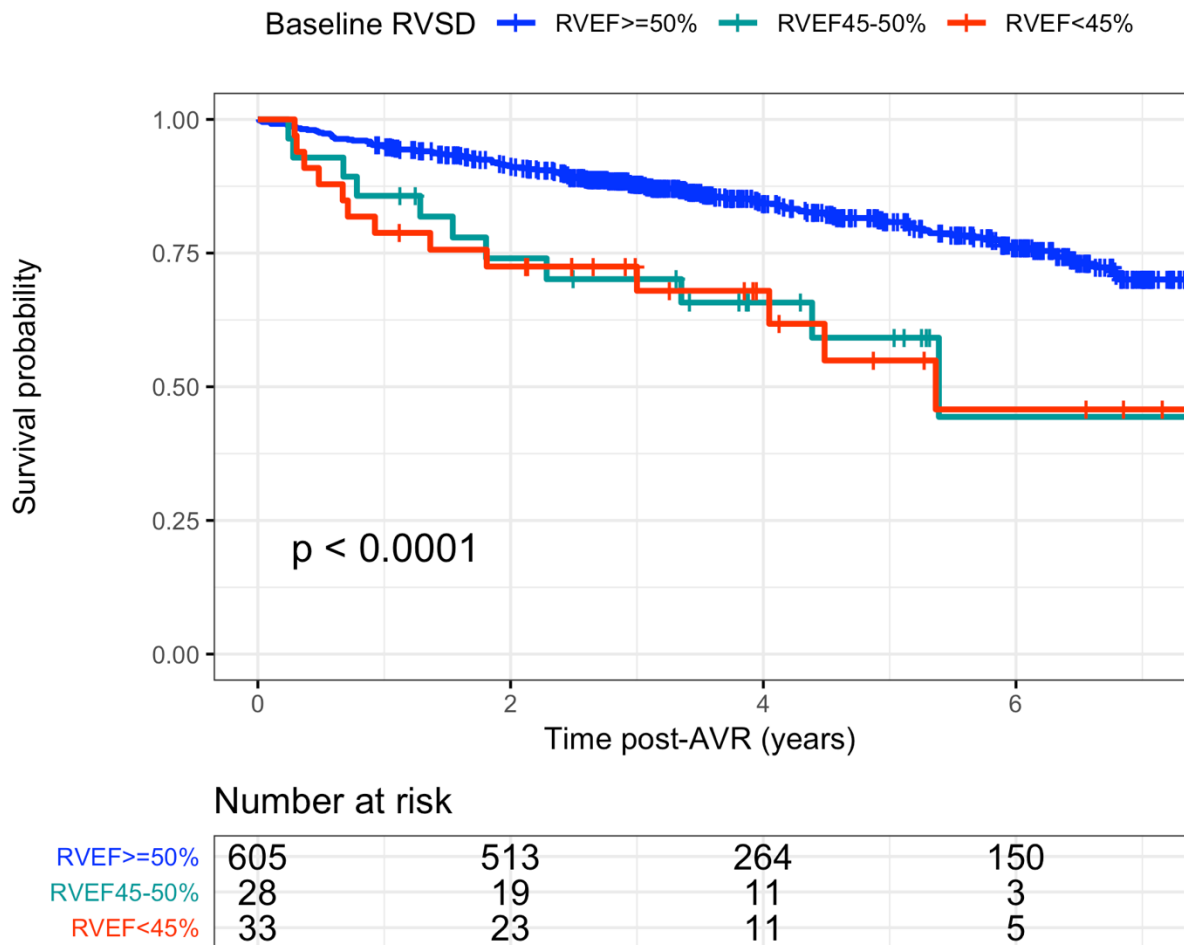


Figure 4-11. **Kaplan-Meier survival curves according to RV dysfunction stages.**

RVEF assessed pre-AVR by CMR in severe AS was a significant prognostic factor after AVR also at early stages of RV systolic dysfunction (RVEF between 45 to 50%) with a survival distribution significantly worse than preserved RV function (RVEF $\geq$ 50%) and comparable to the survival distribution of AS patients with more severe RV dysfunction (RVEF <45%).

Thirty-six variables were assessed as potential all-cause mortality predictors. These included demographic, clinical and imaging parameters. At the univariable Cox regression analyses, 19 of these parameters were associated with outcome. At the multivariable analysis, the factors independently associated with all-cause mortality were age, hospital centre, LA volume, LGE presence, RV systolic dysfunction and RV/PA coupling.

RV systolic dysfunction was the most powerful parameter associated with outcome at the univariate analysis with a HR of 2.5 (95% C.I. 1.6-3.9, $p < 0.0001$). The prognostic impact of RV dysfunction was independent from other statistically significant clinical and aortic valve disease parameters and was part of the simplest and most powerful multivariable model predicting all-cause mortality, together with age and LGE.

Table 4-10. Univariable Cox regression analysis for all-cause mortality.

Patients (n=674)			
All Cause Mortality (n= 145)			
	HR (95% CI)	Z	P value
Baseline Clinical Characteristics			
Age	1.1 (1.1-1.1)	52	<0.0001
Male Sex	0.76 (0.55-1.1)	2.5	0.11
Body mass index	0.98 (0.94-1)	1.9	0.16
Atrial Fibrillation	2.3 (1.6-3.5)	18	<0.0001
Diabetes Mellitus	1.3 (0.92-1.9)	2.2	0.14
Hypertension	1.1 (0.77-1.5)	0.15	0.7
Bicuspid aortic valve	0.28 (0.16-0.49)	20	<0.0001
Previous coronary treatment	1.5 (1.0-2.2)	2.1	0.037
Previous myocardial infarction	0.74 (0.44-1.2)	1.4	0.24
NYHA Functional Class	1.6 (1.3-1.9)	28	<0.0001
ACE inhibitor or ARB	1.4 (0.97-1.9)	3.2	0.07
Beta-blocker	1.2 (0.86-1.7)	1.1	0.3
Aldosterone Antagonist	0.82 (0.38-1.8)	0.26	0.61
Statin	1.2 (0.81-1.6)	0.67	0.41
STS score	1.2 (1.1-1.2)	61	<0.0001
Euroscore	1.1 (1.1-1.1)	27	<0.0001
Hospital Centre	1.2 (1.1-1.3)	3.16	0.001
Aortic Valve disease			
Mean aortic valve gradient, mmHg - echo	1 (0.99-1)	0.73	0.39
Peak aortic valve gradient, mmHg - echo	1 (1-1)	0.71	0.4
Aortic valve area, cm ² – echo	0.33 (0.13-0.85)	5.3	0.021
Aortic regurgitant fraction, % - cmr	0.99 (0.98-1)	0.64	0.42
Left heart parameters			
LV end diastolic volume indexed, mL/m ²	1 (1-1)	1.4	0.23
LV end systolic volume indexed, mL/m ²	1 (1-1)	11	0.00074
LV stroke volume indexed, mL/m ²	0.97 (0.95-0.98)	18	<0.0001
LV ejection Fraction, %	0.98 (0.97-0.99)	24	<0.0001
LV ejection fraction <50%	2.1 (1.5-2.9)	17	<0.0001
LV mass index, g/m ²	1 (0.99-1)	0.09	0.2
LA volume indexed, mL/m ²	1.01 (1.00-1.02)	3.2	0.0014
LGE presence	2.21 (1.50-3.27)	4.0	<0.0001
LGE mass	1.04 (0.99-1.09)	1.7	0.088
Right heart parameters			
RV end diastolic volume indexed, mL/m ²	1 (0.99-1)	0.22	0.64
RV end systolic volume indexed, mL/m ²	1 (1-1)	2.6	0.11
RV stroke volume indexed, mL/m ²	0.98 (0.96-0.99)	7.6	0.0058
RV ejection fraction, %	0.98 (0.96-0.99)	11	0.00096
RV ejection fraction <50%	2.5 (1.6-3.9)	18	<0.0001
RV ejection fraction/SPAP(RV/PA coupling)	0.99 (0.98-1)	9.8	0.0018

NYHA: New York Heart association; LV: left ventricular; LGE: late gadolinium enhancement; RV: right ventricular; LA: left atrium; SPAP: systolic pulmonary artery pressure.

Table 4-11. **Multivariable Cox regression analysis for all-cause mortality.**

Patients (n=674)			
All Cause Mortality (n= 145)			
	HR (95% CI)	Z	P value
Clinical Model: Comorbidity/AS Disease/Right Heart* $r^2=0.11$, $p<0.001$			
Age	1.05 (1.02 – 1.08)	3.58	0.0003
Atrial Fibrillation	1.77 (0.99-3.12)	1.84	0.06
Previous coronary treatment	0.87 (0.63-1.20)	-0.86	0.39
NYHA Functional Class	1.29 (0.94-1.77)	1.32	0.19
Hospital Centre	1.27 (1.01-1.58)	2.03	0.04
Bicuspid aortic valve	0.85 (0.41-1.76)	-0.45	0.65
Aortic valve area, cm^2 – echo	0.57 (0.19-1.69)	-1.00	0.31
RV ejection fraction $<50\%$	2.00 (1.01 - 3.88)	2.02	0.04
Imaging Model: Left Heart/Right Heart* $r^2=0.06$, $p<0.001$			
LV ejection fraction $<50\%$	1.42 (0.85 - 2.38)	1.33	0.18
LA volume indexed, mL/m^2	1.01 (0.10 - 1.03)	2.09	0.036
LGE presence	2.03 (1.32 – 3.13)	-0.44	0.0013
RV ejection fraction $<50\%$	1.49 (0.77 – 2.88)	1.19	0.23
RV/PA coupling	0.98 (0.97 - 0.99)	-2.69	0.012
Simplest Most Powerful Model $r^2=0.13$, $p<0.001$			
Age	1.08 (1.06 – 1.10)	7.04	<0.0001
RV ejection fraction $<50\%$	1.67 (1.03 – 2.67)	2.09	0.036
LGE presence	2.24 (1.51 – 3.32)	4.00	<0.0001

* Listwise deletion (complete-case analysis): Clinical model: patients $n=462$, events=83; Imaging model: patients $n=544$, events =104; Clinical and imaging model: patients $n=462$, events=83. Simplest model: patients $n= 608$, number of events = 125. Parameters have been limited in consideration to number of events, those with relevant and significant HR values at univariate cox regression have been selected. Overall model p for likelihood ratio test. NYHA: New York Heart association; RV: right ventricular; LV: left ventricular; LA: left atrium; LGE: late gadolinium enhancement; RV/PA coupling: right ventricular ejection fraction divided by systolic pulmonary arterial pressure.

DISCUSSION

This chapter describes the first prospective study to investigate RV function and strain by CMR in AS with normal LVEF, showing that a hyperdynamic RV was a marker of decompensated severe AS and cardiac recovery after AVR. In addition, RV dysfunction by CMR in a multi-centre outcome study of severe AS undergoing AVR was proven common and the most powerful predictor of all-cause mortality even at early stages of RVEF reduction. These results are in keeping with the hypotheses that:

- the RV plays an important role in the compensatory mechanism to increased LV afterload by severe AS
- the RV inability to compensate associated with severe AS and LV maladaptation affects clinical decompensation pre AVR and survival post AVR.

4.1.6 Right Ventricular Systolic Function and Degree of Aortic Stenosis

RV systolic function was highest in symptomatic severe AS awaiting AVR, and strongly correlated with multi-imaging parameters of valve obstruction, and clinical decompensation.

Previous studies in systemic hypertension suggested an interventricular relationship in the early stages of increased left afterload (139). The prognostic importance of RV impairment and its close relationship with the LV were also observed in severe AS with variable degrees of LV systolic dysfunction (133). In contrast, the single-centre prospective study here described focused on AS with normal LVEF and explored the potential for early RV changes preceding LV impairment and overt pulmonary hypertension.

Although the RV has been often overlooked in AS with normal LV function, there is limited evidence in the literature to support our findings. One retrospective echo study reported an association between TAPSE and trans-aortic flow in severe AS with preserved LVEF (241). However, they did not report increased RV systolic function which is a novel finding. Although echocardiography often provides a good evaluation of RV longitudinal dysfunction, it may not be sufficiently sensitive to explore subtle alterations in normal biventricular function. In addition, CMR is superior for assessing RVEF and transverse shortening which is less sensible to variation induced by cardiac surgery (242). Another previous study assessed pre and post-AVR changes, reporting RV volumes by CMR in AS with preserved/mildly reduced LVEF (243). Despite the authors concluding that the RV remained unaffected at this stage, their results are consistent with ours showing significantly smaller end-systolic cavity and a tendency to higher RVEF in severe AS, returning to lower normal values similar to controls after AVR. The fact that RVEF differences did not previously reach statistical significance may be accounted for by the limited number of subjects and the confounding effect of including mild LV systolic dysfunction.

4.1.7 Right Ventricular Systolic Function and Clinical Decompensation

Symptoms onset is a key indicator of invasive treatment in AS (244). However, initial symptoms can be extremely challenging to assess in the elderly patient. In our study, symptomatic AS manifested significantly increased RVEF values compared to all other groups ($p < 0.001$), including asymptomatic severe AS. RVEF was a strong determinant of symptoms, independently of valve obstruction degree, LV systolic function and mass. Moreover, RVEF was also strongly associated with NYHA functional class and BNP levels. The optimal cut-off to identify symptomatic patients was an RVEF $\geq 71\%$, although a lower threshold (RVEF

$\geq 63\%$) had the highest negative predictive value (100%) for discriminating symptomatic patients.

These thresholds may be used as early indicators of clinical decompensation, for example in patients with multiple co-morbidities and possible causes for dyspnoea. In addition, they may prove useful in those with severe AS who are unable to perform a maximal exercise to help unmask symptoms and indicate future benefit from AVR.

4.1.8 Right Ventricular Systolic Function in Aortic Stenosis

RV systolic dysfunction was common in patients with severe AS undergoing AVR. Almost 1 patient every 5 had an RVEF $< 55\%$ detected on CMR. Patients undergoing less invasive treatment options (TAVI) had higher prevalence (22%) of RV systolic dysfunction compared to those treated with SAVR. It is conceivable that those who have been excluded from any type of AVR treatment may have even higher prevalence and degree of RV systolic dysfunction.

The two studies presented that assess similar populations at different stages of aortic valve disease are building a complementary picture. RVEF was strongly associated to LV systolic dysfunction, measures of AS disease (trans-aortic gradients and AVA), clinical decompensation (NYHA class, systolic and diastolic blood pressure) and LV diastolic dysfunction/augmented LV filling pressure (LA volume). In patients with severe AS, the variation in RVEF was mostly and independently explained by LV systolic and diastolic dysfunction, aortic valve disease severity and LV maladaptation to afterload (LGE).

Therefore, the RV may be a global marker of cardiac response and adaptation to chronic and progressive LV increased afterload. In patients with severe AS, the RV is not directly affected

by the systemic afterload and may compensate to it by increasing contractility and helping the LV to preserve stroke volume through the valve obstruction. With more advanced stages of AS, LV diastolic and systolic dysfunction aggravate to determine an unbearable degree of backward afterload transmission through the pulmonary system which may directly affect the RV. At this point, the RV would not be able to compensate anymore and may rapidly evolve to RV dysfunction.

The RV is a useful marker of overall cardiac maladaptation to AS. This theory may also explain the association with LV mass regression after AVR. Patients with an active hyperdynamic RV are those at an earlier well-compensated stage of aortic valve disease which is still in a reversible stage of disease as demonstrated by the normalisation of LV mass after afterload relief. These patients are the ones who would likely benefit mostly from AVR.

4.1.9 Role of the Right Ventricle and Potential Physiological Mechanisms Involved

LV hypertrophy in AS is a compensatory mechanism to normalize wall stress (245). However, this response is extremely variable, and it is still unclear why some patients develop excessive hypertrophy. Mass regression after AVR is also variable and impacts long-term survival (246). Right-sided compensation to LV afterload may play an important role in cardiac adaptation. Concentric LV hypertrophy results in increased stiffness and abnormal myocardial perfusion reserve, which impairs LV performance in severe AS. At this stage, the LV may be aided by increased RV contractility to augment LV filling and maintain stroke volume across the valve obstruction. Increased RVEF may, therefore, be a marker of adaptation and recovery capacity, uninfluenced by the direct effects of LV afterload. Higher pre-operative LV mass is likely to be associated with higher diastolic dysfunction and thus a greater need for RV support for LV filling, with reversal of this compensatory mechanism following AS relief.

This process may be driven by the activation of systemic compensatory mechanisms to help maintain organ perfusion. Systemic adaptations are well recognised even in early stages of heart failure (66) and markers of neuro-hormonal activity have been found in AS with normal LVEF (247). The RV may respond to these compensations and help identify those hearts that hold myocardial recovery reserve prior to irreversible LV dysfunction: patients with the highest RV function showed the greatest degree of reversible LV hypertrophy. The hyperdynamic RV may, therefore, indicate individuals who experienced better systemic adaptation, better local cardiac response to compensation or who were at an earlier stage of disease.

4.1.10 Prognostic Impact of the Right Ventricle in Aortic Stenosis

RV systolic dysfunction (RVEF <50% by CMR) was the most powerful prognostic factor at the univariable analyses of all-cause mortality. Patients with RVEF <50% had more than double the risk of dying after AVR (HR 2.5, $p < 0.0001$) than those with normal RVEF. The prognostic impact was independent from clinical characteristics and RVEF was part of the most powerful and simple model for predicting all-cause mortality together with age, and LGE.

Even early stages of RV systolic dysfunction affected survival in patients undergoing AVR. This is in-keeping with the theory presented above: since well-compensated stages of aortic valve disease are associated with an hyperdynamic RV, a RVEF between 45 to 50% is a significant drop in RV systolic function. This is likely associated with an irreversible maladaptation which translates in significant mortality impact even once LV afterload is normalised with AVR. This rises the hypothesis that patients with even mild RV systolic function reductions are being treated too late. The hyperdynamic RV as a marker of compensation and cardiac recovery may aid the correct timing of AVR. Early AVR treatment at compensated severe AS stages with increased RVEF may be best suited for these patients.

This hypothesis should be assessed with randomised trials for early AVR treatment strategies in severe AS.

4.1.11 Limitations

These were observational prospective studies of patients at centres with an interest in CMR and echocardiography for clinical and research indications, potentially introducing selection bias. Due to the contra-indications for contrast enhanced CMR, patients with severe renal impairment and pre-operative pacemaker/defibrillators were not represented. Post-operative RV parameters may have been influenced by cardiac surgery, which is known to result in short term reductions in RV function. However, post-surgical follow-up was performed at least 6 months after surgery to allow RV functional recovery. In addition, post-surgical RV dysfunction is mainly confined to longitudinal shortening, while RVEF and transverse shortening are unaffected (242). Doppler echocardiography was adopted to exclude detectable significant pulmonary hypertension. Although we did not corroborate these findings against invasive pulmonary pressure measurements, non-invasive assessment is an acceptable screening tool for moderate/severe pulmonary hypertension (148). Symptoms are subjective, although they remain the most important determinant of mortality and AVR. Symptomatic status was also confirmed on 6MWT and decompensation by BNP evaluation.

4.1.12 Conclusion

A *hyperdynamic* RV detected by CMR was associated with increasing AS severity, clinical decompensation, and LV recovery after aortic valve replacement, as assessed by the prospective single-centre study. Thus, the hyperdynamic RV may be an adaptive compensatory

mechanism in chronic AS and may result a novel early objective marker of decompensated severe AS, particularly useful when symptoms are difficult to assess.

In addition, the powerful prognostic impact of RV function post-AVR and its association with LV dysfunction and maladaptation, as assessed in the multi-centre outcome study, confirms the relevance of RV compensation in severe AS.

This raises the hypothesis that in patients presenting with even only mild RV systolic dysfunction, current AVR timing may not be adequate. Further assessment with randomised trials for early intervention in AS is required. If confirmed in larger-scale studies, a hyperdynamic RV may result in a stimulus for consideration of valve replacement, and potentially a new treatment target in patients with RV conditions in whom the blunted compensatory response may lead to earlier decompensation.

This chapter provides useful insights into the compensated myocardial response physiology in AS and the potential for problems in specific group of patients. For example, co-morbid AS patients affected by right heart conditions such as COPD or other lung disease may manifest a blunted RV compensatory response which may lead to earlier decompensation. The lack of RV compensation may also explain other less understood pathophysiological states such as paradoxical low-flow, low-gradient AS.

Chapter 5 - Advanced Multi-modality Imaging for the Cardiorespiratory Assessment in Aortic Stenosis: The AMICA-AS Study

HYPOTHESIS AND AIM

- The discrepancy between apparent lung dysfunction (COPD-STIS) and confirmed airflow obstruction (COPD-GOLD) is reduced when spirometry assessment is performed routinely in AS. COPD is also associated with increased symptomatic burden in AS and confounds the indications to AVR.
- The prevalence of morphological lung disease in AS is lower than the prevalence of apparent lung dysfunction by spirometry. COPD is overdiagnosed in symptomatic AS, leading to AVR exclusion in some patients with no significant morphological lung disease.
- Other patients with severe AS have significant morphological lung disease which is likely to be driving symptoms, and results in futility of AVR, with minimal or absent improvement in functional capacity post-AVR
- Hyperpolarised xenon magnetic resonance is feasible in a multi-morbid population with cardio-respiratory disease.

The aims of this chapter were to prospectively assess:

1. The prevalence of lung disease in patients with moderate or severe AS and its association with symptoms
2. Improved ways of discriminating patients with or without lung disease who may either be inappropriately excluded from cardiac treatment in the absence

of lung disease or may not benefit from higher-risk AVR in case of respiratory symptoms

3. Whether morphological lung disease was associated with reduced functional improvement post-AVR

MATERIAL AND METHODS

5.1.1 Study Population

The study population discussed in this chapter is the Prospective Cross-sectional and Longitudinal AMICA-AS Study group. Eligibility criteria are described in Chapter 2 – General Methods. In summary, patients with at least moderate AS were included. Symptomatic patients with AS were selected for presence of dyspnoea as their primary symptom and were followed up after at least 6 months from surgical AVR or TAVI. Common other confounding causes of dyspnoea rather than AS and lung disease were excluded: significant previous myocardial infarction, left ventricular systolic dysfunction (LVEF <55%), atrial fibrillation, other severe valvular disease, any other underlying cardiomyopathy. Patients were recruited between February 2016 and April 2018, follow-up was performed until September 2018.

5.1.2 Sample Size Calculation

Estimation of COPD and emphysema prevalence remains difficult due to the variability of definitions and methods adopted during the years in different studies. To limit this heterogeneity, prevalence used for sample size calculation are pooled prevalence derived from a meta-analysis of studies of the general population conducted by Halbert et al (248). Meta-analysis plays a central role in evidence-based medicine and is graded at the top of the hierarchy of evidence (above randomised clinical trials) where clinical evidence is ranked according to

the strength of the freedom from various biases (249). Meta-analysis is also the most cited form of literature (250).

5.1.2.a Emphysema prevalence

Assuming the width of the 95% confidence interval to be 0.10 (d), an accuracy of ± 0.05 , and an estimate of the prevalence of emphysema of 0.032 ($p = 3.2\%$ given by the known pooled prevalence of physical and radiological emphysema), the sample size needed to estimate the prevalence of emphysema is $n = 1.96^2 \times 4 p (1-p)/d^2 = 48$. Assuming the pooled prevalence of the overall emphysema diagnosis (physical/radiography and patient reported) of 1.8 % (1.3-2.6%) (248) the sample size needed is 28. The subgroup sample size of 60 severe AS allows estimation of emphysema in this population.

5.1.2.b COPD-GOLD prevalence

Assuming the width of the 95% confidence interval to be 0.10 (d), an accuracy of ± 0.05 , and an estimate of the prevalence of COPD of 0.05 ($p = 5\%$ given by the known pooled prevalence of physician-diagnosed COPD 5.2% and patient-reported COPD 4.9%), the sample size needed to estimate the prevalence of COPD is $n = 1.96^2 \times 4 p (1-p)/d^2 = 73$. The moderate-severe AS total sample size of 80 fulfils the above criteria. Subgroups of approximately 20 patients for moderate, severe asymptomatic and symptomatic AS were obtained to allow group comparisons for secondary endpoints evaluations.

5.1.3 Advanced Lung Assessment

5.1.3.a Chest CT

Unenhanced low dose CT scans were performed with a 64-slice scanner (Revolution GSI, GE Healthcare) adopting the following parameters: 0.625mm slice thickness, 60 mA current, 100 kV voltage, 40mm tube collimation, 0.984 beam pitch, 0.5sec rotational time. All the scans were performed during inspiratory breath hold from functional residual capacity + 1 L to allow respiratory evaluation and co-registration with HP-Xe MRI. Neither contrast nor beta-blocker were used for the purpose of the examination. Subjects underwent breath-hold training by radiographer instruction to ensure reproducibility. No data were acquired in expiration. The CT protocol was standardised and reproduced previous published studies in the division for COPD assessment with CT and HP-Xe MRI (111).

Scans were analysed with the Pulmonary Toolkit (PTK, *Doel T. Pulmonary Toolkit*. <https://github.com/tomdoel/pulmonarytoolkit>) to quantify the whole-lung emphysema extent (Figure 5-1). Emphysema % was reported as percentage low attenuation area (%LAA), the percentage area of the whole-lung with attenuation values inferior to -950 HU. Presence of emphysema was defined when the CT-emphysema % on baseline chest CT was $\geq 10\%$. Additional parameters of emphysema degree and chronic bronchitis are also reported: emphysema density in Hounsfield units (HU), percentage of air (air %), mean airway lumen radius and wall thickness in mm. A low-dose CT was chosen to lower radiation dose and in consideration of the minimal effect on CT quantification of emphysema (251).

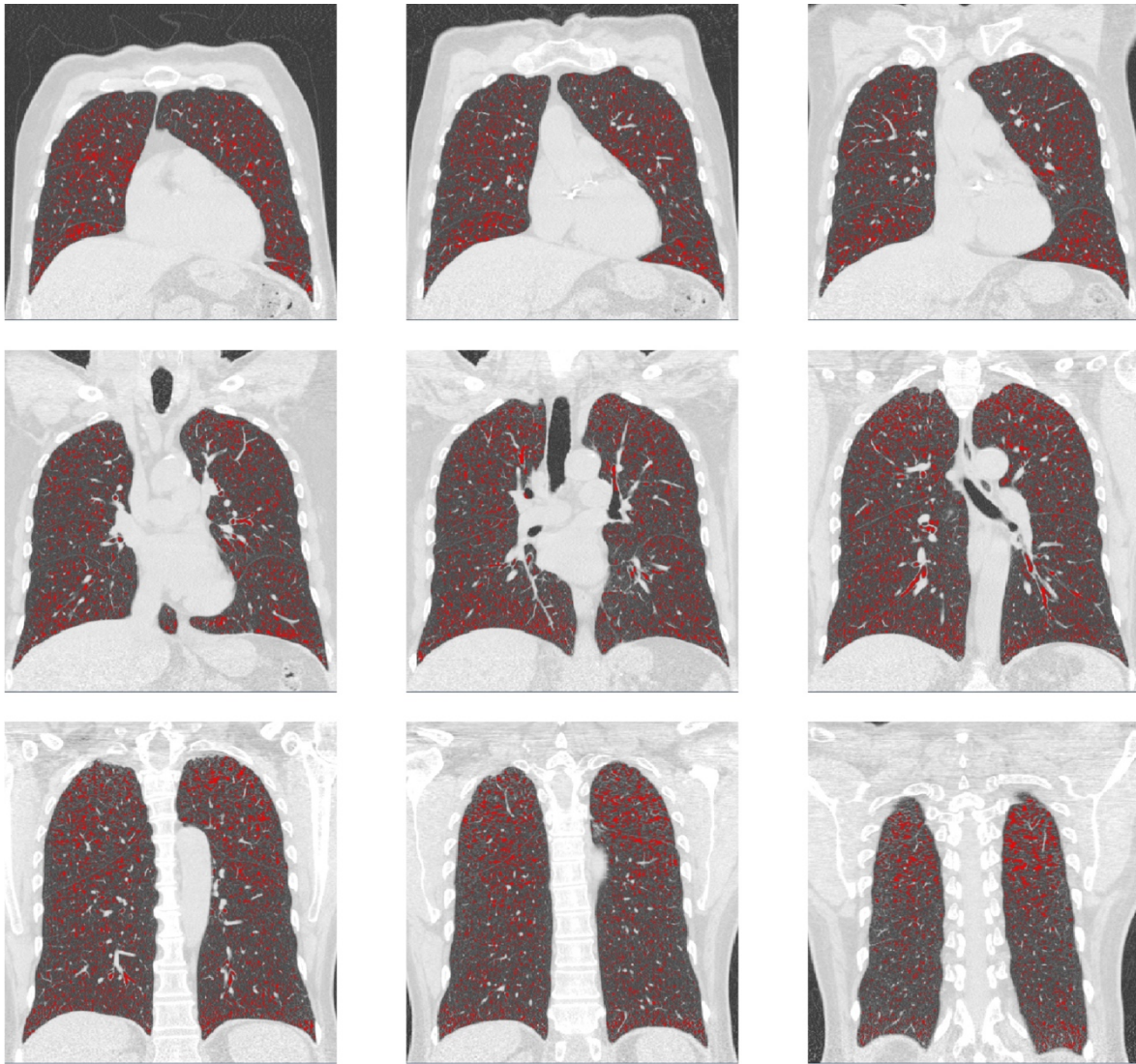


Figure 5-1. Quantification of emphysema on computed tomography.

Coronal chest CT performed in an AMICA-AS participant with automatic identification of low attenuation areas under the threshold of -950 HU (red areas) by the PTK software. CT-emphysema percentage was derived from the percentage of lung voxels with attenuation less than -950 HU (%LAA).

5.1.3.b HP-Xe MRI

MR images were obtained with a 1.5-T whole-body system (Signa HDx; GE Healthcare). Subjects were fitted with a flexible twin Helmholtz transmit-receive coil (Clinical MR Solutions, Brookfield, Wis) resonating at the ^{129}Xe Larmor frequency (17.7 MHz). Images were acquired with patients in the supine position. After initial hydrogen MR localizer images, HP-Xe MRI ventilation images were acquired during a breath hold of approximately 25 seconds in the anteroposterior direction by using a broad banded two-dimensional spoiled gradient-echo sequence. Imaging parameters were as follows: 15-mm coronal sections covering the whole lung, 40 x 40 cm field of view, 96 x 96 matrix resolution, 4-kHz bandwidth, 20 msec repetition time 4.2 msec echo time, and 9° flip angle. HP-Xe MRI diffusion-weighted images were obtained by using an interleaved two-dimensional gradient-echo sequence with two b values ($b = 0, 20.855 \text{ sec/cm}^2$). Imaging parameters were as follows: 30 mm coronal sections covering the whole lung in the anteroposterior direction, 40 x 40-cm field of view, 96 3 96 matrix resolution, 4-kHz bandwidth, 20 msec repetition time 13.2 msec echo time, and 7° flip angle. Anatomic proton MR images were obtained during a separate 15 second breath hold after both hyperpolarized ^{129}Xe MR ventilation and diffusion-weighted imaging. Subjects inhaled 1.0 L of oxygen via a Tedlar bag from functional residual capacity before breath holding. These images were acquired by using a multi-section balanced steady-state free precession sequence, and image location was copied from the preceding HP-Xe MRI for co-registration purposes. Imaging parameters were as follows: 15-mm coronal sections covering the whole lung, 40 x 40 cm field of view, 128 x 128 matrix resolution, 125-kHz bandwidth, 1.2 msec repetition time 2.8 msec echo time, and 45° flip angle.

For each HP-Xe MRI scan, the patient breathed out, and then breathed in from a bag containing up to 1L of xenon, balance nitrogen. HP-Xe MRI was performed using xenon hyperpolarized by a xenon hyperpolarizer (Polarean) and imaged on a 1.5T MRI scanner. Xe-129 was polarised via spin exchange optical pumping by laser, using the Polarean Xenospin. All staff involved in the process of Xe-129 manufacture was trained to ensure that the manufacture is conducted safely to the correct technical specification. Product was released according to the quality system for the licensed production facility. During each scanning session, up to a maximum of three HP-Xe MR sequences were acquired with the participant undergoing a maximum of three separate xenon breath-holds. The participant spent a total of approximately one hour within the MRI scanner during each visit. Image acquisition strategy involved proton imaging for co-registration purposes, ventilation imaging and diffusion-weighted imaging.

5.1.4 Functional Lung Assessment

Basic spirometry to assess volume, time and flow was performed for research purposes in all the participants of the AMICA-AS study. This was performed by a trained research lung technician in blind from the participants clinical characteristics. Participants with a reduced FEV₁/FVC ratio (FEV₁/FVC <0.7) performed additional full PFT. This included body plethysmography and the single breath test of carbon monoxide uptake performed with Jaeger MasterScope Body, Carefusion by a dedicated research respiratory technician. Full protocol of respiratory functional testing is described in Appendix 7.

5.1.5 Clinical Respiratory Assessment

5.1.5.a Symptomatic evaluation

Dyspnoea is a subjective sensation and, therefore, multiple definitions of dyspnoea were recorded including clinician reported and patient reported dyspnoea as a dichotomous variable,

self-reported questionnaire assessment (CAT, Appendix 1) and clinical symptomatic assessment (NYHA class, Appendix 2). Dyspnoea was objectively assessed at a 6-minute walking test performed uniquely for research purposes with presence and symptomatic onset distance recorded. The 6-minute walking test was performed following the SOP reported in Appendix 3.

5.1.6 Cardiovascular Assessment

5.1.6.a Echocardiographic evaluation

Transthoracic echocardiography was performed using an IE33 machine (Philips Medical Systems, Best, Netherlands) to evaluate AS grading parameters, LV diastology, and right-side parameters according to guidelines. Tissue doppler echocardiographic was used for the assessment of diastolic function: E/E' medial ratio was reported over lateral due to its better diagnostic utility (252).

5.1.6.b Cardiovascular magnetic resonance imaging

CMR was performed as detailed in Chapter 2 – General Methods with the additional acquisition of four-dimensional whole-heart flow data during free breathing using a retrospective ECG triggered, respiratory navigator gated three-dimensional, time resolved phase contrast CMR sequence.

CMR data was analysed by a second trained operator in blind from the clinical characteristics of the study participants. Participants scans were recorded with anonymised consecutive numbered IDs and random allocation to different AS subgroups (moderate, severe asymptomatic, severe symptomatic). In addition, controls with a non-significant AS (moderate

AS subgroup) were specifically chosen to prevent the issue of unconscious bias in imaging analysis. These patients have a similar degree of LV hypertrophy and valve calcification/obstruction which cannot be distinguished from severe AS if not specifically assessed in the appropriate images. On the contrary, healthy controls without LV hypertrophy and normal aortic valve morphology are easily recognised. CMR analyses were performed with Circle CVI42 as specified in Chapter 2 – General Methods.

5.1.7 Statistical analyses

Data are expressed as mean $\pm$ standard deviation for continuous variables, or numbers and percentages for categorical variables. Normality was assessed by exploring quantile-quantile plots and by performing the Shapiro-Wilk test for its best power at a given significance and its better suitability at small samples sizes compared to other tests for normality. Differences between two groups were assessed with the independent Student T test for approximately normally distributed variables with equal variances, the Welch test was used if variances were unequal (heteroscedasticity), and the Mann-Whitney-Wilcoxon test for variables with non-normal errors. For categorical variables, the Fisher exact test was used if any expected cell frequency was inferior or equal to five, the Chi-squared test with Yates correction if expected cell frequencies were over five but under ten, and the Pearson's Chi squared test with no Yates correction if the frequencies were above ten. Differences between three groups were assessed with one-way analysis of variance (ANOVA) if normality of residuals and homogeneity of variance were met. Otherwise one-way Welch if unequal variances or the Kruskal-Wallis rank sum tests if no-normality of residuals, were adopted. The Cochran-Armitage test of trend was used to determine whether there was an association between degree of aortic valve stenosis disease and exposure to smoke. Logistic regressions with generalized linear models were adopted for the assessment of risk factors associations with aortic stenosis degree; odds ratios

and relative risk were presented with 95% confidence intervals. Differences between pre and post-AVR characteristics were assessed in the follow-up participants with paired Student T tests if the distributions of the differences were not significantly different from the normal distribution. Otherwise the non-parametric paired two-samples Wilcoxon test was adopted.

RESULTS

5.1.8 Baseline Clinical Characteristics according to Aortic Stenosis

Baseline characteristics of the study population according to clinical degrees of AS are shown in Table 5-1. Patients with various degrees of AS were similar in terms of age, gender, BMI, blood pressure and renal function, but differed in smoking exposure, symptoms and laboratory evidence of congestion (BNP). The proportion of symptomatic AS treated with diuretics was also higher (statistical trend).

Almost half of the moderate AS patients were reported by their clinician as having a degree of dyspnoea. In most cases, the dyspnoea was recorded by the clinician as atypical or likely not related to the AS disease.

Table 5-1. Baseline clinical characteristics according to degree of aortic stenosis.

	Severe AS*		Moderate AS*	p-value
	Symptomatic	Asymptomatic		
	(n=45)	(n=15)	(n=20)	
Clinical				
Age, years	74 (15)	71 (16)	77 (10)	0.47
Gender Male	67%	60%	75%	0.64
BMI, kg/m²	28 ± 5	26 ± 3	29 ± 5	0.09
Systolic BP, mmHg	141 ± 20	136 ± 17	147 ± 20	0.31
Diastolic BP, mmHg	72 ± 10	72 ± 11	73 ± 9	0.92
Haemoglobin, g/dl	13.4 ± 1.3	13.8 ± 1.4	13.6 ± 1.3	0.62
BNP, pmol/L	29 (40)	20 (16)	15 (15)	0.01
eGFR, mL/min/1.7	77 (24)	80 (18)	72 (21)	0.23
COPD-STS	47%	33%	45%	0.66
Smoking status, exposed	64%	53%	30%	0.05
Smoking years in exposed	4 (25)	5 (15)	5 (20)	0.19
Medical therapy				
ACE/ARB inhibitors	41%	53%	50%	0.63
Beta-blockers	27%	20%	25%	0.85
Diuretics	25%	1%	1%	0.08
Bronchodilators	25%	20%	25%	0.92
Steroids	25%	13%	30%	0.51
Symptomatic status				
Any dyspnoea*, n (%)	100%	0%	30%	<0.0001
NYHA class, 1-2	48%	100%	79%	0.0006
CAT score	13 ± 8	9 ± 5	13 ± 8	0.27
EuroQoL scale	7.7 (1.8)	7.9 (1.5)	7.5 (1.8)	0.49
Echocardiographic parameters				
Peak aortic velocity - echo, m/s	4.4 ± 0.9	4.1 ± 0.5	3.1 ± 0.9	<0.0001
Mean aortic gradient - echo, mmHg	47 ± 15	39 ± 9	24 ± 6	<0.0001
Aortic valve area - echo, cm²	0.8 (0.2)	0.9 (0.3)	1.2 (0.2)	<0.0001
E/E' ratio# - echo	14 ± 5	14 ± 5	12 ± 3	0.19

*AS degree and dyspnoea presence reported above were defined by the clinician: moderate AS participants with dyspnoea were recorded as presenting atypical dyspnoea or not related to AS dyspnoea. For moderate AS patients, 30% were classified as having a degree of clinical dyspnoea by their clinician, 45% had dyspnoea as reported by the participant. #E/E' median. Continuous variables as mean ± standard deviation or median (interquartile range); categorical variables as percentages. P-values for one-way ANOVA, one-way Welch test, or Kruskal-Wallis rank sum test, as appropriate. BMI: body mass index; BP: blood pressure; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate by Cockcroft; CAT: COPD assessment tool.

5.1.9 Cardiorespiratory Parameters according to Aortic Stenosis

Differences were present in functional capacity (distance and symptomatic onset at 6MWT) and respiratory function (FEV1%) between AS degrees (Table 5-2). The asymptomatic severe AS subgroup had the best functional and respiratory capacity compared to both moderate AS and symptomatic severe AS who were more heterogeneous (Figure 5-2). The moderate AS participants also presented with various degrees of atypical dyspnoea and included a considerable proportion (21%) with advanced degrees of NYHA class, reflecting an elderly and co-morbid subgroup. Subgroups of moderate and symptomatic severe AS both included similar COPD % and COPD-GOLD degrees. These groups both included symptomatic and decompensated participants. On the contrary, the asymptomatic severe AS group had a lower prevalence of airway obstruction.

Right ventricular volumes and systolic function were different across AS groups, replicating the findings showed in Chapter 4 - Cardiac function in AS in a different population. Higher degrees of aortic valve obstruction were associated with smaller RV end-systolic cavities (RVESV p: 0.027) and higher RVEF (statistical trend p: 0.09). These differences became more significant when patients with LVEF <55% were excluded with CMR rather than with echocardiography, as shown in Figure 5-3. Symptomatic AS patients with higher levels of diuretic treatment had a higher prevalence of COPD compared to asymptomatic severe AS, and also showed a trend to lower RVEDV compared to asymptomatic ones. These differences may also explain the less significant RVEF increase compared to the previous population described in Chapter 4. AS subgroups differed in terms of LV mass - severe AS had higher LV mass compared to moderate AS, as expected.

Table 5-2. Cardio-respiratory parameters according to degree of aortic stenosis.

	Severe AS		Moderate AS	p-value
	Symptomatic	Asymptomatic		
Functional capacity – 6MWT				
Distance, meters	364 ± 167	480 ± 89	414 ± 166	0.043
Symptomatic onset	67%	1%	47%	0.0004
Oxygen Sat rest, %	97 (3)	97 (1)	96 (1)	0.13
Oxygen Sat exercise, %	97 (3)	98 (1)	97 (2)	0.69
Heart rate rest, bpm	69 ± 11	73 ± 12	67 ± 16	0.49
Heart rate exercise, bpm	101 ± 18	102 ± 12	97 ± 17	0.78
Respiratory function - PFT				
COPD-GOLD	47%	13%	45%	0.06
GOLD grade				0.21
No airway obstruction	54%	87%	55%	
Grade 1-2 (mild/moderate)	36%	13%	30%	
Grade 3-4 (severe/very severe)	54%	0%	15%	
FEV ₁ /FVC	71 (13)	77 (9)	71 (5)	0.17
FEV ₁ %	91 (35)	104 (32)	91 (23)	0.056
FVC %	95 ± 20	106 ± 20	95 ± 17	0.14
PEF %	92 ± 32	97 ± 29	86 ± 31	0.61
TLC %	110 ± 19	104 ± 17	109 ± 16	0.96
RV %	121 (36)	105 (15)	114 (30)	0.37
IC %	118 ± 26	114 ± 16	116 ± 25	0.91
DLCOc %	81 ± 24	85 ± 13	84 ± 20	0.86
Respiratory morphology - CT				
Emphysema %	7.9 (9.9)	3.8 (7.5)	10 (10.1)	0.19
Emphysema density (HU)	-920 ± 32	-908 ± 33	-929 ± 32	0.20
Air %	81 (5)	81 (6)	82 (4)	0.75
Mean airway lumen radius (mm)	9 ± 1.3	8.9 ± 1.2	9.4 ± 1.8	0.55
Mean airway wall thickness (mm)	3.8 (1.8)	3.7 (1.1)	4.1 (1.1)	0.99
Cardiac function - CMR				
LV end diastolic volume, mL	142 (46)	148 (42)	158 (53)	0.51
LV end systolic volume, mL	47 (26)	57 (30)	59 (36)	0.48
LV stroke volume, mL	90 ± 20	96 ± 25	99 ± 25	0.88
LV ejection fraction, %	65 (14)	65 (13)	62 (8)	0.68
LV mass, g	138 ± 38	134 ± 36	111 ± 26	0.024
RV end diastolic volume, mL/m ²	123 ± 40	153 ± 38	139 ± 40	0.061
RV end systolic volume, mL/m ²	40 (26)	61 (28)	53 (17)	0.027
RV stroke volume mL/m ²	82 ± 19	93 ± 23	86 ± 23	0.33
RV ejection fraction, %	69 (10)	64 (7)	63 (8)	0.09
RV mass, g	32 (12)	29 (13)	27 (17)	0.78

Bpm: beats per minute; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; DLCOc: corrected diffusing capacity for carbon monoxide; HU; Hounsfield units; LV: left ventricular; RV: right ventricular.

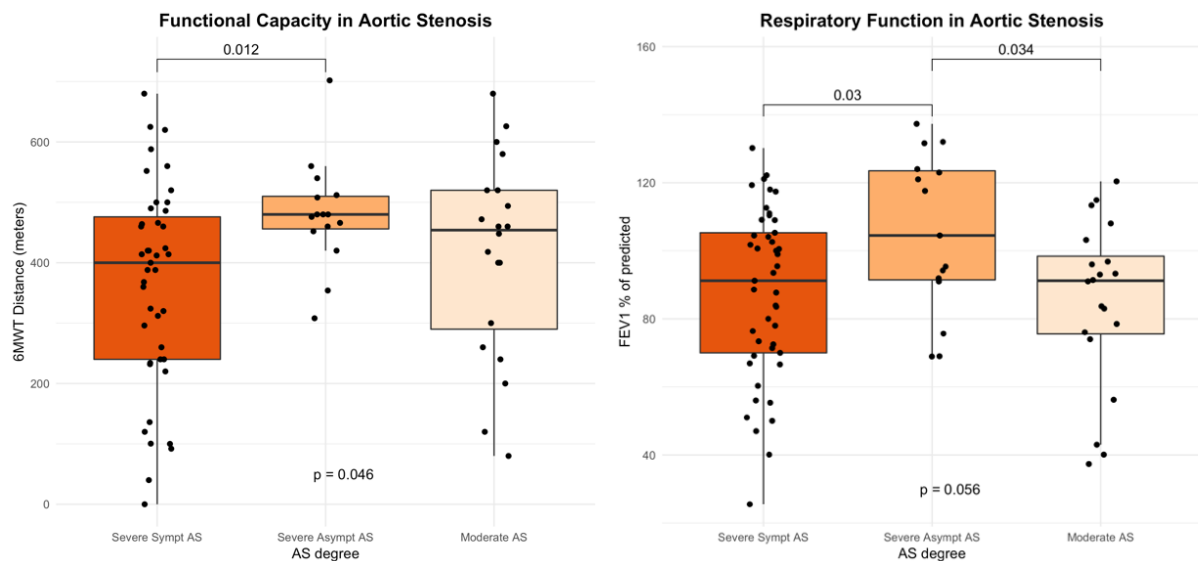


Figure 5-2. **Functional capacity and respiratory function in aortic stenosis.**

Boxplots for 6MWT distance and FEV1% of predicted in AS groups with overall p-values for one-way ANOVA or Kruskal tests and pairwise comparison p-values for independent T-tests or Mann-Whitney-Wilcoxon tests, as appropriate.

Differences were present in functional capacity (distance at 6MWT) and respiratory function (FEV1%) between AS degrees. Importantly, the *asymptomatic severe AS* subgroup was the healthiest while both moderate AS and symptomatic AS had heterogeneously reduced values of walking distance and FEV₁. This might be in-keeping with the elderly co-morbid population characteristics: patients with *moderate AS* may have other comorbidities (i.e. lung disease) which may have impacted on their respiratory and functional capacity regardless of the aortic valve obstruction degree. Moderate AS also presented with various degrees of atypical dyspnoea and NYHA class similar to the symptomatic severe AS subgroup.

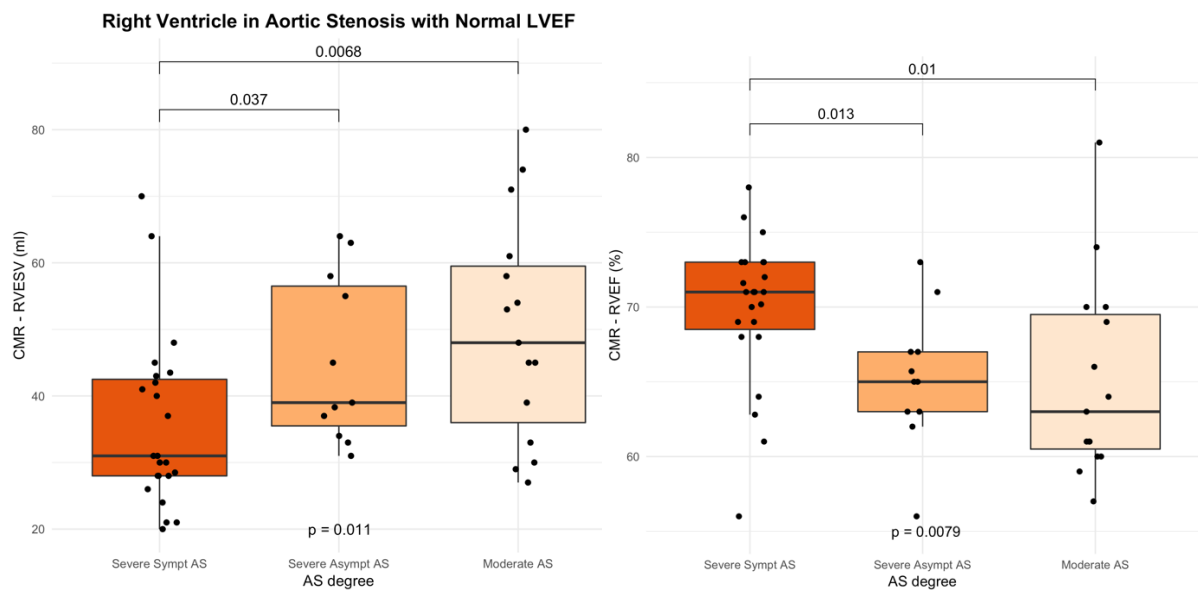


Figure 5-3. **Right ventricular systolic function in aortic stenosis with normal LVEF.**

Beeswarm boxplots for RVESV and RVEF in AS groups with overall p-values for one-way ANOVA or Kruskal tests and pairwise comparison p-values for independent T-test or Mann-Whitney-Wilcoxon test, as appropriate. Small RV end-systolic cavity and increased RVEF were present in patients with *symptomatic severe AS* and normal LVEF. These findings replicate in a different population the results discussed previously in Chapter 4 and confirm that the *hyperdynamic RV* is a marker of symptomatic severe AS.

Note: the participants were reclassified as having normal LVEF based on CMR results (LVEF on CMR > 55%) rather than on echocardiography (AMICA inclusion criteria: LVEF on echo > 55%). This explains the differences between the statistically significant results in the above plots compared to the statistical trends seen in Table 5-2.

5.1.10 Baseline Clinical Characteristics according to Dyspnoea

Baseline clinical characteristics are also reported according to subjective dyspnoea (Table 5-3). Dyspnoea is a subjective sensation and reporting breathlessness according to the clinician definition may have been influenced by other clinical management evaluations. In addition, the definition of AS degree is often difficult due to error in measurement, paradoxical low-flow low-gradient AS and the dichotomous definition of AS stage. Therefore, I report baseline characteristics according to symptoms only.

Patients with moderate-severe AS and dyspnoea had higher BMI, higher prevalence of COPD-STS and more years of smoking. They also differed in symptomatic and quality of life assessments with more clinically recognised dyspnoea, higher NYHA class, higher values of CAT score and lower EUROQOL scale values compared to asymptomatic AS. They did not differ in terms of aortic valve disease severity.

Table 5-3. Baseline clinical characteristics according to dyspnoea presence.

	Moderate-Severe AS		
	Symptomatic AS (n=59)	Asymptomatic AS (n=21)	p-value
Clinical			
Age, years	74 ± 10	71 ± 12	0.32
Gender, Male	68%	67%	0.92
BMI, kg/m²	28 ± 5	26 ± 3	0.01
Systolic BP, mmHg	141 ± 21	141 ± 19	0.97
Diastolic BP, mmHg	72 ± 10	72 ± 10	0.83
Haemoglobin, g/dl	13 ± 1	14 ± 1	0.18
BNP, pmol/L	24 (33)	16 (15)	0.26
eGFR, mL/min/1.7	73 (25)	80 (16)	0.20
COPD-STs	54%	14%	0.001
Smoking Status, exposed	54%	52%	0.99
Smoking years in exposed	30 (25)	15 (3)	0.04
<i>Medical therapy</i>			
ACE/ARB inhibitors	45%	48%	0.83
Beta-blockers	26%	24%	0.85
Diuretics	17%	14%	1
Bronchodilators	28%	14%	0.35
Steroids	31%	5%	0.03
<i>Symptomatic status</i>			
Any dyspnoea, n (%)	100%	-	<0.0001
NYHA class 1-2	53%	100%	
class 3-4	47%	-	<0.0001
CAT score	15 (11)	6 (4)	
EuroQoL scale	7.5 (1.6)	8.1 (2.0)	0.01
Echocardiographic parameters			
Peak aortic velocity - echo, m/s	4.1 (1.3)	4.1 (0.9)	0.81
Mean aortic gradient - echo, mmHg	39 ± 17	39 ± 12	0.98
Aortic valve area - echo, cm²	0.87 (0.42)	0.94 (0.32)	0.31
E/E’ ratio [#] - echo	14 ± 5	13 ± 3	0.37

BMI: body mass index; BP: blood pressure; BNP: brain natriuretic peptide; eGFR: estimate glomerular filtration rate; NYHA: New York Heart association; CAT: COPD assessment tool.

5.1.11 Cardiorespiratory Parameters according to Dyspnoea

Cardiorespiratory parameters at first visit are described in Table 5-4. Patients with moderate-severe AS and dyspnoea had severely reduced functional capacity (6MWT distance) and in most cases (64%) symptomatic onset was exacerbated during the flat surface walk performed for research purposes.

Almost half of the symptomatic patients had a degree of COPD-GOLD which was mostly mild-moderate, compared to only 14% of the asymptomatic patients. Significant differences in lung function tests were also seen with reduced FEV₁, FVC, PEF and DLCO in the symptomatic group. However, no morphological differences were noted on CT regarding emphysema presence, degree and airway alterations.

Cardiac volumetric and functional parameters were similar between the two groups.

Table 5-4. Cardio-respiratory parameters according to dyspnoea presence.

	Moderate-Severe AS		
	Symptomatic AS (n=59)	Asymptomatic AS (n=21)	p-value
Functional capacity – 6MWT			
Distance, meters	359 ± 160	509 ± 95	<0.0001
Symptomatic onset	64%	5%	<0.0001
Oxygen Sat at rest, %	97 (3)	97 (1)	0.21
Oxygen Sat at exercise, %	97 (2)	97 (2)	0.58
Heart rate at rest, bpm	71 ± 11	65 ± 16	0.13
Heart rate at exercise, bpm	99 (23)	102 (12)	0.67
Respiratory function - PFT			
COPD-GOLD	49%	14%	0.008
GOLD grade			0.016
No airway obstruction	51%	86%	
Grade 1-2 (mild/moderate)	37%	9%	
Grade 3-4 (severe/very severe)	12%	5%	
FEV ₁ /FVC	71 (12)	75 (9)	0.03
FEV ₁ %	84 (32)	115 (26)	<0.0001
FVC %	92 ± 18	112 ± 16	<0.0001
PEF %	87 ± 33	103 ± 24	0.038
TLC %	108 ± 19	116 ± 20	0.66
RV %	118 (33)	110 (21)	0.19
IC %	114 ± 33	122 ± 28	0.11
DLCOc %	80 ± 24	92 ± 15	0.0009
Respiratory morphology - CT			
Emphysema %	7.9 (12.1)	9.1 (7.8)	0.81
Emphysema density (HU)	-920 ± 34	-921 ± 30	0.86
Air %	82 (5)	81 (5)	0.73
Mean airway lumen radius (mm)	9.1 ± 1.6	9.0 ± 0.8	0.65
Mean airway wall thickness (mm)	3.8 (1.5)	3.7 (1.1)	0.69
Cardiac morphology and function - CMR			
LV end diastolic volume, mL	146 (54)	148 (48)	0.35
LV end systolic volume, mL	48 (31)	59 (35)	0.19
LV stroke volume, mL	92 ± 21	98 ± 25	0.28
LV ejection fraction, %	65 (13)	63 (13)	0.38
LV mass, g	128 ± 38	135 ± 32	0.52
RV end diastolic volume, mL/m ²	130 ± 36	139 ± 50	0.39
RV end systolic volume, mL/m ²	44 ± 28	54 ± 29	0.15
RV stoke volume mL/m ²	83 ± 21	90 ± 23	0.25
RV ejection fraction, %	65 ± 8	63 ± 9	0.32
RV mass, g	30 ± 9	32 ± 11	0.31

Bpm: beats per minute; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; TLC: total lung capacity; RV: residual volume; inspiratory capacity; DLCOc: corrected diffusing capacity for carbon monoxide; HU; Hounsfield units; LV: left ventricular; RV: right ventricular.

5.1.12 Smoking Exposure and Aortic Stenosis

The odds of a person exposed to smoke being at a severe stage of AS were 3.5 times higher (odds ratio 3.5, 95% C.I. 1.18, 10.38) than the odds of a person never exposed to smoking. Of the smokers, 36 (86%) had severe AS compared to only 24 (63%) of the non-smokers (Figure 5-4). The study population proportion of severe AS was about 36% higher in the smokers compared to the non-smokers (relative risk 1.36 with 95% CI 1.03, 1.78).

A Cochran-Armitage test of trend was run to determine whether a linear trend existed between the degree of AS (symptomatic severe, asymptomatic severe and moderate) and the proportion of patients exposed to smoking. The smoking status was divided in non-smokers (n =36) and exposed to smoke (n=42): 62% of symptomatic severe AS were smokers compared to 53% of asymptomatic severe and 30% only of moderate AS. The Cochran-Armitage test of trend showed a statistically significant linear trend, $p = 0.0019$, with advanced AS degree associated with a higher proportion of patients being exposed to smoke.

Generalised linear models were used to assess the association between common cardiovascular risk factors and AS degree. The analysis of covariance (ANCOVA) with a binary response variable (moderate/severe AS) was conducted for assessing the following cardiovascular risk factors: age, BMI, gender, hypertension, dyslipidaemia and smoking exposure. The only significant independent risk factor associated with AS class was smoking exposure ($p = 0.00875$).

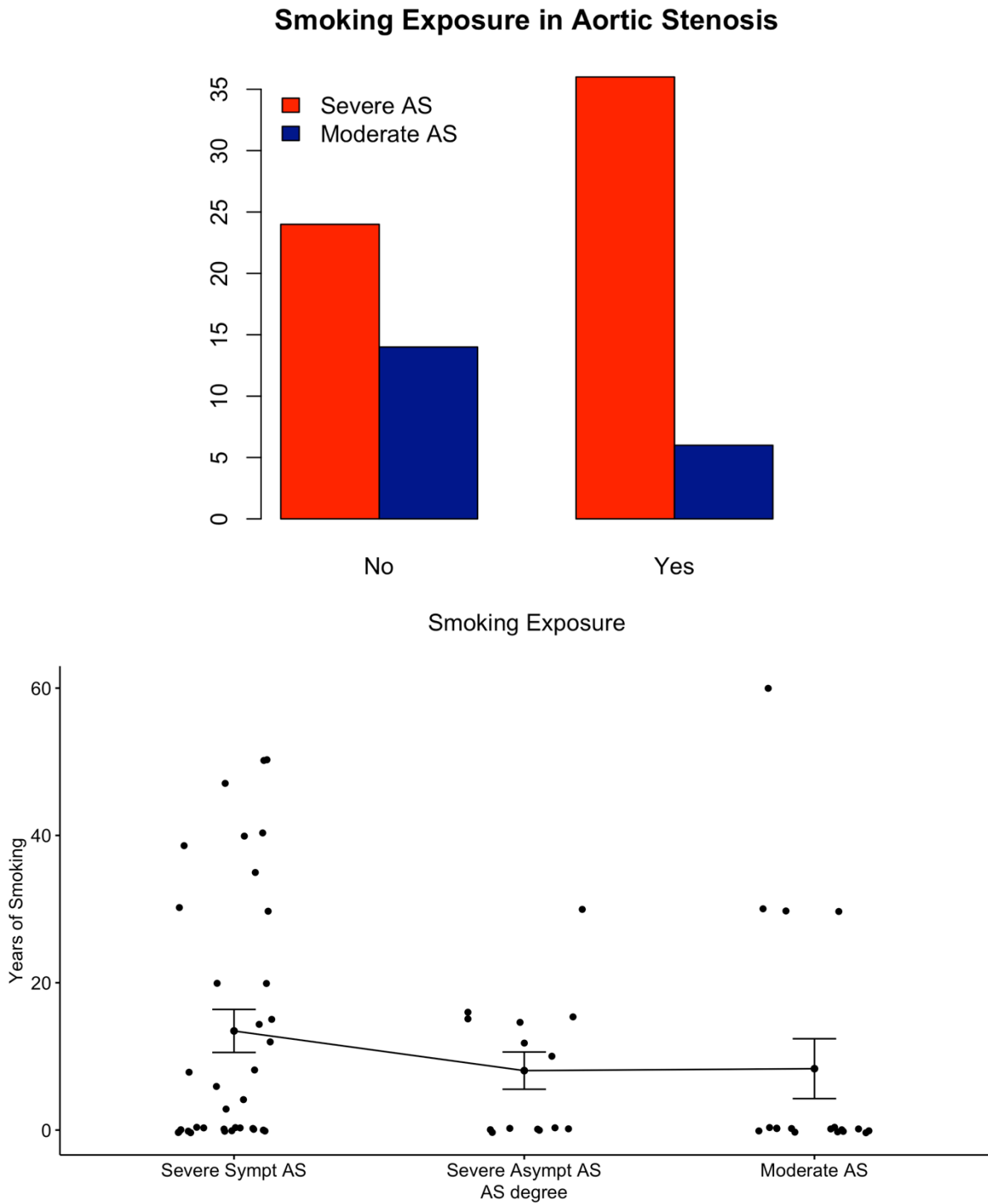


Figure 5-4. **Smoking exposure association with aortic stenosis.**

Top panel: Of the patients exposed to smoke, 36 (86%) had severe AS compared to only 24 (63%) of the non-smokers (odds ratio 3.5, 95% C.I. 1.18 - 10.38). Bottom panel: mean plot for numbers of years of active smoking in the degree of AS subgroups.

5.1.13 Prevalence of Lung Disease in Aortic Stenosis

All participants (100%) underwent spirometric assessment and most (72%) completed full PFTs. The prospective prevalence of COPD-GOLD in this group was 40% with 32 participants having a $FEV_1/FVC < 0.7$. The distributions of spirometry values are shown in the top panel of Figure 5-5.

Emphysema was present in 39,7% of the AMICA-AS population. Chest CT parameters distributions are shown in the middle and lower panel of Figure 5-5. The prevalence of emphysema was 34,7% in severe AS with a clear difference between morphological lung disease presence in asymptomatic severe AS (only 21,4%) compared to symptomatic severe AS (emphysema % ≥ 10 in 40%).

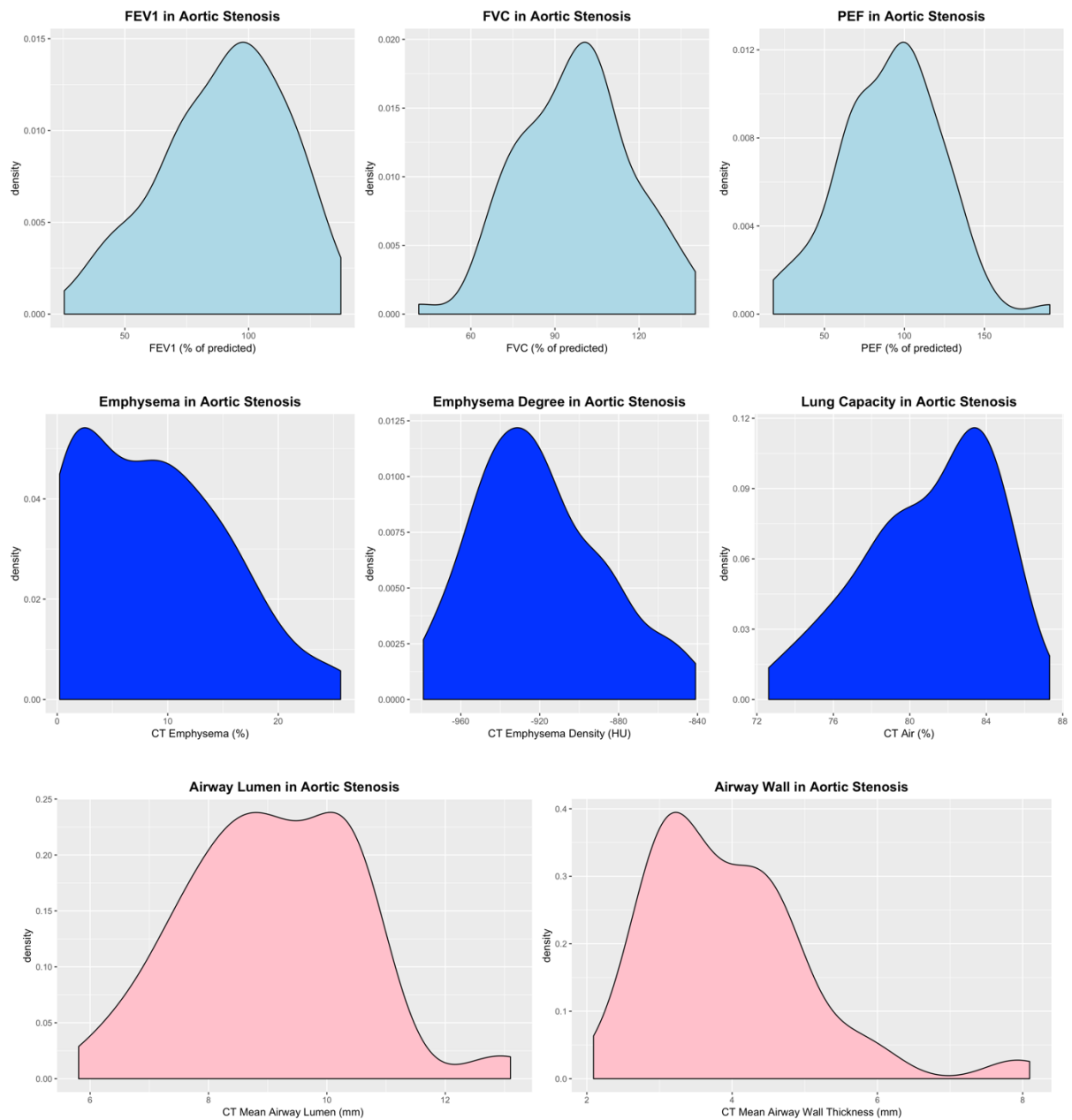


Figure 5-5. Smooth density plots of population distributions for respiratory functional and morphological characteristics in aortic stenosis.

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; CT: computed tomography; HU: Hounsfield units.

5.1.14 COPD Discrepancy in Aortic Stenosis

The prevalence of COPD was high in this cohort for both COPD-GOLD and COPD-STS, as shown in Figure 5-6. The degree of COPD was mostly mild-moderate only (74% of COPD-AS, Figure 5-7).

In the symptomatic AS undergoing valve replacement, COPD-GOLD prevalence was 44% in the surgical subgroup and 60% in the TAVI one (Figure 5-8). There was a statistically significant discrepancy in COPD-STS and COPD-GOLD (Chi-squared test χ^2 13.545, $p=0.0002$), despite the similar overall percentages with/without COPD: 13 patients (37%) defined as COPD-STS had no airflow limitation and 10 (22%) of those with no COPD-STS had underlying obstruction.

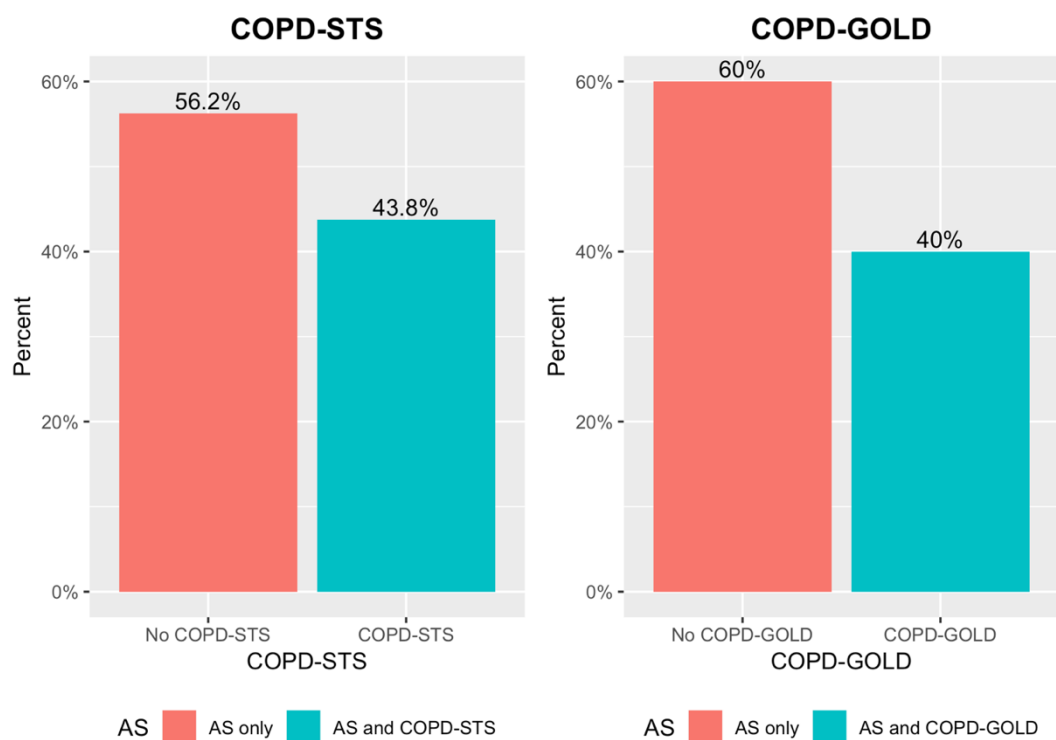


Figure 5-6. Prevalence of COPD-STS and COPD-GOLD in aortic stenosis.

When assessment of apparent and confirmed COPD was performed prospectively, COPD prevalence was high (44% and 40% for COPD-STS and COPD-GOLD, respectively). The burden of COPD prospectively recorded was higher than what found in the retrospective multi-centre study of severe AS described in Chapter 3 - Respiratory function in Aortic Stenosis.

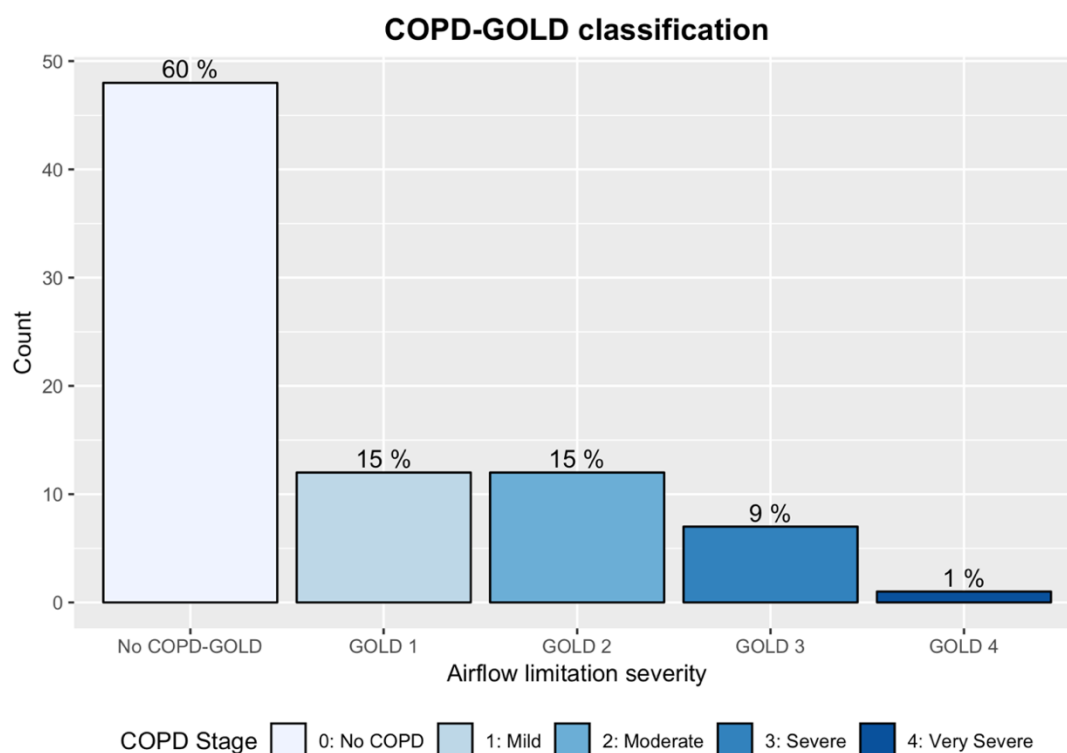


Figure 5-7. **COPD-GOLD stage in aortic stenosis.**

Classification of COPD-GOLD stages based on airway limitation severity prospectively assessed in moderate-severe AS. All participants underwent complete spirometry performed for research purposes. Most COPD was mild-moderate only. COPD grade percentages in AS.

Mild $FEV1 \geq 80\%$ predicted, moderate $50\% \leq FEV1 \leq 80\%$ predicted, severe $30\% \leq FEV1 \leq 50\%$ predicted, very severe $FEV1 < 30\%$ predicted.

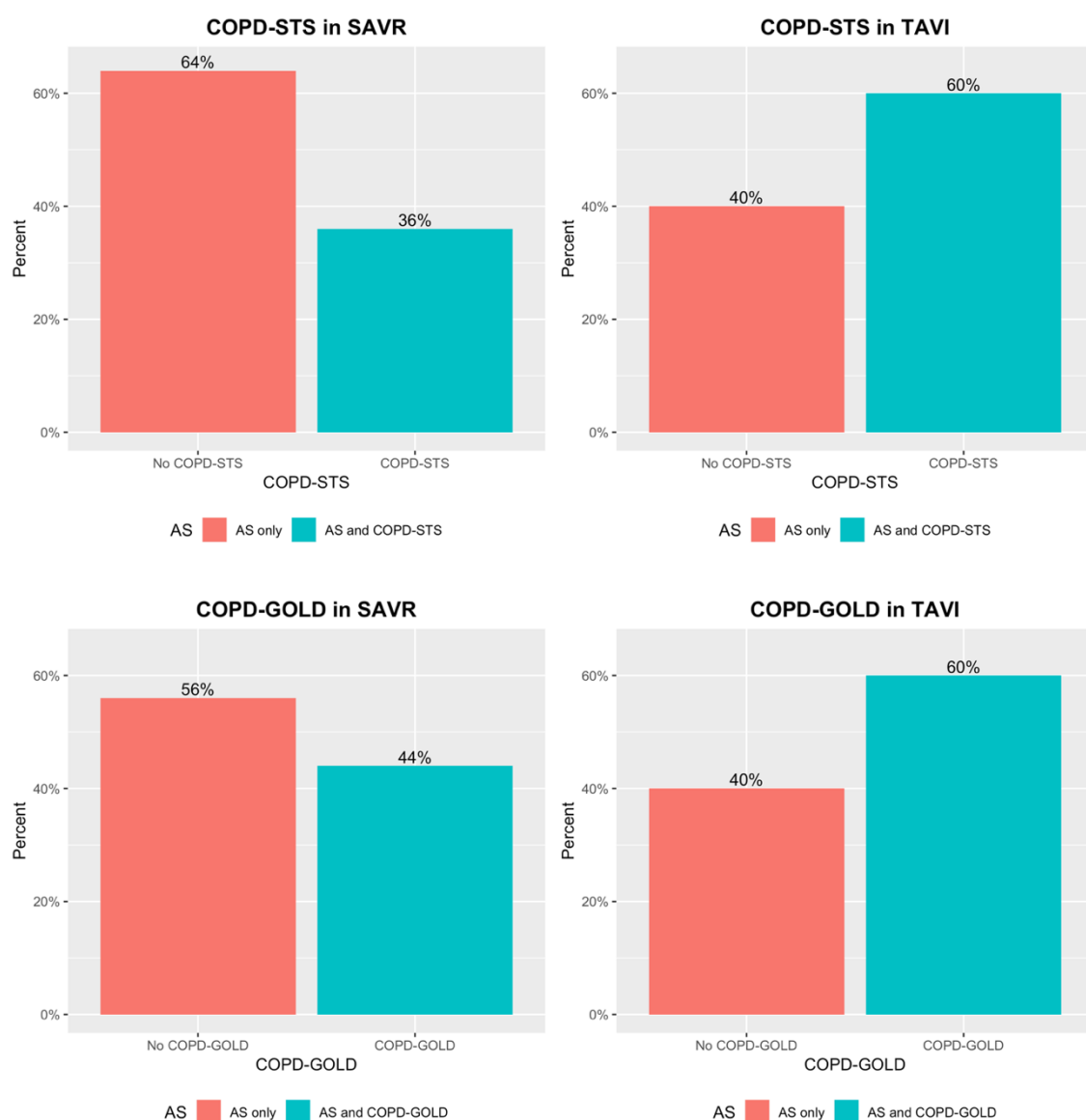


Figure 5-8. Prevalence of COPD-STS and COPD-GOLD in symptomatic aortic stenosis undergoing valve replacement.

The majority of patients undergoing TAVI (60%) had a degree of confirmed airflow obstruction (COPD-GOLD) compared to 44% of those undergoing surgery. The discrepancy between COPD diagnosis was evident in the surgical group who was at lower risk (lower COPD-STS) compared to the higher levels of spirometric dysfunction. TAVI patients when spirometry was prospectively performed, had similar COPD prevalence with both classifications.

5.1.15 COPD Associations in Aortic Stenosis

Simple linear regressions were conducted to assess the relationship between FEV₁ and baseline characteristics of the study population (Table 5-5). FEV₁ was associated with medical therapy (bronchodilators and steroids), white blood cells, smoking years, NYHA class, respiratory symptoms, quality of life, symptomatic onset on the six-minute walking test and rest oxygen saturation.

A multiple linear regression was run adopting a stepwise progression from the maximal model to the minimal adequate model to explain the variation in FEV₁ in AS.

The minimal adequate model could predict 48% of the variation of FEV₁ in symptomatic AS, a medium-large effect size, and accounted for laboratory signs of inflammation, bronchodilators use and symptomatic onset on exercise. Of these, only white cells count was independently associated to FEV₁, but the other parameters manifested a statistical trend to independent association.

Table 5-5. FEV₁ associations in aortic stenosis.

<i>Simple linear regression analysis</i>			
	r	r²	sig.
Age, yrs	-0.02	0	0.84
Gender, male	0.15	0.02	0.18
BMI, kg/m ²	-0.12	0.01	0.3
Smoking, yrs	-0.29	0.08	0.02
BNP, pmol/L	0.008	0	0.95
WBC, 10 ⁹ /L	-0.43	0.18	<0.001
Bronchodilator use	-0.43	0.18	<0.001
Steroid use	-0.35	0.12	0.002
NYHA functional class	-0.43	0.18	<0.001
CAT score	-0.42	0.18	<0.001
EuroQoL	0.32	0.10	0.005
6MWT symptomatic onset, meters	0.45	0.20	0.01
6MWT distance, meters	0.37	0.14	0.001
6MWT oxygen saturation at rest	0.38	0.14	0.001
6MWT oxygen saturation at exercise	0.04	0	0.77
AVA, cm ²	-0.08	0	0.54
LVEF, %	0.08	0	0.52
LV mass index, g/m ²	0.01	0	0.9
<i>Multiple linear regression analysis</i>			
Minimal model: r 0.69, r² 0.48, p 0.001	B	SE	sig
WBC, 10 ⁹ /L	-5.45	2.17	<0.001
Bronchodilator use	-14.1	7.61	0.07
6MWT symptomatic onset, meters	0.07	0.03	0.06

BMI: body mass index; BNP: brain natriuretic peptide; WBC: white blood cells; NYHA: New York Heart association; CAT: COPD assessment tool; 6MWT: six-minute walking test; AVA: aortic valve area; LVEF: left ventricular ejection fraction.

5.1.16 COPD Morphological Characteristics in Aortic Stenosis

Patients with AS were assessed based on their COPD-GOLD presence and degree, as shown in

Figure 5-9. FEV₁ defined the degree of COPD in groups with reduced FEV₁/FVC ratio but different FEV₁ percentage values were present in those with normal ratio who might either had no airflow obstruction or manifested a concomitant FVC reduction which maintained the fixed spirometric diagnostic COPD criteria into the normal range. FEV₁% values were 110% ± 19% in the 48 AS participants with no COPD-GOLD, 84% ± 20% in the 24 AS/COPD-GOLD mild-moderate, and 44% ± 9% in the 8 participants with AS/COPD-GOLD severe or very severe (p<0.0001).

Morphological differences were detected on chest CT between no airflow limitation patients compared to mild-moderate and severe-very severe COPD-GOLD stages: CT air % was 80% ± 3% in isolated AS, 83% ± 3% in COPD 1-2, and 84% ± 2% in COPD 3-4, p=0.0012; CT emphysema density was -918 HU (43.5) in AS only, -941 HU (40) in COPD 1-2, -942 HU (25) in COPD 3-4.

However, no significant morphological differences were present on chest CT between COPD-GOLD subgroups (pairwise comparisons presented in

Figure 5-9). Patients with no airflow limitation (FEV₁/FVC ratio >0.7) and those with mild-moderate limitation (FEV₁/FVC < 0.7 and FEV₁ > 50 % of predicted) were the most heterogeneous groups.

The discrepancy between emphysema/airway disease presence and respiratory function may be explained by other confounding effects such as heart failure and elderly age which may have impacted on FEV₁ and other functional measurements in patients with similar degree of morphological alterations. Moreover, while the severe/very severe COPD subgroup were a homogeneous group, the most represented AS groups with mild-moderate FEV₁ reduction showed heterogeneous values. This is likely composed by patients with true lung disease and patients with apparent lung dysfunction driven by other modifiable factors (heart failure in AS).

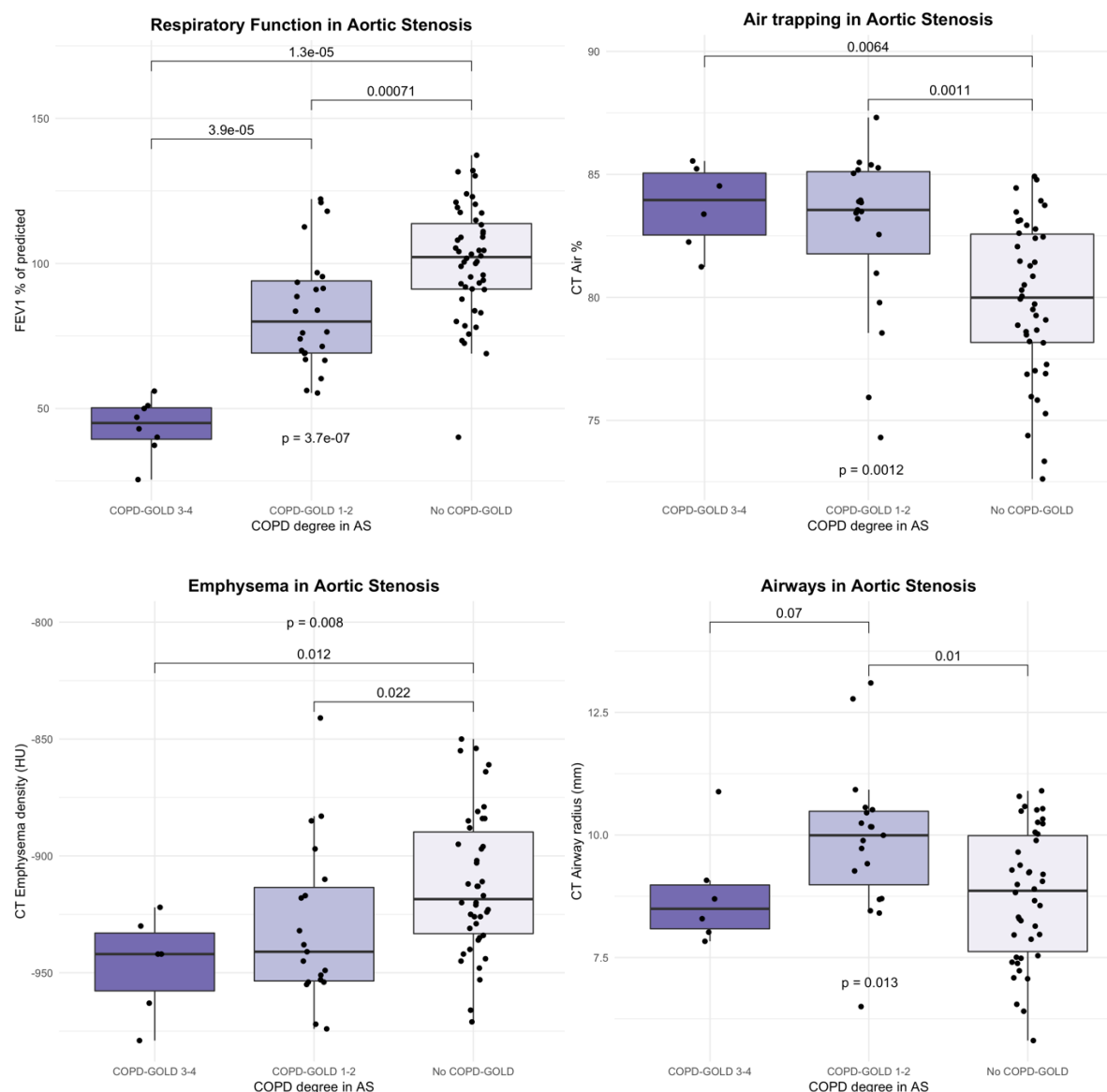


Figure 5-9. COPD-GOLD characteristics in aortic stenosis.

Beeswarm boxplots for FEV1 and CT lung parameters. Morphological lung differences were present between isolated AS and both mild-moderate COPD AS and severe-very severe COPD AS. However, there were no significant differences between COPD stages. In addition, only COPD-GOLD 3-4 group had homogeneous characteristics; other AS groups with mild-moderate FEV1 reduction (isolated AS and COPD 1-2) were heterogeneous and might have been composed by true lung alterations patients and those with apparent lung dysfunction driven by cardiac disease. This is in-keeping with the hypothesis that FEV1 reduction is only partially determined by lung disease in AS. P-values for one-way ANOVA or Kruskal tests, and pairwise comparisons with independent T-test or Mann-Whitney-Wilcoxon test.

5.1.17 Hyperpolarised Xenon Magnetic Resonance Imaging

A subgroup of 25 participants of the AMICA-AS Study underwent HP-Xe MRI for ventilation and diffusion imaging. An example of HP-XE MRI performed in an AMICA-AS participant is shown in Figure 5-10.

Safety in the elderly and co-morbid population with cardiac and lung disease was proven with no adverse events experienced and a good tolerability profile.

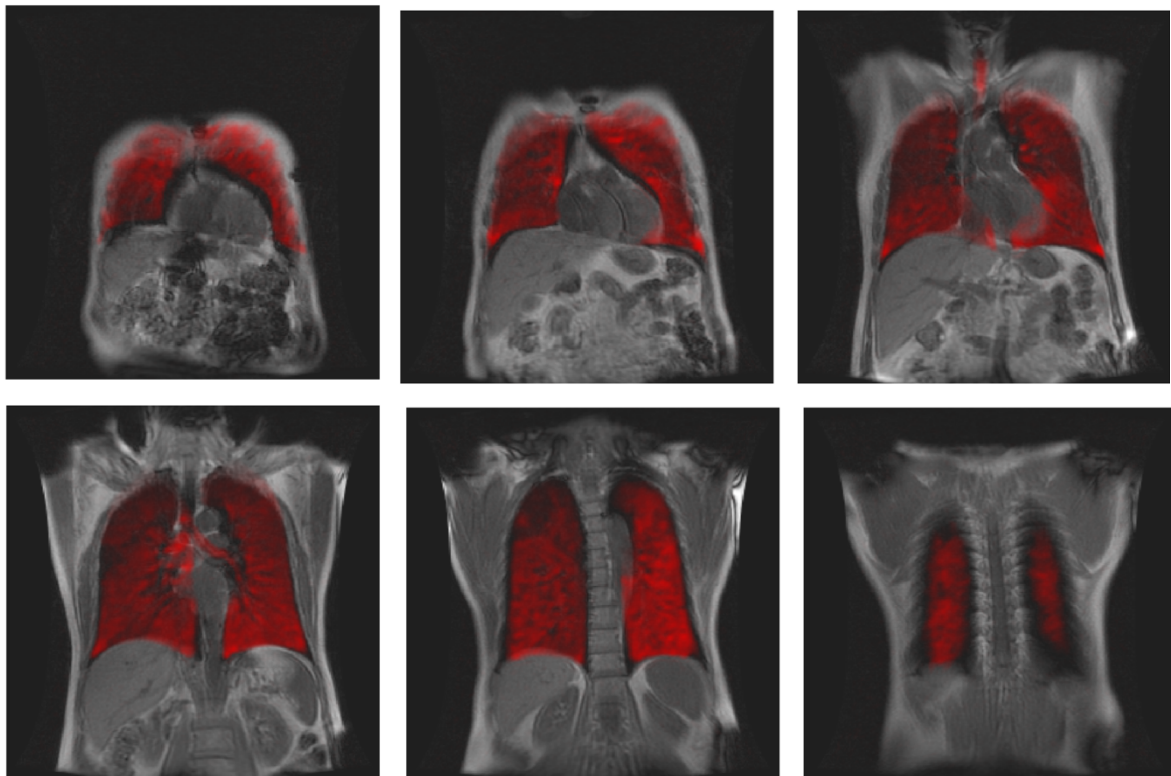


Figure 5-10. **Coronal co-registration between HP-Xe and proton MRI.**

Coronal chest MRI showing overlapping co-registered HP-Xe MRI ventilation imaging (red) and conventional proton MRI (grey scale) which enables visualisation and definition of lung boundaries, important particularly in areas of xenon ventilation defects.

A new technique was developed in the AMICA-AS study to assess gas exchange. Its feasibility was proven in four participants (253). The new technique was developed to capture the diffusion dynamics of Xe-129 from the alveolar air sacs to the pulmonary tissue and blood plasma (PTBP), and the red blood cells (RBCs) compartments in the human lung in a single breath-hold. The gas-transfer dynamic of HP ^{129}Xe from its gas phase in the alveolar spaces to the PTBP and RBC compartments of the lungs and heart were obtained from the mean signal intensity of time-series Iterative Decomposition of water and fat with Echo Asymmetry and Least-square estimation approach (IDEAL) images for three ROIs (left lung, right lung and left ventricular cavity of the heart). The time-series IDEAL technique enabled the visualisation and quantification of inhaled xenon from the alveoli to the LV during a single breath-hold, in healthy and diseased lungs, example shown in

Figure 5-11.

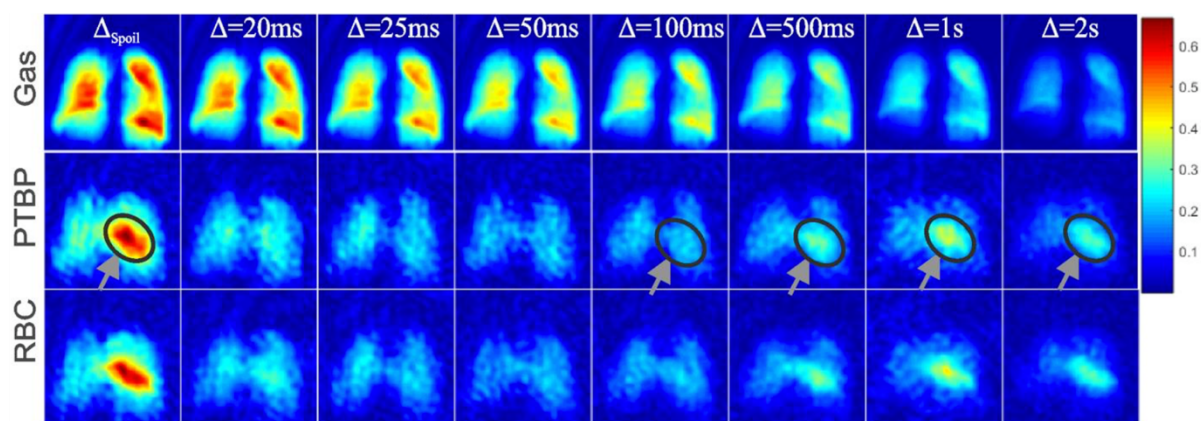


Figure 5-11. **Coronal time-series IDEAL images of gas-transfer time steps.**

IDEAL images in a healthy subject showing the diffusion dynamics of Xe-129 in the gas phase (alveolar space) and dissolved phase in the pulmonary tissue and blood plasma (PTBP compartment) and in the red blood cells (RBC compartment). The grey arrows point at the dissolved phase signal from the heart.

Additional images published in Doganay O. et al. European Radiology 2018, Epub ahead of print (253) Rigolli M. co-authored the article.

5.1.18 Follow-up after Aortic Valve Replacement

Forty-two AMICA participants underwent valve replacement after a median of 1.2 months (IQR 2.4 months) from baseline visit. Those who were actively removed from the invasive waiting list or who remained pending for longer than 12 months were considered excluded since the delay period was unreasonably longer than the usual maximal waiting time of 3 months for SAVR and 6 months for TAVI.

Of the 5 patients excluded from any type of invasive treatment, the main exclusion reason was “COPD or other lung disease”. This was present in 4 out of 5 participants, while the remaining one refused to undergo any procedure. The invasively treated participants underwent either SAVR (n=28) or TAVI (n=14). In those treated with TAVI, the exclusion reasons from SAVR were: “COPD or other lung disease” in 4 participants, “frailty” in 3, “other co-morbidities” in 2 and one was randomised to TAVI treatment being contemporarily involved in another research (the UK TAVI trial).

Of the 42 participants who underwent valve replacement, 37 performed their follow-up visit after a median time of 6.6 months (IQR 1.2 month) from AVR. Six participants did not perform their follow-up visit due to the following reasons: one died of cancer, two were severely functionally impaired due to procedural TAVI complications (one had a debilitating stroke and one severe peripheral vascular disease with inferior limb amputation), one had a moderate AS only at baseline, one was lost to follow-up and one refused follow-up.

The AMICA follow-up characteristics are described in Table 5-6.

Table 5-6. Cardiorespiratory parameters pre- and post-AVR in follow-up participants.

	Follow-up (n = 37)		P-value
	Pre-AVR	Post-AVR	
Clinical parameters			
Subjective improvement	-	78%	-
CAT score	12 ± 6	7 ± 5	<0.0001
EuroQoL scale	7.5 (1.5)	8.2 (1.5)	0.01
BNP, pmol/L	31 (38)	31 (28)	0.21
eGFR, mL/min/1.7	76 ± 13	76 ± 14	0.92
Functional capacity – 6MWT			
Distance, meters	442 (135)	450 (105)	0.01
Symptomatic onset	62%	26%	
Oxygen Sat at rest, %	97 (3)	97 (2)	0.73
Oxygen Sat at exercise, %	97 (2)	97 (2)	0.3
Heart rate at rest, bpm	68 ± 11	68 ± 14	0.46
Heart rate at exercise, bpm	101 ± 19	103 ± 25	0.54
Respiratory parameters - PFT			
FEV ₁ /FVC	72 (13)	72 (11)	0.7
FEV ₁ %	97 (31)	93 (26)	0.76
FVC %	102 (21)	99 (18)	0.38
PEF %	96 ± 27	102 ± 25	0.22
TLC %	108 (15)	105 (11)	0.88
RV %	121 ± 22	119 ± 18	0.07
IC %	126 ± 23	119 ± 21	0.22
DLCOc %	87 (27)	85 (22)	0.11
Cardiac parameters - CMR			
AV peak gradient, mmHg	83 (42)	23 (15)	<0.0001
LV end diastolic volume, mL	144 (45)	127 (39)	0.0002
LV end systolic volume, mL	54 ± 29	47 ± 17	0.22
LV stroke volume, mL	92 ± 20	80 ± 20	<0.0001
LV ejection fraction, %	65 ± 11	63 ± 8	0.15
LV mass, g	140 ± 36	123 ± 29	0.01
RV end diastolic volume, mL/m ²	122 (44)	125 (57)	0.05
RV end systolic volume, mL/m ²	43 ± 23	43 ± 17	0.40
RV stroke volume, mL/m ²	84 ± 20	78 ± 24	0.01
RV ejection fraction, %	68 ± 7	65 ± 6	0.16

Continuous variables as mean ± standard deviation or median (interquartile range), categorical variables as percentages. P-values for paired Student T-tests, paired Wilcoxon test, or McNemar test. CAT: COPD assessment tool; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; bpm: beats per minute; 6MWT: six-minute walking test; PFT: pulmonary function test; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak

expiratory flow; TLC: total lung capacity; CMR: cardiovascular magnetic resonance; RV: residual volume; IC: inspiratory capacity; DLCOc: corrected diffusing capacity for carbon monoxide; AV: aortic valve; LV: left ventricular; RV: right ventricular.

Most of the follow-up participants (78%) manifested a subjective improvement after AVR. Significant differences were noted in respiratory symptomatic status (CAT score) with improvement in most participants (pre-AVR CAT 12 ± 6 vs post-AVR CAT 7 ± 5 , $p < 0.0001$). Small significant differences were seen in quality of life and functional capacity (distance at the 6-min walking test), as shown in Figure 5-12.

In addition, patients experienced cardiac reverse remodelling with a significant reduction in LVEDV and LV mass. Both left and right stroke volumes were also reduced after AVR in-keeping with a reduction in volume overload and compensatory hyperdynamic response (Table 5-6).

On the contrary, there were no significant differences in respiratory functional parameters pre and post-AVR, as shown in Table 5-6.

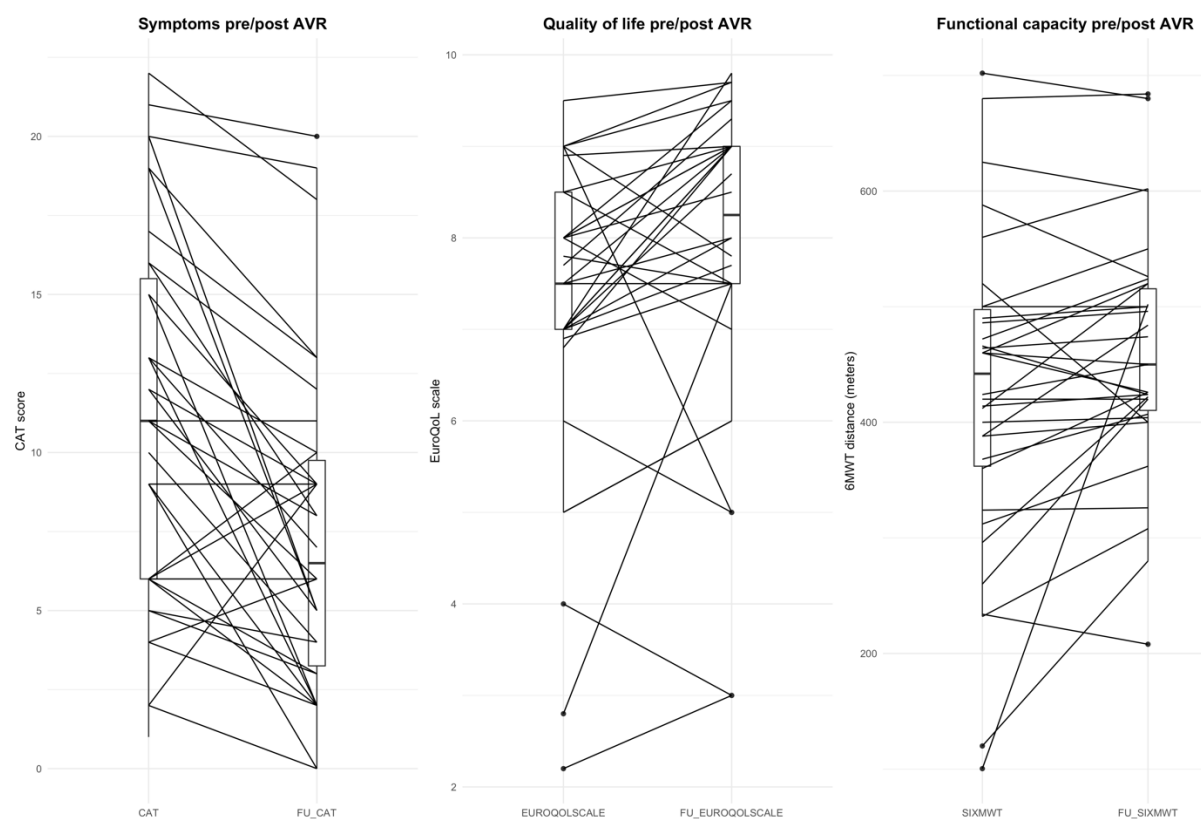


Figure 5-12. **Differences pre and post-AVR in follow-up participants.**

Most participants improved their respiratory symptoms as recorded by the COPD assessment test (CAT) with an important reduction in symptomatic score after AVR ($p < 0.0001$). They also generally experienced a small improvement in quality of life (EuroQoL scale) and 6-min walking test distance ($p = 0.01$ for both), although these responses were more variable with participants improving consistently and others worsening or not experiencing any change.

5.1.18.a Was COPD present in participants excluded from surgery?

COPD or other lung disease was the main reason of exclusion from surgical AVR, present in 29% of those who underwent TAVI. COPD was also the main reason of exclusion from any type of invasive treatment, present in 80% of those who were not treated (palliative medical therapy).

No differences in COPD morphological characteristics were detected between participant excluded from surgery due to lung disease compared to those excluded due to other reasons and to those treated with SAVR. Functional respiratory differences (FEV₁ % of predicted) were presented between SAVR patients and COPD excluded, although these might be also due to heart failure and be the reason for TAVI treatment (as seen in Chapter 3). In fact, most fragile patients manifested similar airflow obstruction: patients excluded due to COPD and those excluded due to other reasons (frailty and co-morbidities) had similar FEV₁ (Figure 5-13).

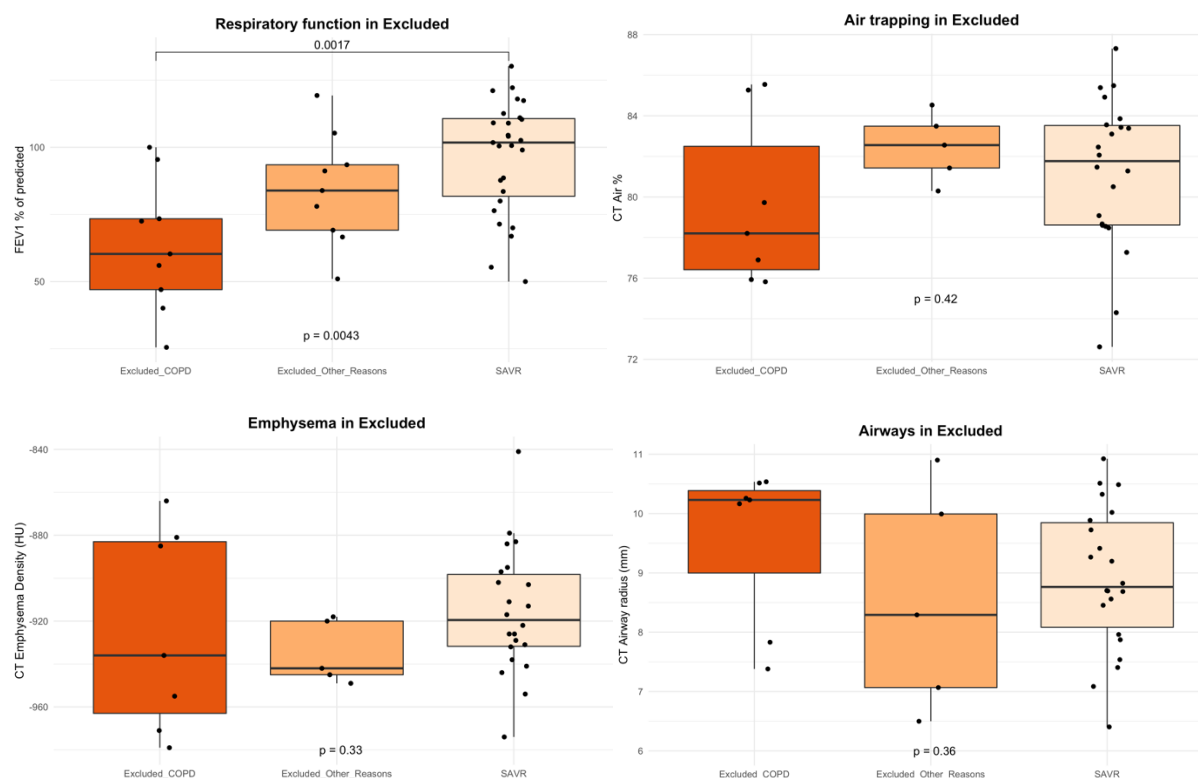


Figure 5-13. **Respiratory characteristics in participants excluded from surgery due to lung disease.**

Significant FEV₁ differences were present only between surgical patients compared with those who were excluded due to COPD. However, excluded due to COPD were not different from those excluded due to other reasons (frailty, other co-morbidities or refusal). No morphological differences in air trapping, emphysema degree or airway wall thickness were detected with CT between participants excluded due to COPD and other groups (SAVR treated or excluded for other reasons).

5.1.18.b Associations with functional improvement after AVR

Participants were reclassified based on lung functional and morphological characteristics pre-AVR to evaluate if novel COPD definitions were able to discriminate between those who would improve after AVR. The different thresholds and results are shown in Table 5-7. Patients with baseline higher values of FEV1, PEF, CT air and with lower emphysema degree significantly improved their walking distance after AVR.

Table 5-7. **Reclassification of COPD based on functional and morphological characteristics and its association to changes in functional capacity after AVR.**

Baseline lung parameters	6MWT distance change post-AVR		P-value
	Threshold	Mean Difference	95% C.I.
FEV ₁ %			
	≤75	-45	-114 / 24
	>75	-47	-81 / -12
PEF %			
	≤80	-19	-43 / 4
	>80	-43	-85 / -2
CT air %			
	>83	-65	-134 / -3
	≤83	-29	-68 / 10
CT emphysema (HU)			
	>-925	-45	-114 / 24
	≤-925	-47	- 81 / - 12

Follow-up patients were reclassified based on novel morpho-functional thresholds assessed pre-AVR to evaluate the discriminatory ability of baseline PFT and lung CT for post-AVR functional capacity improvement. P-values for paired T-tests in follow-up participants post-AVR. A negative mean difference stands for an improvement in walking distance at the 6MWT after AVR.

AVR: aortic valve replacement; 6MWT: six-minute walking test; FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; CT: computed tomography; HU: Hounsfield units.

DISCUSSION

5.1.19 Prevalence of Lung Disease

The importance of COPD as a relevant comorbidity in AS is shown in the AMICA-AS study. COPD-GOLD was prospectively diagnosed in 40% of moderate-severe AS. In addition, 40% presented significant emphysema on chest CT (emphysema $\geq 10\%$). Morphological lung disease was particularly significant in moderate AS and symptomatic severe AS. On the contrary, asymptomatic severe AS had the lowest prevalence of emphysema (only 21%). Differences between AS groups were even more pronounced when respiratory functional characteristics were adopted to diagnose respiratory dysfunction: COPD-GOLD was present in approximately 45% of the severe symptomatic AS and the moderate AS subgroups, while only 13% of the asymptomatic severe AS had a FEV₁/FVC ratio < 0.7 .

These results reflect an elderly and comorbid population in which controls with moderate AS are affected by lung disease and symptoms (30% were symptomatic for dyspnoea and 20% had a NYHA class 3-4) in a similar way to symptomatic severe AS participants. On the contrary, participants with severe AS who remain asymptomatic at a more advanced stage of AS are a selected group with less comorbidities, less lung disease and, therefore, less symptoms and better functional capacity. Symptomatic severe AS may reflect in some cases a continuum with symptomatic moderate AS rather than a progression of valve obstruction to determine cardiac symptoms.

5.1.20 Possible Explanations of the Elevated Prevalence of Lung Disease in Aortic Stenosis

The prevalence of COPD varies widely in the literature depending on definition, diagnostic criteria and patient selection. In our population, almost one every two patients with symptomatic AS was affected by COPD, while the worldwide prevalence of this disease in adults is estimated to be 9-10% (248). This higher prevalence could be explained by two main co-existing reasons: the shared risk factors (elderly age and smoking) and the overlapping symptoms between the two diseases.

Firstly, higher COPD prevalence would be reasonably expected in AS patients due to the typical advanced age at the time of symptomatic onset. Our results are more in-keeping with those found in the elderly population: a multinational, cross-sectional population-based study revealed a COPD prevalence of 19.2% in over 70s with a two-fold increase for every 10-year increment in age (42). This is also reflected in the higher COPD prevalence seen among individuals frequenting senior community centres (254). However, the COPD prevalence found in the AMICA-AS is even higher and may be consistent with the presence of another important shared risk factor: smoking. The chapter results show how smoking is linked to advanced stages of aortic valve obstruction: the odds of a person exposed to smoke being at a severe stage of AS were 3.5 times higher (odds ratio 3.5, 95% C.I. 1.18, 10.38) than the odds of a person who had never been exposed to smoking.

Secondly, a common symptomatic pattern between severe AS and COPD, including dyspnoea, exercise intolerance, chest discomfort, and respiratory failure, could also explain a higher prevalence of clinically diagnosed COPD in this particular group of patients. Those who are elderly and unable to perform an optimal spirometry may be misdiagnosed with COPD.

However, emphysema diagnosis which is independent from the patient ability to perform a respiratory test was also high. This is more in-keeping with a truly higher prevalence of lung disease in cardiac disease and confirms the important need of differentiating cardiac and lung symptoms in this significant group of patients who have both underlying conditions.

5.1.21 Discrepancy in COPD Diagnosis

Although prevalence of COPD-GOLD and COPD-STS was more similar when spirometry was prospectively performed, the discrepancy between diagnosis was still present when spirometry was prospectively performed (no missing data): a consistent group of patients had COPD-STS without evidence of any airflow obstruction. This confirms the findings of Chapter 3 that COPD-STS and COPD-GOLD are two distinct entities. COPD classification in cardiac risk scoring is currently based on the mere evaluation of the long-term use of bronchodilators or steroids and has been previously validated in a younger population undergoing bypass surgery (255). In this type of elderly population with respiratory symptoms, such risk scores may be over simplistic, and a more extensive respiratory evaluation needed.

5.1.22 COPD and Symptoms in Aortic Stenosis

In patients with AS, respiratory function was associated with symptoms: FEV₁ was associated with NYHA class, respiratory symptoms, quality of life and exertional symptomatic onset. In addition, FEV₁ was associated with inflammation, medical therapy for lung disease and oxygen saturation at rest. The simplest model that accounted for symptomatic onset, inflammation and the use of bronchodilators could predict 48% of the variation of FEV₁ in symptomatic AS.

Therefore, respiratory dysfunction needs to be taken into consideration when assessing for symptomatic onset. In 49% of symptomatic AS, a COPD-GOLD diagnosis was present. On

the contrary, only 14% of asymptomatic AS were classified as COPD patients. However, there were no differences in morphological lung disease (similar degrees of emphysema and airway disease on CT).

Respiratory dysfunction may be determined by age, frailty and incapacity to perform a good quality spirometry and by heart failure in AS. A morphological evaluation of lung disease, which is not confounded by the above, may result in a better way to discriminate the origin of symptoms in patients who are misclassified.

5.1.23 Distinguishing between Cardiac and Respiratory Effects in Aortic Stenosis

Patients with AS and COPD-GOLD stage 3-4 ($FEV_1 < 50\%$) had homogeneous morphological lung characteristics on CT (low attenuation < -930 HU) and elevated degree of air trapping. However, isolate AS patients and those with mild-moderate COPD (stage 1-2) showed very heterogeneous characteristics on CT. These subgroups included patients with normal lungs and those with significant morphological lung alterations. In addition, there were no important morphological differences between mild/moderate and severe/very severe COPD stages who were classified based on FEV_1 values.

These results are in-keeping with the hypothesis that FEV_1 reduction is only partially determined by lung disease. Subgroups with $FEV_1/FVC > 0.7$ and those with only mid-moderate FEV_1 reduction were likely composed by participant with confirmed lung alterations and by those with apparent lung dysfunction (FEV_1 reduction determined by elderly age and heart failure). The complexity in distinguishing between emphysema and heart failure is demonstrated by the absence of significant lung alterations on CT between those excluded from surgery due to COPD, those surgically treated and those excluded due to other reasons.

Importantly, the novel imaging reclassification of lung disease based on functional and radiological thresholds allowed the distinction of a subgroup who was associated with improved functional capacity after AVR. Patients with lower degrees of lung disease significantly improved their walking distance after AVR. On the contrary, those with more lung disease did not manifest a significant improvement.

This novel morphological classification of lung disease in cardiac disease might help in the prediction of intervention futility. Patients with advanced stages of lung disease who would not likely improve after AVR would be saved from a high-risk futile intervention. On the contrary, those who have a respiratory dysfunction determined mainly by the cardiac disease might benefit from AVR and avoid being under-treated. CT evaluation is particularly easy to perform and already widespread. If these innovative results are confirmed in larger studies, the clinical applications are broad and may be translated to other cardiac diseases in which respiratory symptoms are predominant such as heart failure and cardiomyopathies.

In addition, HP-Xe MRI was a feasible and safe technique to assess lung ventilation, diffusion and gas exchange in AS. This method may prove useful in the future as a tool in discriminating decompensated AS from COPD.

5.1.24 Hyperdynamic Right Ventricle in Aortic Stenosis

The findings presented in the AS population described in Chapter 4 - “*Cardiac Function in Aortic Stenosis*” were replicated in the AMICA-AS population in this chapter. The hyperdynamic RV in symptomatic AS was seen in the AMICA cohort: RVESV was

significantly smaller in symptomatic severe AS compared to asymptomatic severe AS and RVEF showed a trend to being increased.

The minor differences in results between the two populations (Chapter 4 and Chapter 5) can be ascribed to different recruitment criteria: LV systolic dysfunction was excluded on CMR in the AS participant of Chapter 4 while in the AMICA-AS an echocardiographic evidence of LVEF <55% was adopted. This may have determined the inclusion of patients with LV systolic dysfunction not detected on echocardiography. Importantly, a sub-analysis of the AMICA patients which adopted the stricter CMR cut-off for cardiac dysfunction showed very similar results to Chapter 4. In addition, patients in Chapter 4 were included if having any type of symptoms and if undergoing surgical AVR. On the other hand, the AMICA-As cohort was symptomatic for dyspnoea only and also included TAVI participants.

These recruitment differences may have selected a more real-world comorbid and fragile population. In fact, the AMICA-AS patients were older with higher degree of clinical decompensation (symptoms, NYHA class, BNP) and reduced functional capacity. The more aggressive treatment with diuretics in the AMICA-AS participants may also explain why RVEDV difference were found: a volume depletion state was likely present in the symptomatic AS subgroup explaining the smaller RVEDV compared to patients in chapter 4.

5.1.25 Limitations

A morphological evaluation of lung disease is different from a functional respiratory assessment. COPD is a complex and heterogeneous syndrome characterised by functional airflow limitation. The presence of emphysema does not imply similar characteristics and outcomes to COPD. However, as shown in chapter 3, only the limited COPD-STS definition

has been proved prognostic in patients with cardiac disease. Very limited evidence is present in COPD-GOLD and further studies that evaluate the associations of lung disease and outcome are needed.

In addition, previous studies in respiratory medicine have shown that symptoms of lung disease are not associated with emphysema degree or spirometry parameters. In COPD patients, symptoms are more commonly related to other clinical evaluations (104). However, emphysema is associated with outcome and may prove useful in risk stratifying patients undergoing cardiac interventions especially when associated with other functional assessment.

5.1.26 Conclusion

COPD is a relevant co-morbidity in AS, present in 40% of the moderate-severe valve obstruction patients when functionally diagnosed. In addition, almost half of the AS patients presented significant morphological lung disease features.

COPD was shown to be a significant confounder in AS: functional measures were strongly associated with symptoms and clinical decompensation, while morphological lung disease was not present in many participants turned down for AVR due to COPD.

A reclassification based on functional and morphological respiratory parameters was able to detect the subgroup of participants who benefitted the most from AVR treatment. This could have important implications for future clinical practice. Patients with advanced stages of lung disease who would not likely improve after AVR may in the future be saved from a high-risk futile intervention. On the contrary, those who have a respiratory dysfunction mainly determined by the cardiac disease might avoid under-treatment.

Chapter 6 - Conclusions and Future Work

SUMMARY OF FINDINGS

Apparent lung dysfunction (COPD-STS) and confirmed airflow limitation (COPD-GOLD) are two distinct entities with different prevalence and prognostic impact in AS. COPD-STS was confirmed useful to risk stratify patients with severe AS showing a significant association with all-cause mortality. This may perhaps reflect its ability as a predictor of outcome based on the combined impact of cardiac and respiratory disease. However, when COPD was assessed more accurately in the subgroup with spirometry, confirmed lung dysfunction (COPD-GOLD) was generally only mild-moderate in severity and associated with aortic treatment choice. COPD-GOLD did not show significant association with all-cause mortality at a low statistical study power due to the limited number of patients being formally assessed with spirometry and diagnosed with COPD. This discrepancy between apparent and confirmed respiratory dysfunction should be recognised for the optimal evaluation and treatment of patients needing cardiac management.

COPD and morphological lung disease are relevant in AS being present in almost half of these patients. A potential cause explaining the high prevalence of COPD in AS is the shared risk factor of smoking which was prevalent in severe AS. COPD was also a significant confounder of symptoms in AS: respiratory function was strongly related to symptoms and clinical decompensation. In addition, participants excluded from AVR due to COPD did not manifest significant morphological lung disease, underlying the complexity of defining lung disease in this type of population.

Novel and direct cardio-respiratory assessment is promising to discriminate lung disease from decompensated AS. A reclassification of symptomatic AS based on respiratory functional and CT parameters was able to differentiate patients who most benefitted from AVR. HP-Xe MRI was feasible and safe in multi-morbid patients affected by cardiac and lung disease. In addition, an hyperdynamic RV on CMR was an objective marker of early decompensation and cardiac recovery potential in AS. The RV may prove particularly useful in patients in whom symptoms are difficult to assess, for example those with COPD.

The reduced long-term survival of RV systolic dysfunction patients even at mild pre-AVR RVEF reduction rises the hypothesis that these patients are being treated too late. Early AVR at the compensated severe AS stage defined by increased RVEF may improve survival. Therefore, increased RVEF might result in a stimulus for consideration of early surgery. In addition, the RV may provide insights into the compensated myocardial response physiology and the potential for problems in specific patients. For example, the RV response may be blunted in COPD and lead to earlier decompensation and symptoms in AS.

The assessment of cardio-respiratory interactions was proven clinically useful in AS and entails important future applications.

FUTURE WORK

6.1.1 Morphological Lung Disease and Aortic Valve Treatment Futility

Larger studies are needed to assess the clinical utility of discriminating lung alterations from heart failure and decompensated AS. The morphological CT assessment of lung disease holds a promising and clinical applicable potential. Chest CT is conventionally acquired in the planification of TAVI procedures. TAVI participants are those with the highest prevalence of co-morbidities including lung disease. It is increasingly recognised that some of these patients simply fail to derive a functional, morbidity, or mortality benefit post-TAVI (256). Futility is often defined as either mortality or absence of clinical improvement after the aortic valve procedure. TAVI with COPD-STs patients have the highest rates of futility and around 30% of them either die or do not experience any clinical improvement after 6 months (83). In addition to the need of preventing them from enduring a futile operation, ongoing scrutiny of the economic implications of TAVI calls for accurately identifying the subgroup of patients in whom an invasive procedure would be futile. As shown in Chapter 5, the assessment of morphological lung disease is promising for this purpose. The next step will be to evaluate a larger cohort of TAVI participants who underwent a CT assessment before their valve implantation to assess the association between pre-procedural morphological lung disease and outcome.

6.1.2 The Influence of COPD and Lung Disease on the Right Ventricle in Aortic Stenosis

RV involvement may explain potential for problems in specific group of patients in whom limited evidence is present. For example, the RV response may be blunted in other right heart conditions, such as COPD or other lung diseases. These co-morbid patients are known to be

affected by increased RV afterload and degrees of RV involvement which may lead to compromised cardiac reserve and earlier clinical decompensation.

The AMICA-AS Study with its comprehensive cardiac and respiratory assessment has the unprecedented ability to evaluate the influence and interaction between lung disease and RV function. This will be helpful to assess whether a hyperdynamic RV response is blunted in participants with COPD and associated to more severe symptoms and decompensation.

6.1.3 The Right Ventricle in Paradoxical Aortic Stenosis

RV dysfunction is common in patients with severe AS, involving up to 25% of patients affected by severe valve obstruction (257) RV dysfunction occurs even more frequently in patients with low-flow low-gradient AS (258). The RV may be important in paradoxical AS in which a reduced right-sided compensation may fail to maintain LV stroke volume, even before overt RV dysfunction. The RV assessment may help explain clinical decompensation and negative prognostic features in this particular group of patients in whom contrasting evidence is present in the literature. The RV failure to compensate and, eventually, progression to dysfunction, may explain the low-flow and low-gradient state associated with normal/preserved LV ejection fraction.

Appendix

1. Questionnaires adopted for the AMICA-AS study

- **EuroQoL**



Health Questionnaire

English version for the UK

(Validated for Ireland)

UK (English) © 1990 EuroQoL Group EQ-5D™ is a trade mark of the EuroQoL Group

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain / Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety / Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

- COPD Assessment Tool (CAT)

Your name:	Today's date:
------------	---------------



COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy ☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very sad

SCORE	
I never cough ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I cough all the time	
I have no phlegm (mucus) in my chest at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very limited doing activities at home	
I am confident leaving my home despite my lung condition ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am not at all confident leaving my home because of my lung condition	
I sleep soundly ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I don't sleep soundly because of my lung condition	
I have lots of energy ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I have no energy at all	
COPD Assessment Test and the CAT logo is a trade mark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline group of companies. All rights reserved. Last Updated: February 24, 2012 TOTAL SCORE	

2. NYHA functional classification

Class Patient Symptoms

- | | |
|-----|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath). |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath). |
| III | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea. |
| IV | Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. |

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

3. SOP Six-Minute Walking Test adopted for the AMICA-AS study

* interventions

STANDARD OPERATING PROCEDURE

Division of Cardiovascular Medicine

SOP Reference: CVM_i000_v0

SOP Title: Procedure title

DIVISION OF CARDIOVASCULAR MEDICINE
UNIVERSITY OF OXFORD



SOP Number i000_v0

SOP Title Six minute walk test (6MWT)

	NAME	TITLE	SIGNATURE	DATE
Original Author	Polly Whitworth	Senior Research Nurse Manager		29/7/14
Reviewer and authoriser	Dr Saul Myerson	Consultant Cardiologist, Clinical Lead Cardiac Imaging		29/7/14

Effective and Review Dates:	see change history
-----------------------------	--------------------

Review Date 27th July 2015

READ BY			
NAME	TITLE	SIGNATURE	DATE

PURPOSE The purpose of this Standard Operating Procedure (SOP) is to describe the standard procedures to be followed when performing a six-minute walk test (6MWT) in clinical studies sponsored by the University of Oxford. It provides practical guidelines for safety of a patient and staff during the 6MWT.

INTRODUCTION This document outlines the considerations and principles of a 6MWT for use within the Division of Cardiovascular Medicine, Oxford. It is important that all clinical staff working within the Division of Cardiovascular Medicine use the same procedure to carry out a 6MWT

SCOPE This SOP applies to all clinical researchers in which 6MWT is performed within the Division of Cardiovascular Medicine where the University of Oxford or OUH Trust has accepted role of 'sponsor', which is hosted by the Division of Cardiovascular Medicine. Where appropriate this SOP may apply to commercially sponsored research or research sponsored by an external non-commercial organisation.

RESPONSIBILITIES It is the responsibility of the study investigators to ensure the safety of the patient and correct conduct of all testing, this includes appropriate screening investigations to ensure the safety of all participants prior to the test.

PATIENT PREPARATION Comfortable clothing should be worn with appropriate shoes for walking. Patients should use their usual walking aids during the test (cane, walker, etc.). Patient's usual medical regime should be continued.

A light meal is acceptable before early morning or early afternoon tests.

Patients should not have exercised vigorously within 2 hours of beginning the test.

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait at least half an hour before the second test and report the highest 6-minute walk distance (6MWTD) as the patient's 6MWD baseline.

PROCEDURE **Contraindications** Before starting it is essential to obtain verification from both the investigator and subject that they have no known contraindications for the 6MWT. These include but are not limited to: Unstable angina, Myocardial Infarction during the previous month. Relative contraindications

include the following: Resting heart rate of more than 120 beats per minute, Systolic blood pressure > 180 mmHg and a diastolic blood pressure >100mmHg.

Safety issues the 6MWT should be performed indoors, along a long flat, straight, enclosed corridor. The walk must be approximately 30 meters in length and should be marked every 2 meters. Subjects should not exercise vigorously within 2 hours of the test. Testing is performed with at least one member of staff who is certified to undertake basic life support.

Testing is performed in the dedicated location which has a telephone, resuscitation trolley and portable oxygen and suction in close proximity. Baseline pulse and blood pressure are performed on each subject prior to and on completion of the 6MWT (or if the subject feels unwell during the test). Oxygen saturations may also be performed on subjects if deemed applicable to the study. If the subject has known respiratory disease, cylinder oxygen should be in the immediate area. If the subject is on long-term oxygen therapy, then oxygen should be prescribed throughout the 6MWT at their normal rate. The floor area is checked prior to the test commencing, for obstructions or spillages to avoid the subject slipping and the subject is advised prior to the test to wear appropriate footwear and comfortable clothing in which to do the test. The subject should use their usual walking aids to do the test e.g. walking stick.

A chair is situated at either end of the walk test and a wheelchair will be in the test area in case it is required. Two small cones are placed at the turnaround points of the walk which will highlight to other users of the corridor to keep as clear as possible from the testing area.

STOP the 6MWT for the following reasons: Chest pain, Intolerable dyspnoea, Leg cramps, Staggering, Dizziness/ light-headedness, Sweating and/or pale or ashen appearance

Test procedure A full explanation should be given to the participant. A 'warm-up' period before the test should not be performed. Repeat testing should be performed about the same time of the day to minimise intraday variability. The patient should sit and rest in a chair for at least 10 minutes before the test starts. During this time check for contraindications measure pulse and blood pressure and make sure that clothing and shoes are appropriate. Have the patient stand and rate their baseline dyspnoea and overall fatigue using the Borg scale. Assemble all necessary equipment (stop-watch, timer, clipboard, Borg scale (for respiratory studies) worksheet) and move to the starting point. Set the stop-watch to zero and the timer to 6minutes.

Instruct the patient as follows: "the object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this corridor. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. Do not talk during the exercise. You may lean against the wall while resting but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation" Demonstrate walking one lap yourself. Walk and pivot around a cone briskly. Ask the patient "Are you ready to do that? I am going to keep track of the numbers of laps you complete. Remember that the objective is to walk AS FAR AS POSSIBLE for 6 minutes but do not run or jog. Start now or whenever you are ready". Position the patient on the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, mark the lap on the worksheet. Let the participant see you do it.

Verbal Instructions during 6MWT After the first minute, tell the patient the following 'You are doing well. You have 5 minutes to go' When the timer shows 4 minutes remaining, tell the patient the following: 'Keep up the good work. You have 4 minutes to go' When the timer shows 3 minutes remaining, tell the patient the following: 'You are doing well. You are halfway done.' When the timer shows 2 minutes remaining, tell the patient the following 'You are doing well. You only have 1 minute to go' Do not use other words of encouragement (or body language to speed up). If the patient stops walking during the test and needs to rest, say this: 'You can lean against the wall if you would like; then continue walking whenever you feel able'. Do not stop the timer. If the patient stops before the 6 minutes are up and wishes to stop (or you decide that they should not continue) wheel the chair over for the patient to sit on, discontinue the walk and note on the worksheet the distance, the time stopped and the reason for stopping prematurely. When the timer is 15 seconds from completion, say this: 'In a moment I'm going to tell you to stop. When I do just stop right where you are, and I will come to you.' When the 6 minutes are up say this; Stop!' Walk over to the patient. Consider taking a chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape in the floor.

Post test procedures for respiratory patients - measure the oxygen saturation and pulse rate from the oximeter and then remove the sensor. Record the number of laps from the tick marks on the worksheet. Record the additional distance covered (the number of metres in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest metre and record it on the worksheet.

Congratulate the patient on good effort and offer a drink of water.

Practice Tests A practice test is not needed on most clinical settings but should be considered. If a practice test is done, wait at least 1 hour before the second test and report the highest 6-minute walk distance (6MWD) as the patient's 6MWD baseline

Equipment Countdown timer (or stopwatch), mechanical lap counter, two small cones to mark the turnaround points, a chair that can be easily moved along the walking course, worksheets on a clipboard, a source of oxygen, sphygmomanometer, telephone, resuscitation trolley and portable oxygen and suction in close proximity.

REFERENCES

American Thoracic Society. ATS Statement: Guidelines for the six-minute walk test. *Am J Resp Crit Care Med* 166 (1): 111-117 (2002).

4. MRI Safety Screening Form



University of Oxford
Centre for Clinical Magnetic Resonance Research



VOLUNTEER MRI SAFETY SCREENING FORM

Please complete both sides

Volunteer name: _____

Date of birth: _____ Weight: _____ kg Height: _____ m

Please carefully check the following. Some items can interfere with MR examinations, and may be hazardous to your safety. Your answers will be kept strictly confidential. **Clearly mark your answer with a circle. Additional details can be recorded overleaf.**

IF YOU HAVE ANY QUESTIONS THEN PLEASE ASK US BEFORE YOUR SCAN		
Do you have a pacemaker, pacing wires or implanted cardiac defibrillator (ICD)?	YES	NO
Have you had any heart surgery?	YES	NO
Have you had any surgery to your head (including eyes/ears/brain)?	YES	NO
Have you had any surgery to your neck or spine?	YES	NO
Do you have any implanted devices (e.g. programmable hydrocephalus shunt, nerve stimulator, cochlea implant or aneurysm clip)?	YES	NO
Have you had any operation involving metallic pins, plates, screws, wires or mesh?	YES	NO
Have you ever had any other surgical procedure of any kind? (Please list overleaf)	YES	NO
Have you ever had a capsule endoscopy (PillCam ®)	YES	NO
Have you ever sustained any injuries involving metal to the eyes or any other part of the body?	YES	NO
Have you ever had a serious accident (e.g. road traffic accident, industrial accident, explosion injury, shooting injury or shrapnel injury)?	YES	NO
Have you ever had a fit or blackout, or do you suffer from epilepsy or diabetes?	YES	NO
Do you have any of the following (if yes please circle):		
Body/dermal piercing/jewellery	Hearing aid	Tattoos
Dentures, dental implants, dental braces, dental bridge	Skin patches (nicotine, pain, contraceptive, HRT, nitro)	Artificial limbs, prosthesis, splints or supports
FOR WOMEN OF CHILDBEARING AGE:	Do you have an IUD (coil)?	YES NO
	Could you be pregnant?	YES NO
Are you wearing any clothing that contains silver fibres or is "anti-microbial"?	YES	NO
Have you removed your watch, spectacles, hearing aids, keys, coins, jewellery, hair grips?	YES	NO
Do you understand that this is a research scan that is not useful for medical diagnosis and that scans are not routinely reviewed by a clinician?	YES	NO

NO METAL OBJECTS TO BE TAKEN INTO THE MAGNET ROOM

Volunteer /Guardian signature _____ Date of study: _____

For admin use		
Screened by	Signature:	Print name:

Use this space to record details of any injury/ surgery or additional information

For scans using contrast agent only: <i>(please ask a member of staff if you don't know whether your scan will involve contrast agent)</i>		
Have you had MR contrast agent before? (please leave blank if unknown)	YES	NO
Are you aware of any problems with your kidneys?	YES	NO
Do you have any allergies to medications? If yes please give details	YES	NO
Are you currently breast-feeding?	YES	NO

Notes (for staff use only) - 1.5T / 3T (please circle magnet used)
Heart rate: Rhythm: Scanned by: The patient has been advised to let staff know if they experience any discomfort or heating during the scan due to the presence of tattoos/non-removable jewellery/piercing/implant Yes / No / NA Signature (Member of staff): Signature (Volunteer): Date:

Contrast	
Contrast name	
Dose/volume	
Batch number	
Expiry date	
Time of administration	
Given by	
Creatinine-Date	
eGFR	

Version: VoIS v1.0 April 2018

Date of Next Review: April 2020

5. SOP Imaging data analysis adopted for the BSCMR Multicentre Outcome study

Pre-specified Standard Operating Procedure for Data Analysis performed in the BSCMR Multi-centre Longitudinal Outcome Study.

Reproduced as original, published in Musa et al. Circulation (239). Figures and references do not refer to thesis but are part of the original standard operating procedure.

Data analysis was pre-specified in the SOP to ensure a consistent approach in respect of image analysis across the six sites. The analysis was performed in a distributed core-lab approach and I personally performed left and right ventricular volume and mass quantification following the below SOP. All patients were uploaded as anonymised scans to a central repository. Each centre analysed a specific domain across the whole cohort.

“Standard Operating Procedure – BSCMR Valve Consortium

Circle Cardiovascular Imaging cvi42: Housekeeping

- The same version of the CVI42 is utilised across the 6 sites (Version 5.1.2, Calgary, Canada). This, in particular, is important for those sites designated LV and RV chamber quantification. There are obvious differences in dashboard aesthetics and “smoothness” of contouring tools and it would be optimal for analysis to be performed on the same software.
- To use a pre-specified zoom ‘%’ of x2.0 or x2.7 for the workspace prior to contouring.
- To use the pre-defined cvi windowing setting of 3 (although custom windowing should obviously be used if this setting is of suboptimal image quality)
- Manual contouring of the LV and RV is performed using the bezier tool (‘click-draw’ icon displayed, see below).
- To employ the following cvi42-specific SOP for standardising backend contour settings:

SubPixel Matrix size = 4X4

Signal Intensity SD = use subpixel weighted SD (and not biased SD)

Contour detection = check contour detection connects to view

Rounded SAX endocardial contour = leave inactive

Papillary muscle detection = check this

SAX chord generation = uncheck this

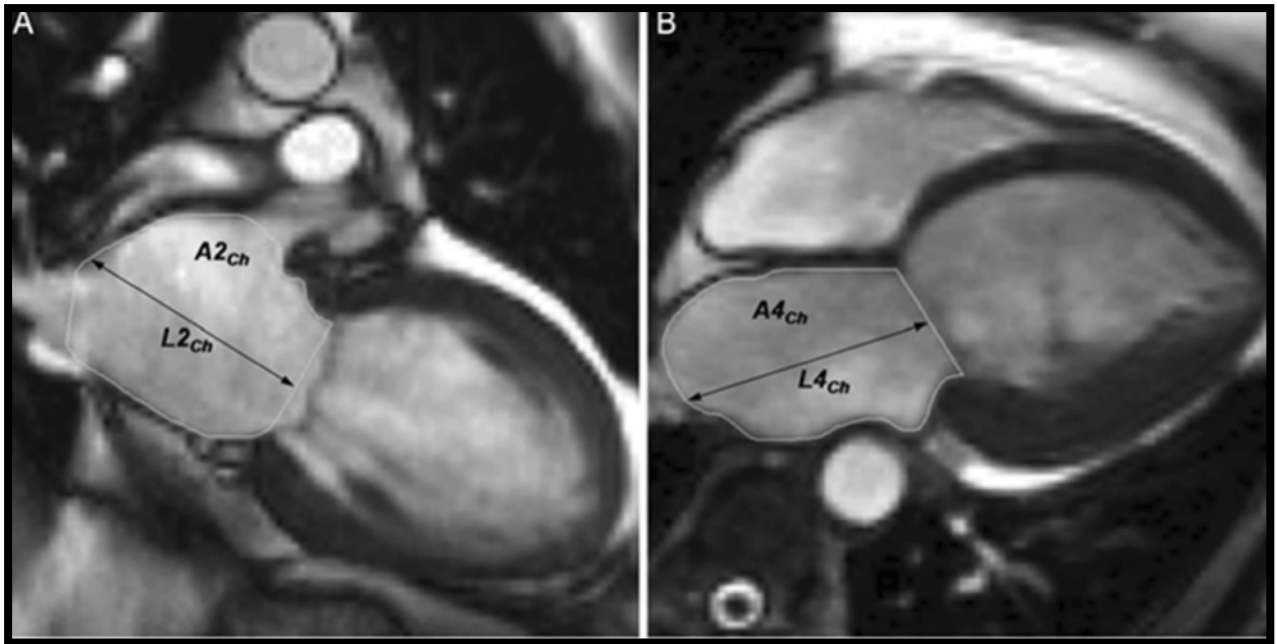
- The contours drawn are saved locally
 - “save workspace DICOM” via workspace option on task bar
 - return to patient list view
 - and choose “extended view” option at bottom left of screen
 - select patient under study
 - scroll down to end of sequence list and select the saved DICOM workspace
 - right click on this and “export series”
 - save in a designated folder on local drive
 - upload contour workspace straight into the research participant's REDCap module using 'File Upload' option
- Similarly, that derived values (e.g. absolute LVEDV, LV mass etc) are manually entered into the CMR variables section of the BSCMR project in RedCAP under the patient being studied.

Left Atrial Volume Quantification

- Measurement of left atrial (LA) volume is by the biplane area–length method.
- Images are analysed in the viewer module of cvi42 with a dual panel display selected to permit synchronisation of HLA and VLA by phase.
- All measurements are taken from the two-chamber (A) and four-chamber (B) views at end-ventricular systole, ensuring maximal LA size.
- The atrial endocardial border is traced to determine LA area with exclusion of the pulmonary veins, LA appendage, and mitral valve recess.
- LA length is measured from the midpoint of the mitral annulus plane to the posterior aspect of the left atrium. Left atrial volume (LAV) was calculated using the formula:

$$LAV = 8(A2Ch)(A4Ch) / 3\pi L$$

- where A2Ch and A4Ch refer to the LA area in the two-chamber and four-chamber views, respectively, and L is the shorter of the two LA length measurements (L2Ch, L4Ch) from these views (see below).



(Adapted from Gulati et al. 2013. *European Journal of Heart Failure*; 15(6); 660-670).

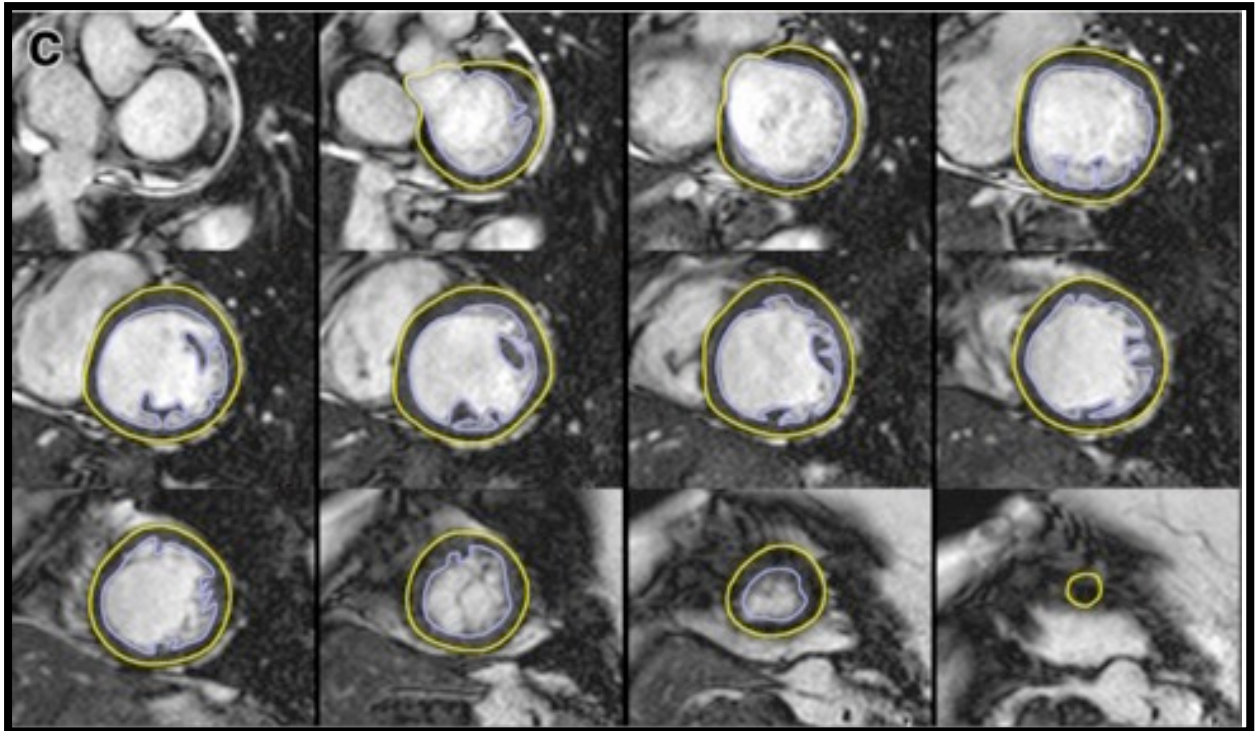
Left and Right Ventricular Volume and Mass Quantification

(adapted from Schulz-Menger et al. *Journal of Cardiovascular Magnetic Resonance* 2013, 15:35)

- For each study, LV and RV volumes and LV mass are to be contoured by the same one individual.
- If no intra- or extracardiac shunts are present, the RV and LV stroke volumes should be nearly equal (small differences are seen as a result of bronchial artery supply). Since the LV stroke volume is more reliably determined than the RV stroke volume, the LV data can be used to validate RV data.
- The dedicated LV short axis cine stack is to be contoured for both LV AND RV quantification.
- Manual contouring performed in cvi42 using the Bezier tool is the suggested method of analysis; the fully automated contour detection option is to be avoided.
- For the purposes of facilitating consistency of standards across different sites, a control sample of 5 cases will all be analysed by each of the three readers quantifying LV and RV parameters. These will then be surveyed by the PI to help provide feedback on technique and assist in answering any outstanding queries.

The Left Ventricle

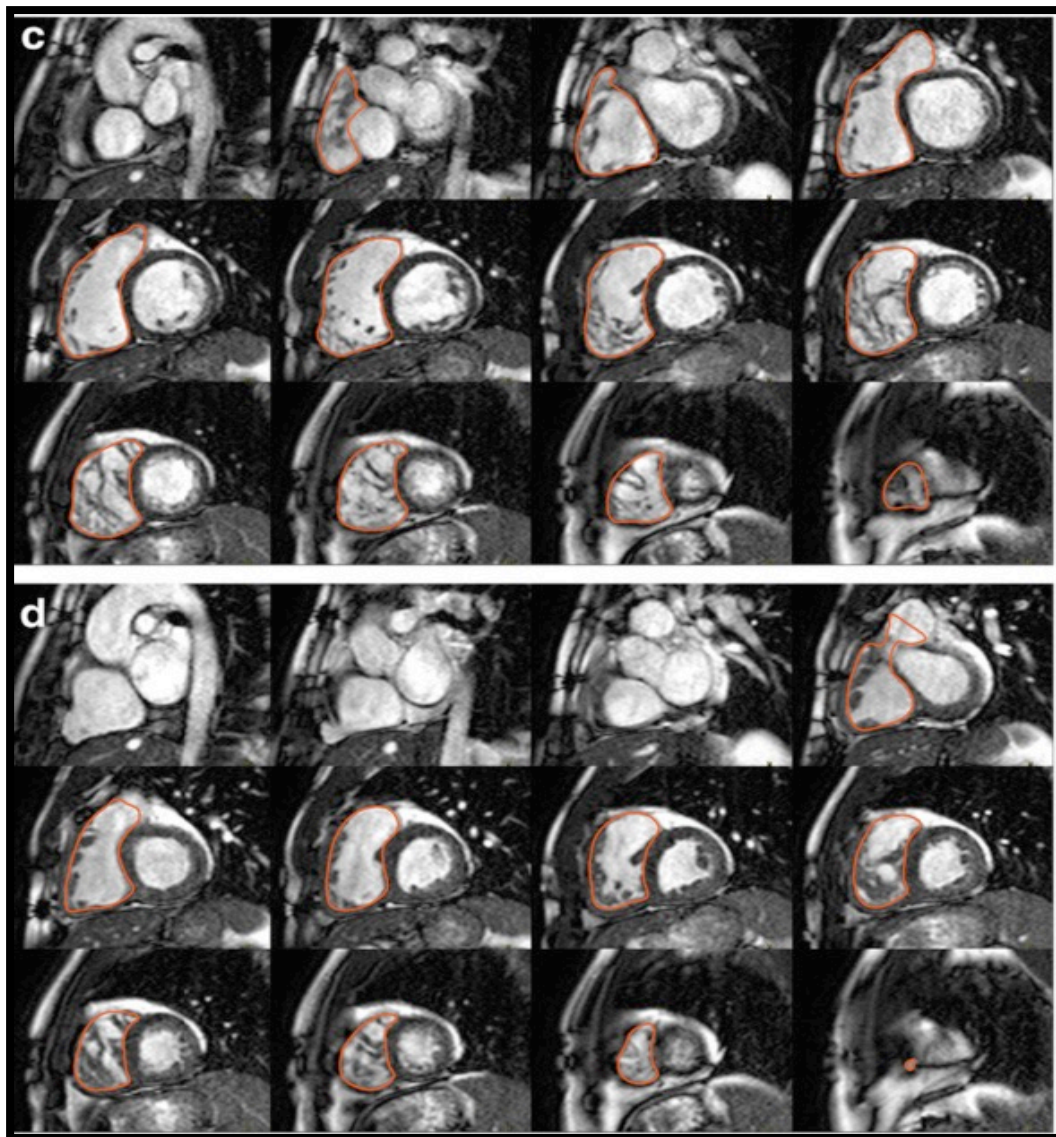
- The LV end-diastolic and end-systolic image should be chosen as the images with the largest and smallest LV blood volumes respectively. (For their identification, the full image stack should be evaluated)
- Deviations may occur and extra care should be taken in the setting of LV dyssynchrony or severe mitral regurgitation. Aortic valve closure defines end-systole.
- If a slice is uninterpretable (e.g. degraded by triggering/breathing artefact) it should be excluded from systolic and diastolic measurements of both the LV and RV.
- The LV outflow tract is included as part of the LV blood volume. When aortic valve cusps are identified on the basal slice(s) the contour is drawn to include the outflow tract to the level of the aortic valve cusps.
- Care must be taken with the one or two most basal slices. A slice that contains blood volume at end-diastole may include only left atrium (LA) without LV blood volume at end-systole. The LA can be identified when less than 50% of the blood volume is surrounded by myocardium and the blood volume cavity is seen to be expanding during systole.
- Papillary muscles are to be EXCLUDED from the LV cavity for the purpose of analysis and included within the LV mass (thus DO require specific delineation).
- Epicardial borders should be drawn on the middle of the chemical shift artifact line (when present).
- Absolute LV mass is derived from diastolic epicardial and endocardial delineation; systolic epicardial contours are NOT required.
- Maximal LV Wall Thickness is measured as the thickest portion of the interventricular septum in short axis at end diastole (mm)
- When the most basal slice contains only a small crescent of basal lateral myocardium and no discernible ventricular blood pool, an epicardial contour for the visible myocardium is included for LV mass only.
- Similarly, when the most apical slice contains only a circle of myocardium without cavitory blood pool, an epicardial contour without an endocardial contour should be drawn for LV mass calculations



Left ventricular (LV) chamber quantification. For LV chamber quantification, the endocardial (blue) and epicardial (yellow) contours are delineated in diastole in a stack of short axis slices that cover the whole left ventricle. c) illustrates the approach with exclusion of the papillary muscles as part of the LV volume.

The Right Ventricle

- As for the LV, it may be necessary to review all image slices in the stack to define end-diastole and end-systole for the RV.
- Trabeculations of the RV are ignored and a smooth endocardial border is drawn to improve reader reproducibility (RV trabeculae and papillary muscles are typically included in RV volumes).
- Again, if no intra- or extracardiac shunts are present, the RV and LV stroke volumes should be nearly equal (small differences are seen as a result of bronchial artery supply).
- Since the LV stroke volume is more reliably determined than the RV stroke volume, the LV data can be used to validate RV data.
- The pulmonary valve may be visualized, and contours are included just up to, but not superior to this level.



Right ventricular (RV) chamber quantification. For RV volume quantification, the endocardial (red) contours are delineated in diastole (top) and systole (bottom) or short-axis (c and d) slices that cover the whole RV.

Aortic Valve haemodynamic assessment from quantification of VENC images

(adapted from Schulz-Menger et al. Journal of Cardiovascular Magnetic Resonance 2013, 15:35)

- Phase and magnitude images are analysed in the Flow module of cvi42 software.

- The dedicated aortic valve short axis cine (typically 8 slices) is viewed in the viewer module to determine the anatomic aortic valve orifice by 2D valve planimetry in peak systole when the opening of the aortic valve is widest. This is done by manually tracing the inner leaflet edges of the aortic valve cusps at the time of maximal opening; recording the average of three consecutive AVA measurements.
- Images are windowed to the appropriate brightness and contrast so that the borders of the ROI are sharp.
- Through-plane phase contrast images are examined to ensure the quality is sufficient and that the VENC chosen was appropriate.
- The borders of the vessel of interest are traced on each phase and magnitude image so that only the cavity of the vessel is included ensuring noise outside the vessel is not included
- Checks are made that this is performed correctly on the magnitude images (as always the phase images contain the encoded information)
- Where a number of phase contrast sequences have been acquired, the highest value for peak flow velocity and forward flow volumes should be recorded. Regurgitant fraction should be derived from non breath held images.

Pitfalls:

- On the phase images, the area of flow may be slightly larger than the area of the magnitude images.
- If aliased the sequence should be disregarded and another analysed.
- The use of software correction to analyse aliased images is to be avoided.
- In general, the area that exceeds the VENC in the ROI is in the centre of the vessel and not at the edges; if at the edges, it is usually (but not always) outside the vessel.

Late Gadolinium Enhancement Quantification

- All images are to be quantified using CVI 42.
- Manual epi and endocardial quantification are performed from the dedicated LV volume short axis cine stack in end diastole in order to quantify LV mass (papillary muscles were excluded).
- The short axis LV stack acquired 10-15 minutes following Gadolinium (Dotarem 0.2mmol/kg) contrast administration is used for the purposes of late gadolinium quantification.

- Each slice is visually inspected by 2 doctors experienced in MRI analysis for the presence or absence of gadolinium enhancement.
- Phase swap and other geometry images were used in order to assist in decision making where required.
- In only those slices deemed to have LGE present, epi and endocardial contours were manually drawn, with care taken to exclude artefact, blood pool, fat and pericardium.
- The auto-identification tool was then applied and an area of normal remote myocardium defined alongside identification of areas with increased signal intensity.
- Any hyperintense regions felt to be related to artefact are manually excluded.
- The 2SD, 5SD and full width half max techniques are used to determine LGE mass.

6. SOP Use of gadolinium-based contrast agents adopted for the AMICA-AS study

STANDARD OPERATING PROCEDURE

Oxford Centre for Clinical Magnetic
Resonance Research (OCMR)

SOP No: OCMR_009

SOP Title: The use of gadolinium-based
contrast agents (GBCA)



SOP Number OCMR_009

SOP Title The use of gadolinium-based contrast agents (GBCA)

	NAME	TITLE	SIGNATURE	DATE
Author	Dr Oliver Rider	Deputy Clinical Director	<i>O. Rider</i>	02/09/2016
Reviewer	Jane Francis	Head of Imaging Applications	<i>J. Francis</i>	02/09/2016
Authoriser	Prof Stefan Neubauer	Clinical Director	<i>S. Neubauer</i>	06/09/2016

Effective Date:	September 2016
Review Date:	September 2018

Adapted from CTRG Template SOP Version 2.1
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SOP OCMR_009 Version 1

1. PURPOSE

The purpose of this SOP is to describe the procedures to be followed when gadolinium based contrast agents (GBCA) are administered for magnetic resonance imaging in OCMR.

2. SCOPE

This SOP applies to all patients and clinical research participants where GBCA are to be administered at OCMR.

3. INTRODUCTION

Nephrogenic systemic fibrosis (NSF) involves fibrosis of the skin, joints, eyes and internal organs and is potentially fatal. It has been directly linked to the administration of gadolinium based contrast agents in patients with reduced renal function. The European Medicines Agency has classified GBCA into three risk groups; low, medium and high based on their chemical composition and ionic structure. In OCMR only GBCA with a low risk of causing nephrogenic systemic fibrosis will be used, unless specifically authorised by the safety committee.

4. RESPONSIBILITIES**Investigator or healthcare professional administering GBCA**

To ensure that these guidelines are followed so that all patients and/ or participants have been adequately assessed for renal impairment prior to the administration of GBCA.

5. SPECIFIC PROCEDURES

- 5.1 All patients/ participants who are to be given GBCA need to be screened for history of renal disease

Those with the following criteria require a laboratory blood result for serum creatinine/ eGFR **within the last 6 months**.

- Age >65 years
- Hypertension
- Diabetes
- History of renal disease
- Any acutely unwell patients - those admitted to hospital for acute care must have a creatinine measurement performed as close as possible to the scan, ideally within 24 hours (especially those with fluctuating renal function), but **no more than 3 days** prior to the scan. All others may receive GBCA without measurement of creatinine

The Cockcroft – Gault formula is used to calculate eGFR in OCMR.

5.2 Obtaining a creatinine measurement

Whenever possible information on creatinine/ eGFR should be requested before the scan is scheduled, so that it is available when the patient arrives. If creatinine/ eGFR is unavailable on the day of the scan creatinine can be measured using the iSTAT laboratory test kit. This provides an immediate result, eGFR can then be calculated.

5.3 Action when creatinine measurement is obtained

- **eGFR >30ml/min** (renal disease stage 1-3): All patients/ participants can receive GBGA.
- **eGFR <30ml/min** (stage 4 and 5 kidney failure)

Clinical patients with strong indications for the scan, outweighing the small risk of NSF may receive GBGA. A risk-benefit assessment must be conducted for each patient and patient consent obtained. If GBGA is administered to patients already on dialysis, dialysis should occur as soon as possible thereafter.

Research participants with an eGFR <30ml/min should not receive GBGA.

5.4 All patients will receive GBGA with a low risk of causing NSF. Research studies proposing to use anything other than a low risk GBGA must gain approval from the OCMR safety committee.

5.5 All studies which involve the use of GBGA need to incorporate these guidelines into the study protocol.

5.6 For dosage and administration advice please refer to OCMR Work Instruction 001 which is available on the website (<http://www.ocmr.ox.ac.uk/documents>).

5.7 Use of GBGA is also contraindicated in patients who have had or are awaiting liver transplantation.

5.8 If an abnormal creatinine result is found refer to the relevant incidental findings SOPs (<http://www.ocmr.ox.ac.uk/documents>).

7. SOP Respiratory assessment adopted in the AMICA-AS study

Forced Spirometry and Lung Volumes – A guide to testing

Respiratory Department – Churchill Hospital
Spirometry Guide Version 1.0 October 2016

Author:
Ben Guan

This Guideline Is For Use By The Following Staff Groups:

- Respiratory Nurse Specialists
- Registered Nurses working in high care areas
- Respiratory Physiologists
- Respiratory Physiotherapists
- Respiratory Clinical Support Workers

Purpose:

“Spirometry is a physiological test that measures how an individual inhales or exhales volumes of air as a function of time. The primary signal measured in spirometry may be volume or flow” (Miller *et al* 2005).

Spirometry is a useful test that provides screening for individuals with underlying respiratory disorders, similar in a way that blood pressure provides information for general cardiovascular health. It must be noted that however, spirometry alone cannot provide an aetiological diagnosis; spirometry is often supported with additional screening tests such as an X-ray or CT scans. See Table 1 (Miller *et al* 2005) for some of the common indications for spirometry.

TABLE 1 Indications for spirometry

Diagnostic

- To evaluate symptoms, signs or abnormal laboratory tests
- To measure the effect of disease on pulmonary function
- To screen individuals at risk of having pulmonary disease
- To assess pre-operative risk
- To assess prognosis
- To assess health status before beginning strenuous physical activity programmes

Monitoring

- To assess therapeutic intervention
- To describe the course of diseases that affect lung function
- To monitor people exposed to injurious agents
- To monitor for adverse reactions to drugs with known pulmonary toxicity

Disability/impairment evaluations

- To assess patients as part of a rehabilitation programme
- To assess risks as part of an insurance evaluation
- To assess individuals for legal reasons

Public health

- Epidemiological surveys
- Derivation of reference equations
- Clinical research

Key measurements during Forced Spirometry:

The following parameters need to be measured correctly and as accurately as possible before testing as these will affect the “reference/normal” ranges used to compare the results:

- **Height**
- **Age**
- **Ethnicity**
- **Gender**

When performing good quality spirometry there are several key measurements which are of great importance to a clinician. These are:

- FEV1 – Forced Expiratory Volume in 1 second
- FVC – Forced Vital Capacity
- FEV1/FVC – the ratio between the volume of air expired in one second vs. the total volume expired

Before performing the forced spirometry test

Prior forced spirometry, the individual needs to be assessed as to whether they are 'fit' for the test as forced spirometry can be fairly exerting and may cause problems or discomfort during testing. Hence, a series of questions are asked before testing, to indicate any reason **not** to test – these are known as **contraindications**.

The following is some of the main absolute contraindications which spirometry would not be recommended in individuals (Cooper 2010):

- Recent Myocardial Infarction (heart attack) within 6 weeks
- Cardiothoracic Surgery within 6 weeks
- Eye, brain, ear, ENT surgery within 6 weeks
- Pneumothorax within 2 weeks
- Known thoracic, aortic or cerebral aneurysm (>6cm)

There are also some contraindications which are more 'relative' requiring some clinical judgement as to whether to proceed with testing or if the benefits of the test outweigh the risks. Such indications are, but not limited to:

- Chest or abdominal pain of any cause
- Oral or facial pain exacerbated by a mouthpiece
- Stress incontinence
- Dementia or confusional state
- Haemoptysis

It should be noted that such contraindications present in individuals (including the absolute) may require clinical judgement from more experienced or senior clinicians to deem whether spirometry would be of more benefit than the discomfort or risk of further injury in an individual.

Performing Forced Spirometry

There are 3 distinct phases in the Forced Vital Capacity manoeuvre;

1) Maximal inspiration

- 2) A maximally forced exhalation
- 3) Continued exhalation to the end of breath
- 4) Maximally forced inspiration to full

Essentially, the clinician should instruct the individual to fully inspire, (“take a deep breath in,”) and as soon as complete inspiration is achieved the instruction to blow with maximal effort should be given (“BLOW!”). Additional encouragement should be given as complete exhalation to empty is achieved (“keep going, keep going etc.”). This should be repeated with resting time of at least **One Minute** in-between manoeuvres. See Table 4 for a summary of the test procedure.

The patient is considered to have reached the end of breath when the flow of air is <25ml/s and/or exhalation time has exceeded 15 seconds and/or the healthcare specialist terminates the test due to the condition of the patient.

Completion of test is determined when **any** of the following conditions occur:

- MAXIMAL effort of 8 separate manoeuvres of varying effort
- 3 ACCEPTABLE and REPRODUCIBLE manoeuvres (FEV₁ and FVC are within 150ml of each other of the two largest values)
- Early test aborted by clinician/patient due to fatigue/pain/discomfort etc.

TABLE 5	Summary of within- and between-manoeuve acceptability criteria	TABLE 4	Procedures for recording forced vital capacity
Within-manoeuve criteria Individual spirometers are “acceptable” if - They are free from artefacts [3] - Cough during the first second of exhalation - Glottis closure that influences the measurement - Early termination or cut-off - Effort that is not maximal throughout - Leak - Obstructed mouthpiece They have good starts - Extrapolated volume <5% of FVC or 0.15 L, whichever is greater They show satisfactory exhalation - Duration of ≥6 s (3 s for children) or a plateau in the volume–time curve or - If the subject cannot or should not continue to exhale Between-manoeuve criteria After three acceptable spirometers have been obtained, apply the following tests - The two largest values of FVC must be within 0.150 L of each other - The two largest values of FEV₁ must be within 0.150 L of each other If both of these criteria are met, the test session may be concluded If both of these criteria are not met, continue testing until - Both of the criteria are met with analysis of additional acceptable spirometers or - A total of eight tests have been performed (optional) or - The patient/subject cannot or should not continue Save, as a minimum, the three satisfactory manoeuvres		Check the spirometer calibration Explain the test Prepare the subject - Ask about smoking, recent illness, medication use, etc. - Measure weight and height without shoes Wash hands Instruct and demonstrate the test to the subject, to include - Correct posture with head slightly elevated - Inhale rapidly and completely - Position of the mouthpiece (open circuit) - Exhale with maximal force Perform manoeuvre (closed circuit method) - Have subject assume the correct posture - Attach nose clip, place mouthpiece in mouth and close lips around the mouthpiece - Inhale completely and rapidly with a pause of <1 s at TLC - Exhale maximally until no more air can be expelled while maintaining an upright posture - Repeat instructions as necessary, coaching vigorously - Repeat for a minimum of three manoeuvres; no more than eight are usually required - Check test repeatability and perform more manoeuvres as necessary Perform manoeuvre (open circuit method) - Have subject assume the correct posture - Attach nose clip - Inhale completely and rapidly with a pause of <1 s at TLC - Place mouthpiece in mouth and close lips around the mouthpiece - Exhale maximally until no more air can be expelled while maintaining an upright posture - Repeat instructions as necessary, coaching vigorously - Repeat for a minimum of three manoeuvres; no more than eight are usually required - Check test repeatability and perform more manoeuvres as necessary	
FVC: forced vital capacity; FEV ₁ : forced expiratory volume in one second.		TLC: total lung capacity.	

Lung volumes are acquired with body pletismography. Equipment used is the the “Masterscreen PFT kit,” by Carefusion (rebranded as Vyaire). To perform lung volumes assessment in a standardised way, the following guidelines are adopted.

Eur Respir J 2005; 26: 511–522

SERIES “ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING”

Edited by V. Brusasco, R. Crapo and G. Viegi

Number 3 in this Series

Standardisation of the measurement of lung volumes

J. Wanger, J.L. Clausen, A. Coates, O.F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C.P.M. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. MacIntyre, R. McKay, M.R. Miller, D. Navajas, R. Pellegrino and G. Viegi

Transfer Factor – A guide to testing

Respiratory Department – Churchill Hospital
Spirometry Guide Version 1.0 October 2016

Author:
Ben Guan

This Guideline Is For Use By The Following Staff Groups:

- Respiratory Nurse Specialists
- Registered Nurses working in high care areas
- Respiratory Physiologists
- Respiratory Physiotherapists
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Purpose:

Transfer Factor is a test that is used to measure Carbon Monoxide (CO) uptake into the body; this is a way of determining the efficiency of an individual’s gas exchange system. Depending on the structural and functional properties of an individual, this will affect the capacity of the lungs to exchange gas across the alveolar-capillary membrane (MacIntyre *et al* 2005). The structural properties of the lung include:

- The lung volume
- The distance the gas must travel to diffuse across the membrane
- The actual thickness and surface area of the alveolar capillary membrane
- The blood flow in the capillaries supplying ventilated alveoli

Functional properties include:

- The balance of ventilation and perfusion within the lungs
- The diffusion characteristics of the capillary membrane
- The concentration of haemoglobin and their binding properties
- The gas tensions in blood entering
- The alveolar capillaries in that part of the pulmonary vascular bed which exchanges gas with the alveoli

Essentially, transfer factor is a useful measurement to determine whether or not an individual's gas exchange system is impaired as a result of disease e.g. IPF or to be used like spirometry in monitoring the condition of the lungs over time.

The test utilises a mixture of medical gases to determine the efficiency of the gas exchange system; most commonly the gases in the mixture are:

- Oxygen (O_2)
- Nitrogen (N_2)
- Methane (CH_4) or Helium (He) (as the Tracer Gas)
- Carbon Monoxide (CO)

The concentrations vary depending on the gas analysers, however most departments use a mix of 18-25% O_2 , 10-15% He, 0.3% CO, the rest of the concentration mixture should be balanced out by N_2 .

Key measurements during Transfer Factor:

The following parameters need to be measured correctly and as accurately as possible before testing as these will affect the "reference/normal" ranges used to compare the results:

- **Height**
- **Date of Birth (to calculate age)**
- **Ethnicity**
- **Gender**

Important values that are obtained from the results of the test are:

- TL_{CO} – Diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor.
- K_{CO} – Transfer coefficient of the lung
- V_a – Alveolar volume
- Hb – Haemoglobin

Before performing Transfer Factor

Similar to performing Forced Spirometry, there are a few contraindications or issues that may need to be considered before testing the individual. The contraindications that outline whether a patient is 'fit' to be tested are more reliant on whether the patient is able to

understand the manoeuvre as well as hold their breath for a sufficient amount of time to ensure accuracy and reliability. Unlike Forced Spirometry, Transfer Factor may still be performed on patients with 'absolute contraindications' such as those whom have had recent cardiothoracic surgery, albeit with extra care and precautions. Therefore, it is important to ensure the wellbeing of the patient before continuing with the measurement of Transfer Factor.

Performing Transfer Factor

There are several phases during the test:

- Set the Transfer Factor test up; depending on the manufacturer this may ask you to specify a volume – normally this should be set to as the biggest Vital Capacity or Forced Vital Capacity with approx. 200mls to ensure a complete fully inspiration of the gas mixture.
- Some do not require this to be set up and will have instead a 'demand-valve' allowing the patient to inspire fully when ready.
- Ensure the patient is comfortable and breathing at a fairly steady rate whilst on the mouthpiece and ensuring there are no air leaks i.e. lips are maintaining a good seal.
- Instruct the patient to 'gently' exhale to 'empty' (to the end of Vital Capacity); this can be done several ways –
 - Instruct the patient to exhale just after the next tidal breath in, and to continue exhaling until a plateau is reached.
 - Instruct the patient to perform a VC manoeuvre; a full inspiration, followed by a full expiration to empty at a steady and gentle speed.
 - Instruct the patient to take a 'slightly' larger tidal breath in and then to exhale out to empty.
- Upon reaching complete or near expiration of the lungs, the medical gas mixture valve should be opened after the patient has reached the end of the breath. The patient should then immediately be instructed to fully inspire to maximum and to 'hold' the breath. Several points should be noted:
 - The inspiration time from empty to maximum should be < 4s.
 - The total volume inspired of the Transfer Factor Gas mixture should be 85% or greater of the biggest Vital Capacity or Forced Vital Capacity.
 - There should be no air leaks at all throughout this testing process as this will affect the results.
- The breath-hold should be around 10s with $\pm 2s$, giving a range of 8-12 seconds.
- After the breath-hold period, the patient should finally be instructed to exhale or 'blow' out again to empty. The breath out at this point should be at a fairly steady pace, too fast and the equipment may have difficulty sampling the gas concentrations, or with being too slow, the gas mixture will remain in the lungs for an extended period of time and may give mis-leading results.
- The test should then be repeated at least once more after a **4 minute** waiting period for the patient to exhale the residual gas mixture of the lungs.

- Reproducibility is achieved when two sets of acceptable measurements are within 10% of each other for TL_{CO} and K_{CO} .

Considerations

Where possible, haemoglobin should be corrected to ensure the accuracy of the values obtained as they will be affected by this value. By default, if there is not a recent value (haemoglobin values can be obtained from the patient's case notes on the Electronic Patient Record system (EPR)) that has been taken within the last 12 months then the software will default haemoglobin depending on gender; for male – 14.6g/dL, for female – 13.4g/dL.

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