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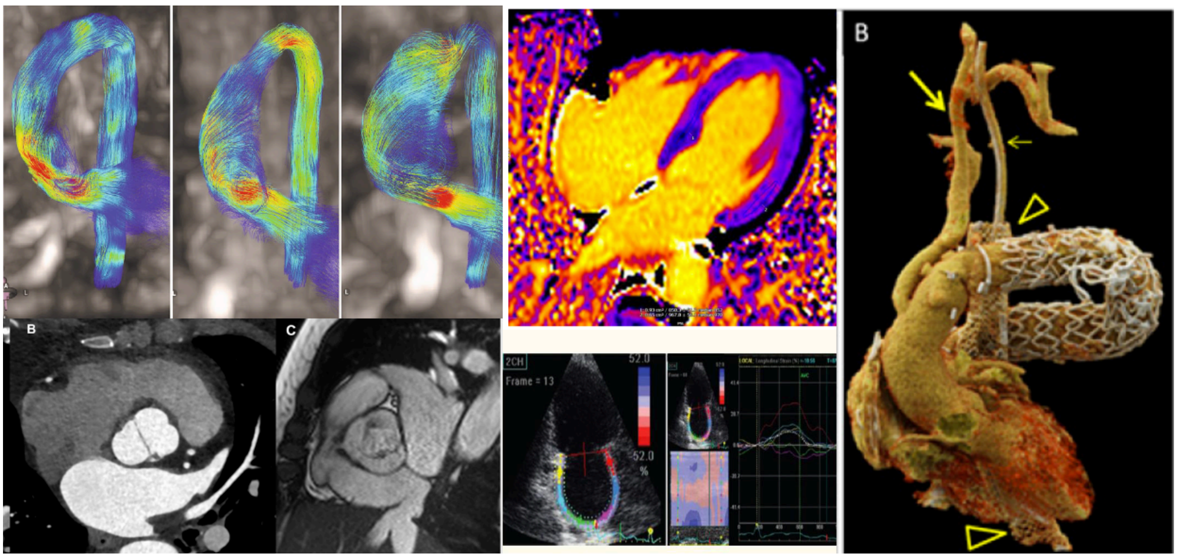

ADVANCED CARDIOVASCULAR IMAGING: NOVEL TOOLS IN CARDIOVASCULAR DIAGNOSIS AND PREVENTION

PhD thesis

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Chapter 1

General introduction and outline of the thesis

In the last years, the development of imaging techniques has marked improved cardiovascular prevention thanks to faster and more correct diagnoses.
Echocardiography, for its wide availability, is considered the first-line examination for all cardiovascular diagnostic pathways. Thanks to the use of ultrasound, it is a well-tolerated and risk-free examination for patients, it allows an anatomical and functional evaluation of the heart in all its components in real time and, thanks to the advancement of technology, it allows early detection of myocardial damage even before clear ventricular systolic dysfunction occurs. The advent of speckle tracking imaging, a tool now present in daily clinical practice, has allowed, for example, early diagnosis of myocardial damage from cardiotoxicity (1) and initial cardiac involvement in storage diseases such as amyloidosis (2) or Anderson-Fabry disease (3). Furthermore three-dimensional (3D) echocardiography allows a more accurate evaluation of cardiac volumes (4).
Among the imaging methods, cardiac magnetic resonance imaging (MRI) and computed tomography (CT) are also increasingly popular. Cardiac MRI, without exposing the patient to radiation, allows not only an anatomical and functional evaluation, but also a tissue characterization of the myocardium because of the different reaction of the tissues to magnetic fields exposure; it is also considered the gold standard for the quantification of cardiac volumes (5), ventricular ejection fraction (EF) and regurgitant volume (RV) in valve regurgitation (6). Thanks to the advent of T mapping sequences it is possible to recognize early myocardial damage or to distinguish between the different storage diseases in an accurate way (7-8), furthermore the use of speckle tracking MRI could help in the diagnostic process (9). 4Dflow in MRI seems to be of great use in congenital heart disease (10) and valve dysfunction (11), however further investigations are needed to be able to include it as a new tool in clinical practice.
Cardiac CT is widely used for the evaluation of coronary arteries and aortic diseases. With the advancement of technology, it is now possible to perform a CT examination by exposing the patient to a very low dose of ionizing radiation and obtaining functional images, making the method even more usable.

Outline of the thesis

The thesis is structured in three parts:

PART I. Advanced cardiovascular imaging in aortic disease

The advent of multi-modality imaging in the assessment and management of aortic disease has multiple applications, not only for the diagnosis, but also for risk stratification and planning of intervention, as well as for the evaluation of potential complications. Acute aortic syndromes are life-threatening conditions with high morbidity and mortality. The principal pathological feature is acute wall damage with possible evolution towards aortic rupture. Accurate and timely diagnosis is mandatory to avoid catastrophic consequences and multi-modality imaging simplifies the diagnostic process (chapter 2). Transthoracic echocardiography (TTE) can be performed at the patient's bedside, as well as in the emergency and critical care units, and for this reason is recommended as first line tool (12). It allows a partial view of the ascending aorta, the aortic arch and a limited part of the descending aorta, thus the diagnosis cannot always be completely ruled out by TTE alone, and further imaging such as transesophageal echocardiography (TOE) or CT of the aorta should be considered.

Thanks to its high spatial resolution, full assessment of thoracoabdominal aorta, short acquisition time, and wide availability, CT represents the ideal technique for diagnosing aortic syndromes and to recognize cardiovascular complications in chronic aortic diseases.

In chapter 3 we describe a case of aorto-esophageal fistula as a late complication of TEVAR implantation in a Stanford type-B chronic dissection diagnosed by CT.

In recent years, cardiovascular MRI imaging has emerged as a potential tool to provide comprehensive information on aortic flow dynamics and stiffness. In particular, time-resolved three-dimensional phase-contrast MRI (4D flow MRI) permits both regional aortic biomechanics (13) and advanced haemodynamic characteristics (14) to be assessed with an unprecedented level of details.

In chapter 4 we assess aortic flow and stiffness in patients with Loeys–Dietz syndrome by 4D flow and cine cardiovascular MRI and we compare the results with those of healthy volunteers and Marfan syndrome patients.
Marfan syndrome is a more common hereditary connective tissue disorder with skeletal manifestations and aortic dilation (15-16). The systematic use of whole-body vascular assessment is recommended to identify other sites of vascular involvement at risk for complications and to define the subgroup of patients with more aggressive aortic disease (chapter 5).

PART II. Advanced cardiovascular imaging in valvular heart disease

In developed countries, degenerative valve disease has replaced rheumatic heart disease as the leading cause of valvular heart disease (VHD). The prevalence of at least moderate VHD is 2.5% and increases with age (17).
Decision making in VHD involves accurate diagnosis for timing of intervention, risk assessment and selection of the most suitable type of intervention.
Echocardiography is the key technique used to confirm the diagnosis of VHD, as well as to assess its aetiology, mechanisms, function, severity, and prognosis.
Apart from the multiparametric valvular evaluation, the TTE also allows the evaluation of the ventricular volumes and systolic function, that are strong prognostic factors. Recent studies suggest that global longitudinal strain has greater prognostic value than left ventricular EF, although cut-off values are not uniform (18-19). TOE should be considered when TTE is of suboptimal quality (20).
In patients with inadequate echocardiographic quality or discrepant results, cardiac MRI should be used to assess the severity of valvular lesions, particularly regurgitant lesions, and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis (21). MRI should be used to quantify the regurgitant fraction when echocardiographic measurements are equivocal or discordant with clinical findings.
In chapter 6 we provide a comprehensive mitral valve prolapse assessment using cardiovascular MRI.

The advent of 4D flow MRI has made it possible to evaluate the flow anomalies that result from anatomical valve alterations and their consequences, as for example in the bicuspid aortic valve (chapter 7).

Cardiac CT may contribute to the evaluation of valve disease severity, particularly in aortic stenosis (22) and regurgitation, possibly associated disease of the thoracic aorta (dilatation, calcification).

The role of multimodality imaging in valvular evaluation is highlighted in chapter 8 about aortic regurgitation in bicuspid aortic valve patients.

PART III: Advanced cardiovascular imaging in myocardial disease

Two-dimensional and Doppler echocardiography remains the first line imaging tool for most forms of heart muscle disease. Some features are important diagnostic red flags but, as with the electrocardiogram, these are only useful when interpreted in the context of other phenotypic findings. Left Ventricular EF remains the most used parameter in clinical practice for the evaluation of myocardial damage, even if the advent of speckle tracking imaging allows early detection of tissue damage.

In oncologic patient a comprehensive TTE evaluation is recommended to monitor any myocardial damage from chemotherapy and to identify eventual embolic sources when atrial fibrillation occurs (chapter 9).

For the evaluation of EF, cardiac MRI is considered the gold standard, however the calculation of the volumes takes place mainly through manual segmentation of the images. The emergence of deep learning has considerably advanced the state-of-the-art in cardiac MRI segmentation. Many techniques have been proposed over the last few years, bringing the accuracy of automated segmentation close to human performance. In chapter 10 we evaluate a range of deep learning solutions for the automated segmentation of multi-centre, multi-vendor and multi-disease cardiac images.

Apart from functional evaluation, MRI allows detailed analysis of early myocardial tissue damage thanks to post-contrast sequences, T mapping sequences and speckle tracking imaging.

The combination of echocardiography and cardiac MRI has allowed us to develop and validate a risk prediction model in patients with left ventricular noncompaction (LVNC) cardiomyopathy (chapter 11).
In the last years, the use of different imaging methods has allowed a simpler and more accurate diagnosis process even in storage diseases considered rare, such as Anderson-Fabry Disease (chapter 12).

PART I. Advanced cardiovascular imaging in aortic disease

Chapter 2

The role of Multimodality Imaging approach in acute aortic syndromes: diagnosis, complications, and clinical management

Acute aortic syndromes (AAS) represent a spectrum of interrelated disorders, characterized by disruption of the aortic integrity, and are associated with high morbidity and mortality. These conditions include aortic dissection (AD), accounting for the majority of AAS (80%), intramural hematoma (IMH, ~15%), and penetrating aortic ulcer (PAU, ~5%)(23-25).
AD is described as a separation of the aortic wall layers caused by an intimo-medial tear, resulting in the creation of a false lumen that propagates within the medial layer. Thus, AD typically shows the appearance of a dissection flap, an entry tear, and two aortic channels (a true and false lumen). No modern classifications have substituted the older Stanford and DeBakey ones, that remain the most commonly used. AD involving the ascending aorta is defined Stanford type A dissection, regardless of distal extension; when the disruption is distal to the left subclavian origin, on the contrary, it is considered type B. The DeBakey classification recognizes types I, II, and, III, with type I affecting both the ascending and descending aorta, type II the ascending aorta and the arch only, and type III involving the descending aorta but sparing the arch and the ascending aorta. IMH is instead a haematoma created within the media layer and secondary to the rupture of

vasa vasorum. Finally, PAU is an ulceration of an atherosclerotic aortic plaque penetrating towards the internal elastic lamina and into the media (26).

The advent of multi-modality imaging in the assessment and management of AAS has multiple applications, not only for the diagnosis, but also for risk stratification and planning of the acute intervention, as well as for the evaluation of potential complications and/or the candidacy for intervention or re-intervention in the subacute or chronic phases (Figure 1).

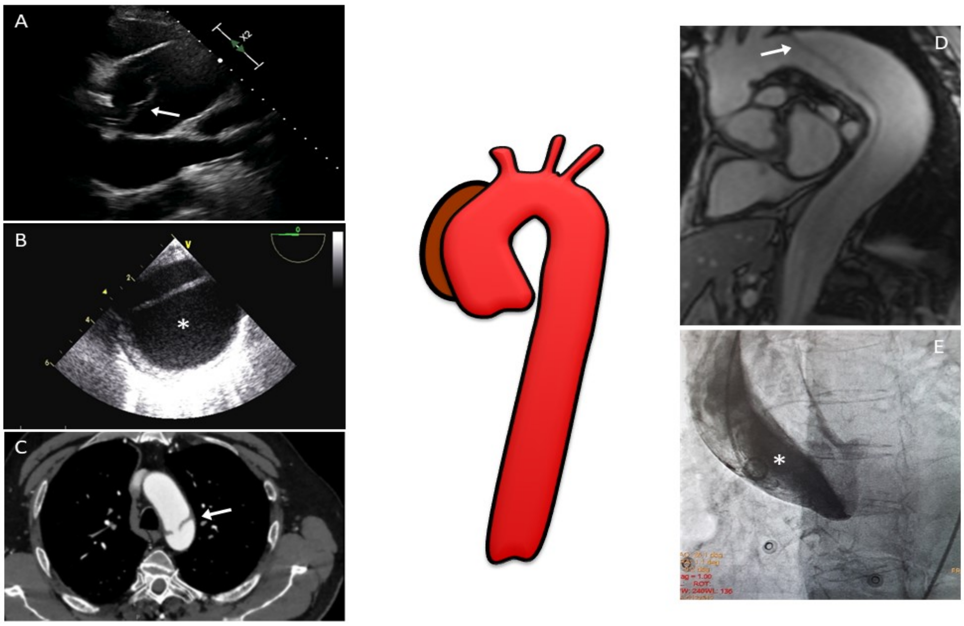


Figure 1. Multimodality imaging assessment of aortic dissection: (A) Two-dimensional transthoracic echocardiography showing a linear echo of an intimal flap (arrow) in a dilated aortic root above aortic valve level; (B) Two-dimensional transesophageal echocardiography in patients with aortic dissection involving the entire aorta, the false lumen (*) is typically larger and often compresses the true lumen potentially affecting distal aortic flow; (C) CT image with evidence of the intimal tear (arrow) at the level of the aortic arch; (D) MRI with SSFP imaging in oblique sagittal plane showing an intimal flap (arrow) from the aortic arch to abdominal aorta; (E) Aortic angiography performed in a patient with suspected inferior ST-segment elevation myocardial infarction revealing a type A aortic dissection (one may note that the pigtail catheter is located in the false lumen (*) of the dissection). CT, computed tomography; MRI, magnetic resonance imaging; SSFP, steady-state free precession.

In this document, our aim is to critically review the distinctive multi-modality imaging features of AAS providing at the same time an update overview of diagnostic strategies and current management of these disorders.

Table 1. Advantages and limitations of imaging techniques in the diagnosis of aortic dissection

Imaging technique	Advantages	Limitations
Transthoracic echocardiography	● Frequently used technique for measuring proximal aortic segments in clinical practice ● Visualization of the aortic valve and ascending aortic structure in real time at the patient's bedside or in the emergency and critical units ● Rapid identification of any complications such as cardiac tamponade, severe aortic dilation, regional wall motion abnormalities, and severe left ventricular systolic dysfunction	● Restricted in patients with abnormal chest wall configuration, obesity, pulmonary emphysema, and in patients on mechanical ventilation ● Low sensibility in detecting distal dissection of the thoracic aorta ● Intra- and inter-operator variability
Transesophageal echocardiography	● Useful in the initial diagnosis and follow up of aortic dissection ● Very high diagnostic accuracy ● Crucial role in the pre-operative, intra-operative, and post-operative control of surgically treated aortic disease	● Presence of a "blind spot" ● False positive results could occur because of reverberation echoes ● Uncomfortable for patient and sometimes may need sedation ● Intra- and inter-operator variability
Computed tomography	● Short acquisition time (suitable for unstable patients) ● Wide availability ● No contraindication in presence of metallic devices ● Full assessment of thoracoabdominal aorta ● High spatial resolution ● Optimal visualization of arterial wall calcification and endovascular stents	● Use of iodinated contrast (risk of contrast induced nephropathy and allergy) ● Use of ionizing radiations (tube parameters and the amount of contrast agents vary according to the type of scanner used. Consider the speed of scan acquisition and coverage to optimize image quality and reduce the amount of contrast agents)
Magnetic resonance imaging	● No radiation exposure ● No iodinated contrast ● Excellent evaluation of aortic wall ● Dynamic assessment of flow ● Gadolinium contrast media not mandatory ● Not controindicated in pregnancy	● Prolonged scan time ● Difficulty in monitoring acutely ill patients ● Risk of nephrogenic systemic fibrosis with GFR < 30 mL/min/1.73 m2 (when gadolinium is used) ● Poor assessment of arterial wall calcification

		• Signal loss within endovascular stent due lack of radiofrequency penetration • Less availability
Aortography	• elevated accuracy • necessary for endovascular procedures	• invasive • requires contrast medium • entails radiation exposure

GFR, Glomerular Filtration Rate.

Table 2. Advantages and limitations of imaging techniques in the diagnosis of intramural hematoma

Imaging technique	Advantages	Limitations
Transesophageal echocardiography	• High-resolution images with direct observation of the aortic wall • Flow assessment with Doppler technique • Complication assessment (e.g. pericardial and pleural effusion and mediastinal haemorrhage)	• Difficulty to visualize all segments of the aorta (e.g. ''Blind spot'') • Semi-invasive technique • Operator dependent
Computed tomography	• Short acquisition time (suitable for unstable patients) • Wide availability • No contraindication in presence of metallic devices • Full assessment of thoracoabdominal aorta • High spatial resolution	• Use iodinated contrast (risk of contrast induced nephropathy and allergy) • Use of ionizing radiations • Difficult the differential diagnosis with aortitis
Magnetic resonance imaging	• No radiation exposure • No iodinated contrast • Excellent evaluation of aortic wall and determination of the age of hematoma • Differential diagnosis between aortitis, thrombus, and dissection • Gadolinium contrast media not mandatory • Not controindicated in pregnancy	• Prolonged scan time • Difficulty in monitoring acutely ill patients • Risk of nephrogenic systemic fibrosis with GFR < 30 mL/min/1.73 m2 (when gadolinium is used)

Aortography	• necessary for endovascular procedures	• limited accuracy • invasive • requires contrast medium • entails radiation exposure

GFR, Glomerular Filtration Rate.

Table 3. Advantages and limitations of imaging techniques in the diagnosis of penetrating aortic ulcer

Imaging technique	Advantages	Limitations
Transesophageal echocardiography	• High-resolution images with direct observation of the aortic wall • Differential diagnosis with ulcer-like projections	• Moderate diagnostic value • Semi-invasive technique • Operator dependent
Computed tomography	• Short acquisition time (suitable for instable patients) • Wide availability • No contraindication in presence of metallic devices • Full assessment of thoracoabdominal aorta • High spatial resolution	• Use iodinated contrast (risk of contrast induced nephropathy and allergy) • Use of ionizing radiations
Magnetic resonance imaging	• No radiation exposure • No iodinated contrast • Excellent evaluation of aortic wall • Differential diagnosis between thrombus, IMH, ulcerated atherosclerotic plaque, and dissection • Gadolinium contrast media not mandatory • Not controindicated in pregnancy	• Prolonged scan time • Difficulty in monitoring acutely ill patients • Risk of nephrogenic systemic fibrosis with GFR < 30 mL/min/1.73 m2 (when gadolinium is used)
Aortography	• elevated accuracy • necessary for endovascular procedures	• invasive • requires contrast medium • entails radiation exposure

GFR, Glomerular Filtration Rate.

Conclusions

Multimodality imaging approach in the AAS is indispensable for accurate and timely diagnosis. In this setting, prompt diagnosis is mandatory considering the life-threatening condition which imply adequate and immediate treatment. In addition, multimodality imaging adds key information about urgency indicators and associated complications. Correct and high-quality diagnostic work-up improves the poor prognosis in this emergency condition. Advances in cardiovascular imaging techniques has led to a better understanding of the pathophysiology and improvement in the diagnosis and management. Appropriate choice of imaging modality is based on the accuracy, advantages, and limitations of the techniques. However, the clinical conditions of the patient and local availability and expertise should be also considered. Correct application of imaging algorithm and cardiovascular techniques is crucial for the diagnosis and management of AAS.

Chapter 3

Hematemesis as a Late Complication after TEVAR in a Stanford Type-B Chronic Aortic Dissection

History of presentation

A 64-year-old male presented to the emergency department for the onset of nausea and hypotension. He also reported episodes of melena in the last 3 days. Blood pressure was 95/60 mmHg, heart rate 60 bpm, body temperature 36°C, and respiration rate 24 bpm. Cardiac and thoracic auscultations were unremarkable, and all peripheral pulses were present.

Past medical history

His past medical history included arterial hypertension, dyslipidemia, and a Type-B Stanford aortic dissection in 2000. Due to the progressive aortic dilation, in 2013, a TEVAR was implanted in zone 1 of the aortic arch associated to total debranching of supra-aortic trunks and ligature of the left subclavian artery. Subsequently, due to progressive aortic dilatation and the suspicion of a type 2 endo leak, the left subclavian artery was embolized through the false lumen in 2017. Since then, the patient underwent annual follow-up at our aortic disease unit with stabilization of the proximal thoracic aortic aneurysm diameter, however, there was aortic arch dilation in the proximal sealing zone with proximal TEVAR migration without evidence of a type I endoleak. The patient was waiting for an elective open thoracoabdominal aneurysm repair.

Differential diagnosis

Given the patient's clinical presentation with gastrointestinal bleeding, the differential diagnosis included primary digestive bleeding secondary to peptic ulcer disease, cancer, reflux esophagitis, or bleeding esophageal varices. However, because of the patient’s history of chronic aortic dissection, the presence of an aortic-esophageal fistula or aortic rupture was also considered in the differential diagnosis.

Investigations

The patient underwent an ECG-gated CT study showing a significant detachment of the proximal portion of the TEVAR (Type I endoleak), proximal descending aorta aneurysm growth with a maximum diameter of 87 mm (including the false lumen peri- TEVAR), and the presence of small air bubbles in the mediastinum between the false lumen and the esophagus (Figure 1).

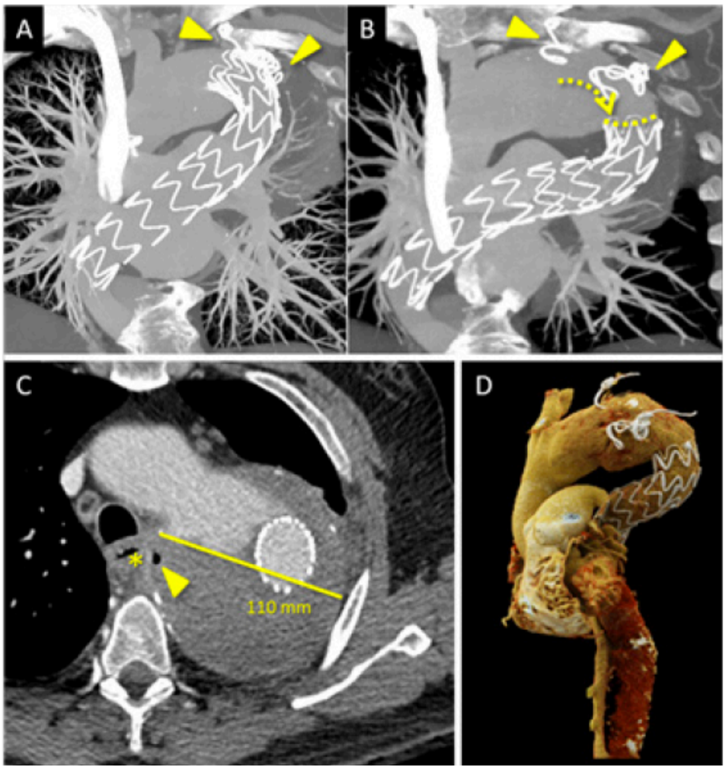


Figure 1: ECG-gated CT angiography. Oblique coronal plane of the TEVAR before (A) and after the current admission (B) showing caudal displacement of the proximal anchorage (dotted lines and dotted arrow). Arrowheads signal the subclavian embolization coils. (C): Increased dilation of the descending thoracic aorta (from 87 mm to 110 mm); intra-aneurysm air bubble (arrowhead), and adjacent esophagus (asterisk). (D): Volume rendering cinematic reconstruction of the thoracic aorta.

The esophageal-gastro-duodenoscopy confirmed the suspicion of Aorto Esophageal Fistula (AEF) for the presence of small clots in the esophageal wall and a clear wall continuity solution.

Management

The patient was hospitalized in the Acute Cardiac Care Unit and the aortic team decided on a hybrid surgical repair.

Three days later, an aortic repair with a Thoraflex hybrid prosthesis implantation was performed with brachiocephalic trunk implantation on the distal ascending aorta. In the same procedure, a new TEVAR was implanted from the distal part of the Thoraflex to the distal thoracic descending aorta (Figure 2). Thus, the aortic arch and the thoracic descending aorta were repaired and isolated from the esophageal fistula.

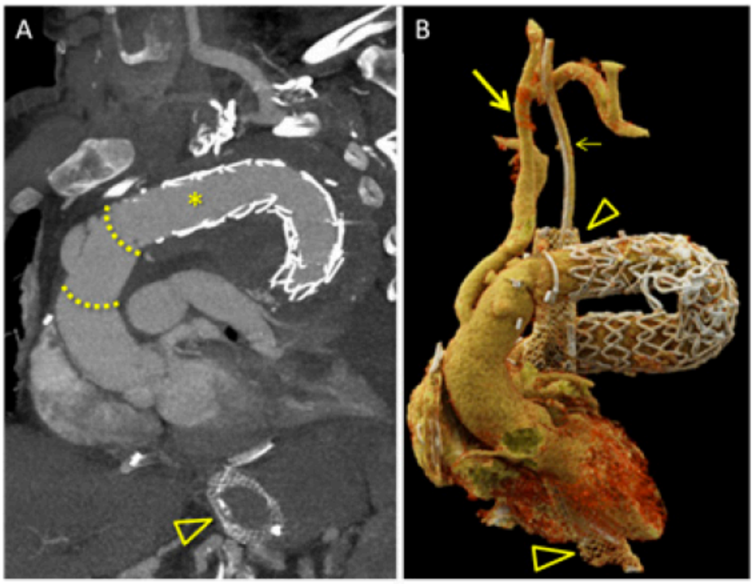


Figure 2: ECG-gated CT angiography after surgery. (A): ThoraflexTM hybrid aortic graft (between the dashed lines) followed by the overlapping TEVAR (asterisk). The distal esophageal stent is also seen (arrowhead). (B): Volume rendering cinematic reconstruction showing the ThoraflexTM and TEVAR as well as the esophageal stent (arrowheads) with the nasogastric tube within it (small arrow). The carotid-carotid bypass (large arrow) is also seen.

Conclusion

There is no clear consensus about the treatment of choice in AEF which is associated with a high mortality rate. The best treatment approach is not known, and a bedside multidisciplinary decision by an aortic team seems to be the best option. In this case, a hybrid surgical aortic approach with a non-invasive esophageal intervention (stent) was chosen with a satisfactory in-hospital clinical stabilization of the patient. However, it underlines the relevance of complete esophageal repair and infection control to improve the negative prognosis of these patients.

Chapter 4

Aortic flow dynamics and stiffness in Loeys–Dietz syndrome patients: a comparison with healthy volunteers and Marfan syndrome patients

Aims

To assess aortic flow and stiffness in patients with Loeys–Dietz syndrome (LDS) by 4D flow and cine cardiovascular magnetic resonance (CMR) and compare the results with those of healthy volunteers (HV) and Marfan syndrome (MFS) patients.

Methods and results

Twenty-one LDS and 44 MFS patients with no previous aortic dissection or surgery and 35 HV underwent noncontrast- enhanced 4D flow CMR. In-plane rotational flow (IRF), systolic flow reversal ratio (SFRR), and aortic diameters were obtained at 20 planes from the ascending (AAo) to the proximal descending aorta (DAo). IRF and SFRR were also quantified for aortic regions (proximal and distal AAo, arch and proximal DAo. Peak-systolic wall shear stress (WSS) maps were also estimated. Aortic stiffness was quantified using pulse wave velocity (PWV) and proximal AAo longitudinal strain (Figure 1).

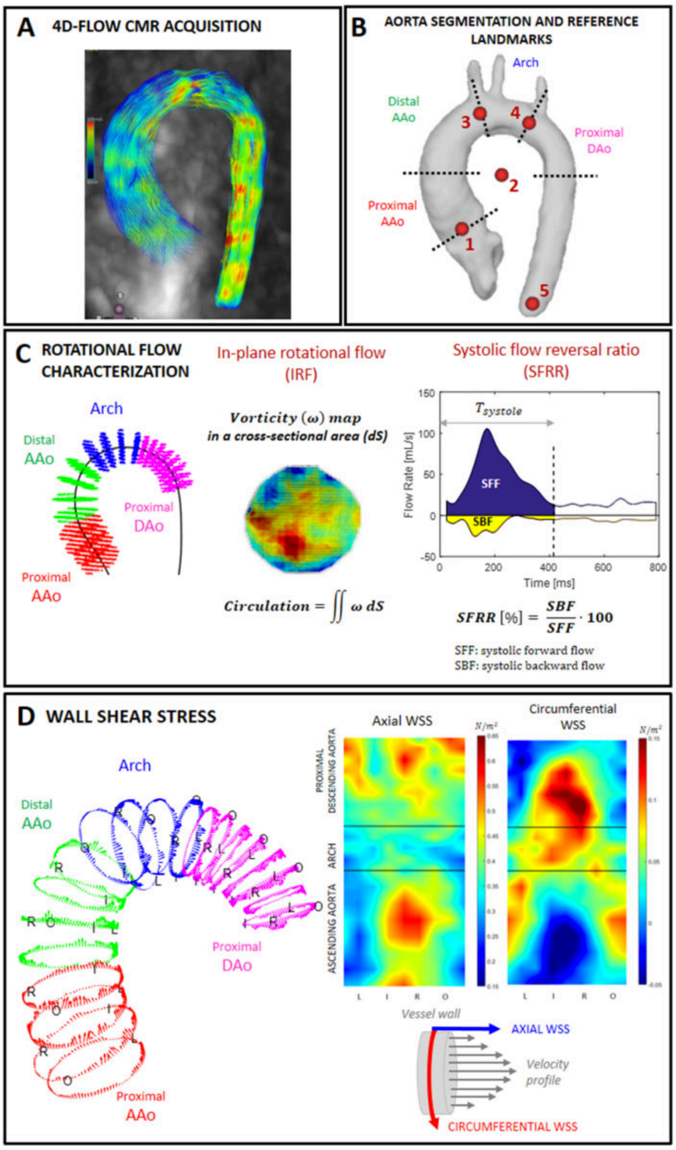


Figure 1. Analysis planes and flow parameters calculated from 4D flow CMR (A). 3D aorta segmentation, aortic regions, centreline, and reference anatomical landmarks (B) at the sinotubular junction,1 pulmonary artery bifurcation, first and third supra-aortic trunks, and diaphragmatic level.5IRF and SFRR (C).WSS vectors (left panel) and, axial and circumferentialWSSmaps (right panel) (D).

Compared to HV, LDS patients had lower rotational flow at the distal AAo (P = 0.002), arch (P = 0.002), and proximal DAo (P < 0.001) even after adjustment for age, stroke volume, and local diameter. LDS patients had higher SFRR in the proximal Dao compared to both HV (P = 0.024) and MFS patients (P = 0.015), even after adjustment for age and local diameter. Axial and circumferential WSS in LDS patients were lower than in HV. AAo circumferential WSS was lower in LDS compared to MFS patients. AAo and DAo PWV and proximal AAo longitudinal strain revealed stiffer aortas in LDS patients compared to HV (P = 0.007, 0.005, and 0.029, respectively) but no differences vs. MFS patients.

Discussion

This study analysed blood flow characteristics and aortic stiffness by 4D flow and cine CMR in the thoracic aorta of adult patients with LDS compared with patients with MFS and HV matched for age, sex, BSA, and blood pressure. The main findings of this work were that: ascending and descending aortic stiffness was greater in LDS than in HV but similar to patients withMFS; in-plane flow rotation and circumferential WSS in the distal AAo, arch and proximal DAo of patients with LDS were lower than in HV; and vortices in the proximal DAo of patients with LDS were characterized by higher SFRR compared to HV and patients

with MFS. To the best of our knowledge, this is the first study to analyse both flow dynamics and aortic biomechanics in a cohort of patients with LDS and compare them to patients withMFS and HV (27-29).

Conclusion

Greater aortic stiffness as well as impaired IRF and WSS were present in LDS patients compared to HV. Conversely, similar aortic stiffness and overlapping aortic flow features were found in Loeys–Dietz and Marfan patients.

Chapter 5

Aortic Branch Aneurysms and Vascular Risk in Patients with Marfan Syndrome

Background

Aortic branch aneurysms are not included in the diagnostic criteria for Marfan syndrome (MFS); however, their prevalence and eventual prognostic significance are unknown.

Objectives

The goal of this study was to assess the prevalence of aortic branch aneurysms in MFS and their relationship with aortic prognosis.

Methods

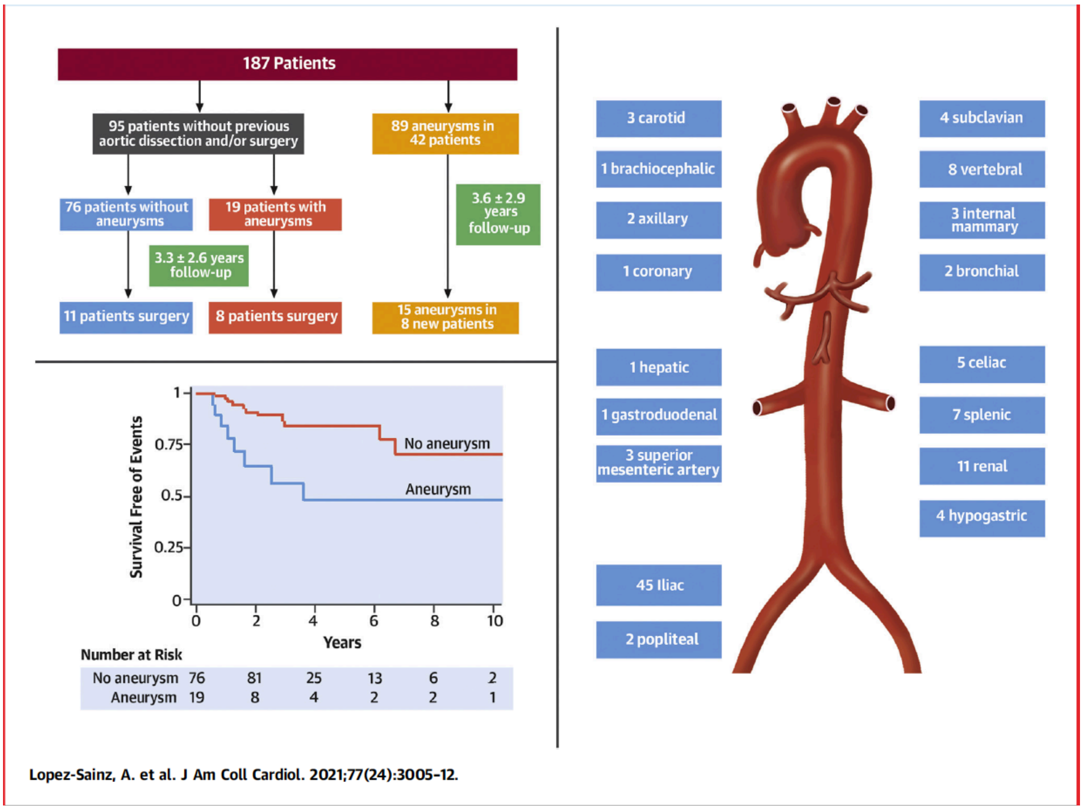
MFS patients with a pathogenic FBN1 genetic variant and at least one magnetic resonance or computed tomography angiography study assessing aortic branches were included. Aortic events and those related to aneurysm complications were recorded during follow-up.

Results

A total of 104 aneurysms were detected in 50 (26.7%) of the 187 patients with MFS (mean age 37.9 _ 14.4 years; 54% male) included in this study, with the iliac artery being the most common location (45 aneurysms). Thirty-one patients (62%) had >1 peripheral aneurysm, and surgery was performed in 5 (4.8%). Patients with aneurysms were older (41.9 _ 12.7 years vs. 36.7 _ 14.8 years; p. 0.040) and had more dilated aortic root (42.2 _ 6.4 mm vs. 38.8 _ 8.0 mm; p. 0.044) and dyslipidemia (31.0%vs. 9.7%; p. 0.001). In a subgroup of 95 patients with no previous aortic surgery or dissection followed up for 3.3 _ 2.6 years, the presence of arterial aneurysms was associated with a greater need for aortic surgery (hazard ratio: 3.4; 95% confidence interval: 1.1 to 10.3; p. 0.028) in a multivariable Cox analysis adjusted for age and aortic diameter.

Conclusions

Aortic branch aneurysms are present in one-quarter of patients with MFS and are related to age and aortic dilation, and they independently predict the need for aortic surgery. The systematic use of whole-body vascular assessment is recommended to identify other sites of vascular involvement at risk for complications and to define the subgroup of patients with more aggressive aortic disease.



Aortic Branch Aneurysms in Marfan Syndrome. Anatomic distribution and survival analysis. Peripheral aneurysm on baseline imaging is associated with an increased risk of aortic surgery during follow-up (log-rank test, p. 0.026), even after adjustment for sex, baseline aortic root diameter, and family history of aortic dissection (hazard ratio: 3.4; 95% confidence interval: 1.1 to 10.3; p. 0.028).

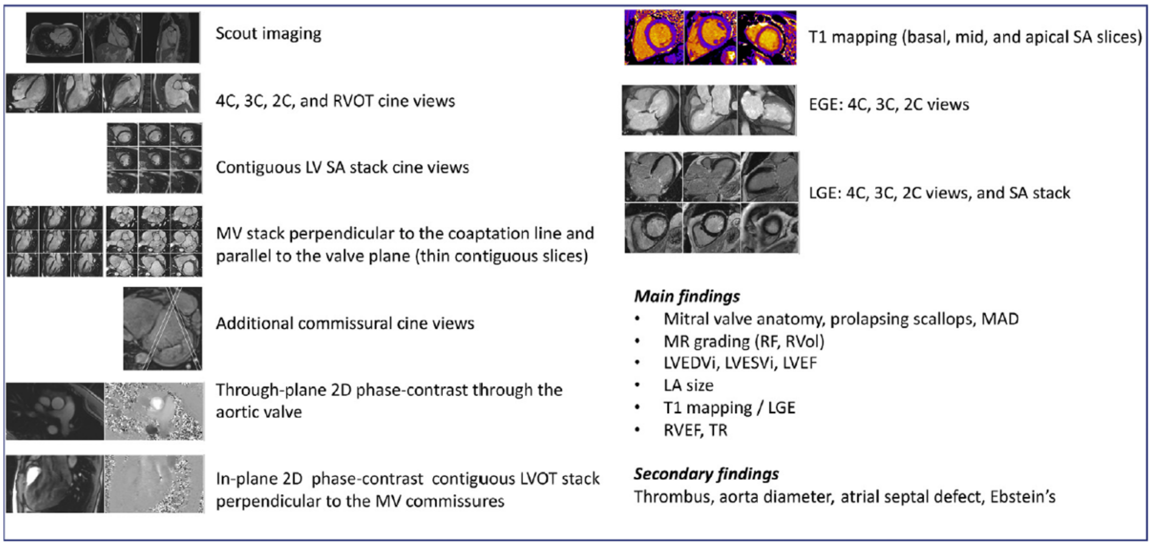
PART II. Advanced cardiovascular imaging in valvular heart disease

Chapter 6

Comprehensive mitral valve prolapse assessment by cardiovascular MRI

Mitral valve (MV) prolapse (MVP) is a common disorder, characterised by superior displacement of the leaflets into the left atrium (LA). MVP is a clinical entity that is not fully understood, despite being known for more than a century (30). The development of sophisticated cardiovascular magnetic resonance imaging (CMRI) sequences over the last decades has allowed more detailed assessment of MVP and provided insight and better understanding of its pathophysiology. CMRI affords the advantage of assessing the severity of mitral regurgitation (MR) associated with MVP, LA size, biventricular volumes/function, and to exclude concurrent and coexisting cardiovascular abnormalities of connective tissue disorders, such as Marfan syndrome (31). Most importantly, recent studies have shown the value of native myocardial T1 mapping and late gadolinium enhancement (LGE) for the assessment of myocardial fibrosis and risk prognostication. As such, there is a growing need for the establishment of a standardised CMRI protocol for comprehensive and detailed study of MVP.

In this review, we provide a detailed description of suggested steps that should be followed when scanning MVP to obtain all the above information and identify possible associated anomalies (Fig 1).



4C: 4-chamber; 3C: 3-chamber; 2C: 2-chamber; RVOT: right ventricular outflow tract; LV: left ventricular; SA: short-axis; MV: mitral valve; LVOT: left ventricular outflow tract; EGE: early gadolinium enhancement, LGE: late gadolinium enhancement; MR: mitral regurgitation; RF: regurgitant fraction; RVol: regurgitant volume; MAD: mitral annular disjunction; LVEDVi: left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction; LA: left atrium; RVEF: right ventricular ejection fraction, TR: tricuspid regurgitation.

Figure 1. Comprehensive protocol for the assessment of mitral valve prolapse. Sequences suggested for a proper morphological and functional assessment of MV and ventricles, quantification of MR, identification of MAD, fibrosis, and associated findings.

In conclusion, further to the assessment of MVP by echocardiography, a comprehensive CMRI study of MVP may provide additional findings regardless of the severity of valve dysfunction. CMRI allows comprehensive evaluation of the prolapsing valve and its haemodynamic impact on cardiac chambers, as well as the presence of mitral annulus disjunction, focal LV hypertrophy, and myocardial fibrosis, which are well-established markers of arrhythmic/SCD risk in MVP.

Chapter 7

Leaflet fusion length is associated with aortic dilation and flow alterations in non-dysfunctional bicuspid aortic valve

Objective

Bicuspid aortic valve (BAV), the most common congenital valve defect, is associated with increased risk of aortic dilation and related complications; however, current risk assessment is not effective. Most of BAV have three leaflets with a fusion between two of them of variable length. This study aimed to ascertain whether the extent of leaflet fusion (often called raphe) is related to aortic dilation and flow abnormalities in BAV with no significant valvular dysfunction.

Methods

One hundred and twenty BAV patients with no significant valvular dysfunction or history of surgical repair or aortic valve replacement were consecutively and prospectively enrolled (September 2014–October 2018). Cardiac magnetic resonance protocol included a 4D flow sequence for haemodynamic assessment. Moreover, a stack of double-oblique cine images of the aortic valve were used to quantify fusion length (in systole) and leaflet length (diastole) (Fig.1). Inter- and intra-observer reproducibility was tested in 30 randomly selected patients.

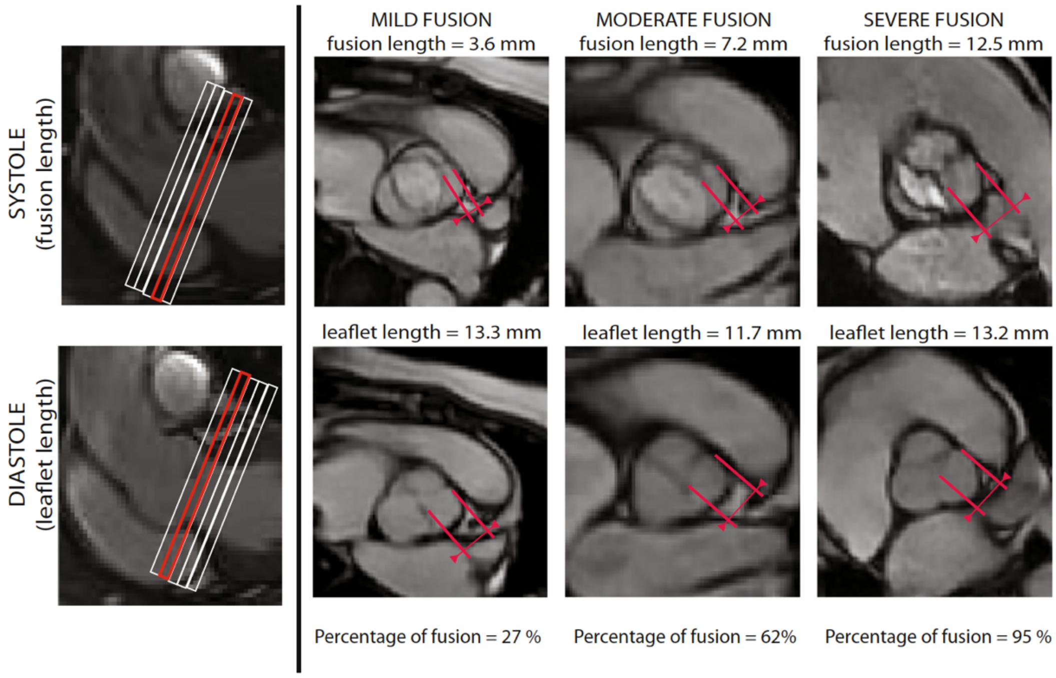


Fig. 1 Left: examples of location of the double-oblique planes and the choice of the one to be used (in red) for systolic (top) and diastolic
(bottom) measurements. Right: examples of double-oblique cine images of the aortic valve in bicuspid aortic valve patients with mild, moderate and severe fusion of two aortic valve leaflets. Red arrows indicate measured fusion length (systole, top) and leaflet length (diastole, bottom).

Results

Aortic valve leaflet fusion was measurable in 112 of 120 (93%) cases with good reproducibility (ICC = 0.826). Fusion length varied greatly (range: 2.3–15.4mm;mean: 7.8 ± 3.2mm).After correction for demographic and clinical conditions, fusion length was independently associated with diameter and z-score at the sinus of Valsalva ($p = 0.002$ and $p = 0.002$, respectively) and ascending aorta ($p = 0.028$ and $p = 0.046$) (Fig.2). Fusion length was positively related to flow asymmetry, vortices and circumferential wall shear stress, thereby possibly providing a pathophysiological link with aortic dilation (Fig.3).

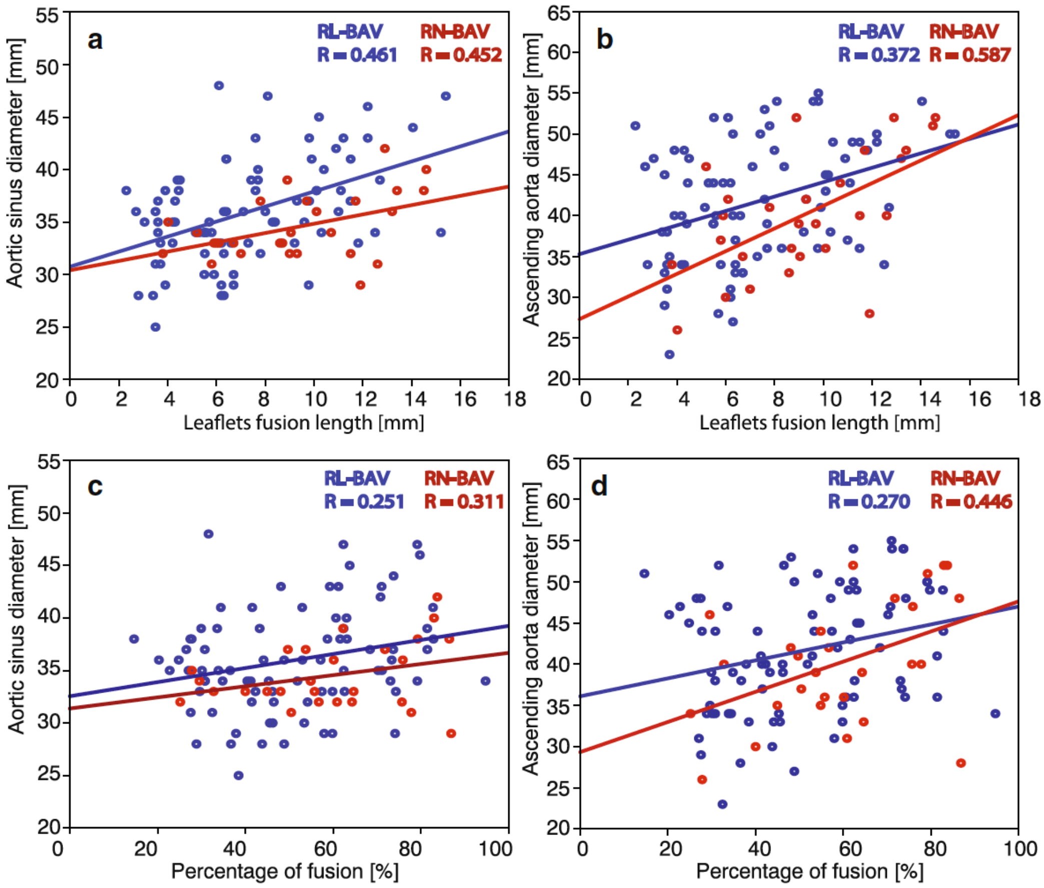


Fig. 2 a–d Scatter plots showing associations between leaflets fusion length (top) and percentage of fusion (bottom) and aortic sinus (left) and ascending aorta (right) diameter. Lines are linear best fit. Blue dots and lines refer to RL-BAV, red dots and lines to RN-BAV

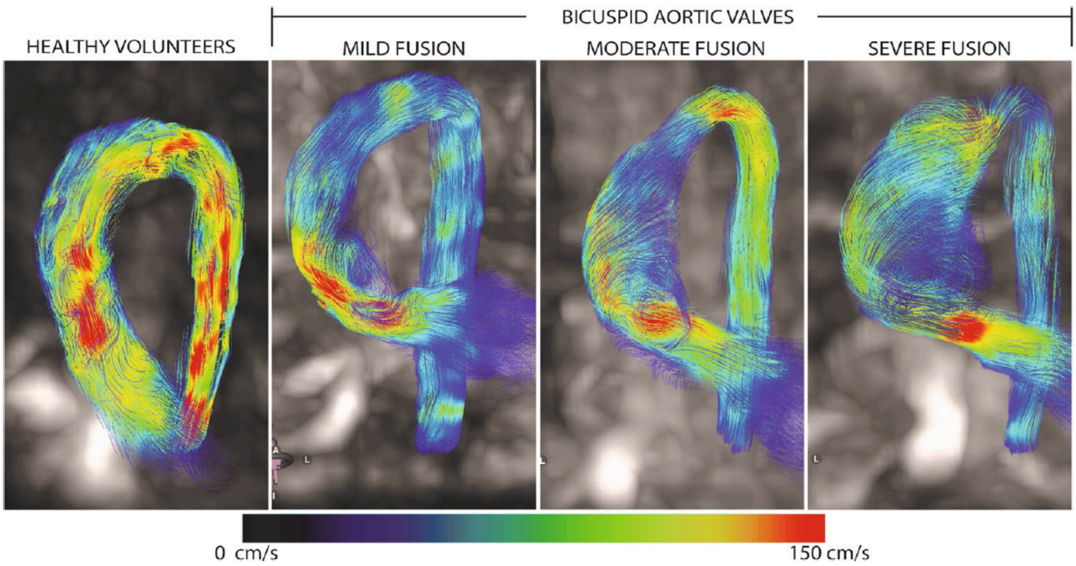


Fig. 3 Representative 4D flow CMR images of systolic aortic streamlines in a healthy volunteer (left) and in BAV patients with mild, moderate and severe fusion length

Discussion

The main findings of this study were that in non-dysfunctional BAV patients the length of the fusion between adjacent

leaflets (often called raphe) varied greatly and was independently related to aortic sinus and ascending aorta diameters and z-scores, even after correction for demographic and clinical conditions, including maximum velocity at the aortic
valve. Moreover, fusion length was positively related to flow alterations, possibly providing a pathophysiological explanation for the relationship between fusion length and aortic dilation.

Although several autopsy and surgical studies reported minor fusion between aortic valve leaflets (32-37), no studies assessed whether the degree of leaflet fusion is related to aortic dilation in non-dysfunctional BAV. Furthermore, no data on fusion length distribution in non-dysfunctional BAV have been reported.

Conclusions

In non-dysfunctional BAV patients, aortic valve leaflet fusion length varies greatly and is independently related to aortic sinus and ascending aorta dilation. Flow alterations consisting of increased flow asymmetry, vortices and circumferential WSS are positively related to fusion length, thereby providing a possible pathophysiological link between fusion length and aortic dilation.

Chapter 8

Aortic Regurgitation in Bicuspid Aortic Valve: The Role of Multimodality Imaging

Bicuspid aortic valve (BAV) is the most common congenital heart disease, with a reported prevalence of 0.4–2.25% (Fig.1). It is considered to be a valvulo-aortopathy characterized by a large individual heterogeneity; the most frequent complications of the BAV condition are aortic valvular dysfunction and ascending aorta dilation. Early and accurate diagnosis of BAV and its complications by imaging techniques is essential to appropriately address the management and possibly improve outcomes of BAV patients.

Figure 1. Different BAV types: (A) Sievers type 0 (no raphe in the valve) by CT scan; (B) Sievers type 1 (only one raphe in the valve) by CT scan; (C) partial-fusion BAV by CMR cine-sequence.

About valvular dysfunction, the evaluation of aortic regurgitation (AR) in BAV is still a challenge because of the eccentricity of the jet that may under/over-estimate the regurgitation. Transthoracic echocardiography (TTE) is used in clinical practice as first line imaging, but the common echocardiography parameters (such as vena contracta, pressure Half-time, etc.) are not often useful in this kind of patients. The use of a multimodality approach which combines echocardiography, cardiac MRI (CMR), cardiac CT, and advanced technologies (4D-flow, strain imaging, etc..) may be useful to better quantify regurgitation and to select patients suitable for valve replacement.

This review provides an overview of the most recent insights about cardiovascular imaging tools and their utility in bicuspid valve evaluation, focusing on chronic regurgitation. We describe the role of multimodality imaging in both diagnosis and risk assessment of this disease, pointing out the advantages and disadvantages of the imaging techniques, aiming to provide a guide to clinicians and cardiovascular imaging specialists in choosing the best imaging tools to use (Tables 1-3).

Table 1. Advantages and limitations about echocardiographic assessment in BAV AR.

	Advantages	**Limitations**
Echocardiography	• Widely available • Cheap • No radiation exposure • No contrast agents required • Information about aortic valve anatomy • Visual estimation of AR jet and information about jet eccentricity by Color flow Doppler imaging	• Operator and window dependent • Irregular shape of the regurgitant orifice and eccentric AR jets in BAV limit quantitative assessment of AR and accuracy in AR grading. • The ratio between the regurgitant jet width and LV outflow tract diameter

	• Quantitative assessment and grading of AR • Vena contracta evaluation appliable even in eccentric jets. • Diastolic flow reversal in the descending aorta by pulsed wave Doppler for evaluation of AR severity • Information about LV and aortic size • Speckle tracking echo provides info about LV deformations in multiple directions and aortic distensibility. • 3D-echo allows visualization of the actual shape of the regurgitant aortic orifice	is not applicable for irregular shaped orifices • Vena contracta evaluation is not applicable in case of multiple jets. • The proximal isovelocity surface area method is limited by low feasibility because of difficulty in detection of the flow convergence zone and possible interposition of valve tissue. • Pressure half time requires adequate Doppler angle and beam alignment, thus it is hardly applicable in eccentric jets.

Table 2. Advantages and limitations about Cardiac Magnetic Resonance (CMR) assessment in BAV AR.

	Advantages	**Limitations**
CMR	• No body habitus/acoustic window limitations • Multiple imaging planes • Accurate and reproducible • Visualization of aortic valve anatomy • Ventricular volumes/function assessment without geometrical assumptions • Qualitative assessment of aortic regurgitation • Accurate quantitative assessment of aortic regurgitation (also for eccentric jets) • Visualization of aorta in toto • Identification of associated abnormalities • Detection of myocardial fibrosis	• Not widely available • Claustrophobia • Difficulties in breath-holding • Longer time of acquisition • Compromised quality in case of arrhythmias • Lower temporal resolution • Quantitative assessment of aortic regurgitation should be done in LVOT or aortic valve plane when extremely eccentric AR jets are present

Table 3. Advantages and limitations about Cardiac CT assessment in BAV AR.

	Advantages	Limitations
Cardiac CT	• No body habitus/acoustic window limitations • Multiple imaging planes • Accurate and reproducible • High spatial resolution • Visualization of aortic valve anatomy • Visualization of aorta in toto • Identification of associated abnormalities • Planimetric measurements of the ARO • Ventricular volumes/dimensions assessment • Optimal visualization of valve calcification	• Use of iodinated contrast (risk of contrast induced nephropathy and allergy) • Use of ionizing radiations • No qualitative assessment of aortic regurgitation • ARO is the only quantitative parameter to be used

PART III: Advanced cardiovascular imaging in myocardial disease

Chapter 9

Atrial Fibrillation, Cancer and Echocardiography

Nonvalvular Atrial Fibrillation (AF) is a relatively frequent arrhythmia in cancer patients; it is possibly due to direct effect of cancer or consequence of cancer therapies (38). AF creates important problems for both therapeutic management and prognosis in cancer patients (39). The anticoagulation of cancer patients presenting AF is a main issue because of the difficult balance between thromboembolic and bleeding risks, both elevated in this clinical setting (40). The echocardiographic evaluation has a pivotal importance in cancer patients affected from any kind of nonvalvular AF. This is due to several reasons which should correspond to subsequent, well-established items, also following European Association of Cardiovascular Imaging (EACVI) standardization of the echo report (41). A comprehensive echo Doppler examination is mandatory. Transesophageal echocardiography (TEE) is fundamental to identify the possible sources of systemic embolism in a clinical setting, which is very prone to the thrombotic risk. The performance of a TEE precardioversion is highly encouraged to detect possible thrombi in LA appendage. In addition, some echo LA parameters such LA size (mainly LAVi) and function (LA emptying fraction or, better, LA strain) (Figure 1) become even more important than in cancer-free AF patients in the prediction of sinus rhythm restoration and/or the possible recurrence of AF paroxysmal episodes in patients who have recovered their normal rhythm and to predict the subsequent development of HF.

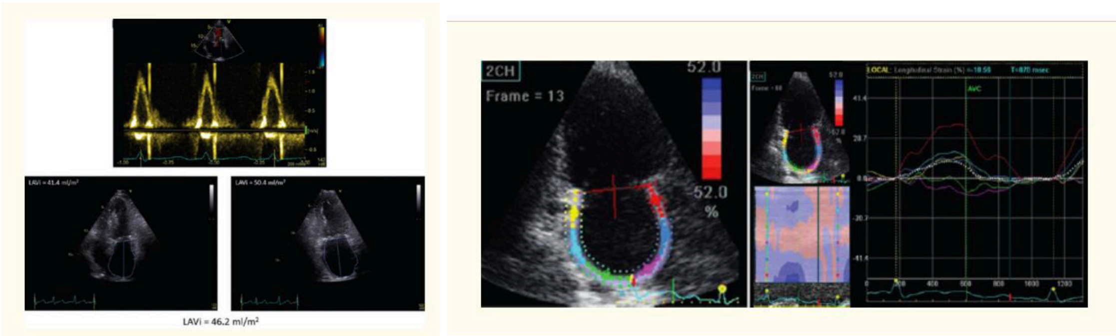


Figure 1. Left Panel: Left atrial dilation in a breast cancer patient with paroxysmal atrial fibrillation. In the top, transmitral pattern showing the absence of A velocity due to atrial fibrillation. In the bottom, left atrial volume in apical four-chamber (left) and two-chamber (right) part. Left atrial volume index is 46.2 ml/m2 Right Panel: Reduction of left atrial strain in apical two-chamber view in a patient with chronic lymphatic leukemia experiencing paroxysmal atrial fibrillation during ibrutinib therapy.

This is in fact a key action, not only from the cardiologic point of view but also for the oncologic perspectives in individual situations. When AF occurs during cancer therapy, the decision whether to continue, adjust the dosage, or withdraw cancer medications is fundamental. Particular attention will be taken to achieve an optimal control of heart rate and to restore normal sinus rhythm with antiarrhythmic drugs, mainly amiodarone. This evaluation is particularly important to graduate anticoagulation and to prevent and manage symptoms/signs of HF. Patients with larger left atrium and more impaired LA function should be addressed toward a less aggressive cancer treatment, with drugs which are not associated or are poorly related with the risk of AF development. A correct and comprehensive echocardiographic assessment could even induce the oncologist to change the cancer management balancing the oncologic and the cardiac risk, taking well into account that the thrombotic and the bleeding complications exert an equal burden in this delicate clinical setting.

Chapter 10

Multi-Centre, Multi-Vendor and Multi-Disease Cardiac Segmentation: The M&Ms Challenge

Accurate segmentation of cardiovascular magnetic resonance (CMR) images is an important pre-requisite in clinical practice to reliably diagnose and assess a number of major cardiovascular diseases (42-43). Currently, the process typically requires the clinician to provide a significant amount of manual input and correction to accurately and consistently annotate the cardiac boundaries across all image slices and cardiac phases. The automation of such a tedious and timeconsuming task has been pursued for a long time by using multiple approaches, such as statistical shape models (44) or cardiac atlases (45). In the last few years, the advent of the deep learning paradigm has motivated the development of many neural network based techniques for improved CMR segmentation, as listed in a recent review (46). However, most of these techniques have been all too often trained and evaluated using cardiac imaging samples collected from single clinical centres using similar imaging protocols. While these works have advanced the state-of the-art in deep learning based cardiac image segmentation, their high performances were reported on samples with relatively homogeneous imaging characteristics. Bai et al.(47) implemented a fully convolutional network that achieved highly accurate results on this large dataset (over 4,875 cases), but the authors concluded that their model might not generalize well to other vendor or sequence datasets. Some researchers proposed to improve CMR segmentation by training neural networks with images from multiple cohorts (48), but these works do not include methods for addressing domain shifts between training and new unseen cohorts. Another multi-centre and multivendor study conducted by Tao et al. (49) relied solely on private data, which makes it difficult to replicate the results and perform community-driven benchmarking. While these recent works confirmed the difficulties encountered by deep learning models to generalize beyond the training samples, they also support the need for well-defined heterogeneous public datasets that can be used by the community to improve model generalizability through scientific benchmarking. In this context, the Multi-Centre, Multi-Vendor and Multi- Disease Cardiac Segmentation (M&Ms) Challenge was proposed and organized as part of the Statistical Atlases and Computational Modelling of the Heart (STACOM) Workshop, held in conjunction with the MICCAI 2020 Conference. The M&Ms challenge was set up as part of the euCanSHare international project, which is aimed at developing interoperable data sharing and analytics solutions for multi-centre cardiovascular research data. Together with clinical collaborators from six different hospitals in Spain, Canada and Germany, a public CMR dataset was established from 375 participants, scanned with four different scanners (Siemens, Philips, General Electric (GE) and Canon) and annotated using a consistent contouring standard operating procedure (SOP) across centres.

The M&Ms challenge is the first study to evaluate a range of deep learning solutions for the automated segmentation of multi-centre, multi-vendor and multi-disease cardiac images. The results show the promise of existing data augmentation and domain adaptation methods, but also calls for further research to develop highly generalizable solutions given the inherent heterogeneity in cardiac imaging between centres, vendors and protocols. More generally, there is a need for more research and development to realise the much-needed shift from single-centre image analysis towards multi-domain approaches that will enable wider translation and usability of future artificial intelligence tools in cardiac imaging and clinical cardiology.

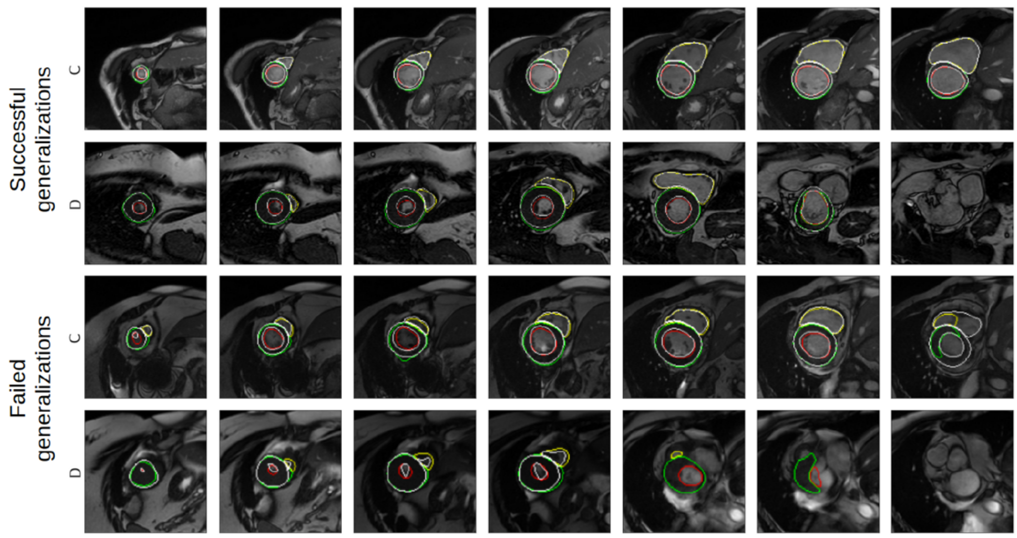


Fig. 1 Prediction examples for method P1 for vendors C (GE) and D (Canon). Top two rows show satisfactory results, while the two bottom rows present some error in the final contours. Color correspondence: left ventricle endocardium (red), left ventricle epicardium (green) and right ventricle endocardium (yellow). Ground truth is drawn in white color.

Chapter 11

Clinical Risk Prediction in Patients With Left Ventricular Myocardial Noncompaction

Background

Left ventricular noncompaction (LVNC) is a heterogeneous entity with uncertain prognosis.

Objectives

This study sought to develop and validate a prediction model of major adverse cardiovascular events (MACE) and to identify LVNC cases without events during long-term follow-up.

Methods

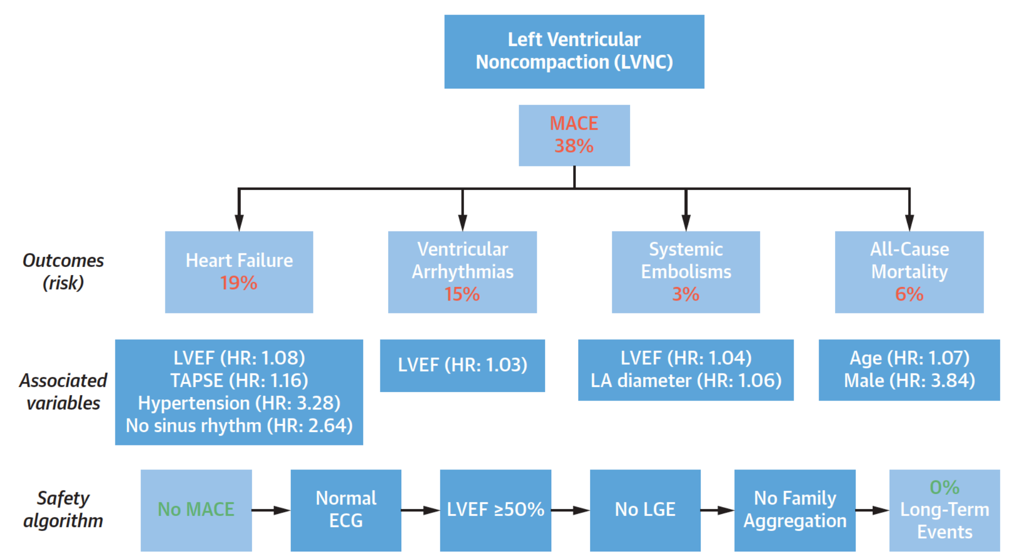
This is a retrospective longitudinal multicenter cohort study of consecutive patients fulfilling LVNC criteria by echocardiography or cardiovascular magnetic resonance. MACE were defined as heart failure (HF), ventricular arrhythmias (VAs), systemic embolisms, or all-cause mortality.

Results

A total of 585 patients were included (45 ± 20 years of age, 57% male). LV ejection fraction (LVEF) was 48%± 17%, and 18% presented late gadolinium enhancement (LGE). After a median follow-up of 5.1 years, MACE occurred in 223 (38%) patients: HF in 110 (19%), VAs in 87 (15%), systemic embolisms in 18 (3%), and 34 (6%) died. LVEF was the main variable independently associated with MACE ($P < 0.05$). LGE was associated with HF and VAs in patients with LVEF >35% ($P < 0.05$). A prediction model of MACE was developed using Cox regression, composed by age, sex, electrocardiography, cardiovascular risk factors, LVEF, and family aggregation. C-index was 0.72 (95% confidence interval: 0.67-0.75) in the derivation cohort and 0.72 (95% confidence interval: 0.71-0.73) in an external validation cohort.

Patients with no electrocardiogram abnormalities, LVEF ≥50%, no LGE, and negative family screening presented no MACE at follow-up.

CENTRAL ILLUSTRATION Outcomes of LVNC



Casas, G. et al. J Am Coll Cardiol. 2021;78(7):643–662.

Left ventricular noncompaction (LVNC) carries an increased risk of major adverse cardiovascular events (MACE), mainly heart failure and ventricular arrhythmias. Variables independently associated with the individual components of the combined endpoint are described, with left ventricular ejection fraction (LVEF) being the most important. The LVNC safety algorithm is shown at the bottom of the figure: patients with morphologic criteria for LVNC, but with no other high-risk features, present no cardiovascular events at long-term follow-up. ECG = electrocardiogram; HR = hazard ratio; LA = left atrial; LGE = late gadolinium enhancement; TAPSE = tricuspid annular plane systolic excursion.

Conclusions

LVNC is associated with an increased risk of heart failure and ventricular arrhythmias. LVEF is the variable most strongly associated with MACE; however, LGE confers additional risk in patients without severe systolic dysfunction. A risk prediction model is developed and validated to guide management.

Age (years)	Points	Abnormal ECG	Points
		N	0
≤35	0	Y	4
36-54	7	**CV Risk Factors**	**Points**
≥55	10	N	0
		Y	3
LVEF (%)	**Points**	**NCCM**	**Points**
		N	0
		Y	4
≥50	0	**Gender**	**Points**
35-50	5	Men	3
≤35	10	Women	0

Risk score: variables associated with major adverse cardiovascular events (MACE) and corresponding punctuation

Chapter 12

Cardiac Imaging in Anderson-Fabry Disease: Past, Present and Future

“Fabry disease-often seen, rarely diagnosed” is how Hoffmann and Mayatepek titled their AFD review (50). Current screening practices likely capture only a small portion of AFD. However, AFD is not a very rare disorder, particularly in high-risk populations in which screening is usually omitted. Particular attention should be given to patients presenting with kidney damage, cryptogenic stroke, unexplained LVH, gastrointestinal symptoms, hearing impairment, lymphedema, diminished perspirations, acroparesthesias, corneal opacities and angiokeratoma, which are considered clinical markers associated with AFD. AFD should be suspected in patients with a family history or in those who present with the clinical features that suggest the diagnosis. The diagnosis is typically confirmed by enzymatic and/or molecular genetic testing. In this review article, we highlight the value and perspectives of standard and advanced cardiovascular imaging in Anderson-Fabry disease. Cardiac imaging is involved in many aspects of the management of Fabry patients: the initial diagnostic suspicion of AFD in case of evidence of unexplained heart damage associated with extracardiac AFD red flags, the differential diagnosis with other cardiomyopathies, the early detection of heart damage in patients with already diagnosed AFD and its evolution monitoring, to allow decisions regarding the initiation of chaperone or enzyme replacement therapy, and to guide its follow-up.

The echocardiographic examination is the first-line technique to suspect and manage AFD. However, there are no pathognomonic echocardiographic features of AFD. STE has an incremental value in differentiating between primary and secondary LVH and in the differential diagnosis with storage diseases. Moreover, STE enables early detection of intrinsic myocardial dysfunction before LVEF reduction (Fig 1).

Advanced Echocardiography	Description	Features
GLS	-Reduction in LV GLS with a prevalent involvement of the infero-lateral wall of the LV	-Correlates with LGE at CMR
GCS	-Reduction in the normal base-to-apex CS gradient	-Differential diagnosis with HCM where GCS increases with a preserved base-to-apex gradient
RVLS	-Reduction in the RV Longitudinal strain	-Early sign of RV dysfunction

GLS: global longitudinal strain; LGE: late gadolinium enhancement; CMR: cardiovascular magnetic resonance; GCS: global circumferential strain; HCM: hypertrophic cardiomyopathy; RVLS: right ventricle longitudinal strain.

Fig 1. Advanced echocardiography in AFD cardiomyopathy. GLS: global longitudinal strain; LGE: late gadolinium enhancement; CMR: cardiovascular magnetic resonance; GCS: global circumferential strain; HCM: hypertrophic cardiomyopathy; RVLS: right ventricle longitudinal strain.

CMR has emerged as a powerful imaging tool to identify lesions of AFD in patients in whom echocardiography fails to detect relevant LVH or other cardiac damage. Its strength is in characterizing tissue using LGE or T1 and T2 mapping. LGE imaging is the non-invasive gold standard for the evaluation of replacement fibrosis/scarring. The tissue damage highlighted by LGE, initially located in the basal inferolateral wall, has prognostic implications and predicts a lack of response to enzyme replacement therapy. Low native myocardial T1 values could represent a useful, early biomarker of cardiac involvement in AFD, superior to left ventricular hypertrophy and LGE imaging (Fig 2).

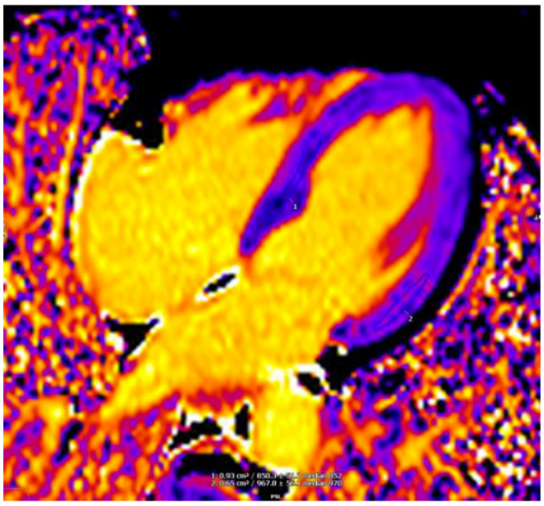


Fig 2. T1 mapping sequence shows a lower T1 time in the posterior interventricular septum in an AFD patient

T2 mapping is sensitive to inflammation. Studies with T2 mapping, supported by histological studies, deny the model of AFD as simple storage cardiomyopathy and have led to the identification of an important role of chronic inflammation in the early progression of the disease. This recognition may have implications on future management strategies including consideration for immunosuppressive therapy in the hope of improving the course of AFD. These observations justify an increasing role of CMR in the routine clinical evaluation of patients with AFD. As with echocardiography, CMR findings in themselves are not diagnostic of AFD and must be considered within the clinical contest of an individual patient and confirmed with enzymatic and genetic analysis. An integrated multi-modality imaging approach including both echocardiography and CMR might be optimal for the management of AFD patients. In the future, echocardiography, by its large availability and low cost, will remain the initial imaging modality of choice in patients with proven or suspected AFD, but the role of CMR will be likely to increase so much as to also become an essential diagnostic test in the initial evaluation.

Conclusions

The articles described in this thesis show the relevant role of cardiac imaging in the cardiovascular diagnostic and therapeutic process. The technological progress of recent years has allowed rapid development of analysis equipment and software, in step with scientific research and the use of new tools in clinical practice. Thanks to this there has been a notable improvement in the diagnostic processes, with faster and more precise diagnoses, and consequently a better and more targeted therapeutic choice. The development and spread of advanced echocardiography (speckle tracking imaging), cardiac MRI and cardiac CT is leading to more effective prevention of all cardiovascular diseases, such as heart failure, sudden cardiac death, coronary artery disease and aortic disease. In this research journey we showed the use of new diagnostic tools in echocardiography, CMR and cardiac CT in the diagnosis and prevention of aortic, valvular and myocardial diseases ... a lot of progress has been made in recent years but there is still a lot to do.

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47. W. Bai, M. Sinclair, G. Tarroni, O. Oktay, M. Rajchl, G. Vaillant, A. Lee, N. Aung, E. Lukaschuk, M. M. Sanghvi, F. Zemrak, K. Fung, J. Paiva, V. Carapella, Y. Kim, H. Suzuki, B. Kainz, P. Matthews, S. Petersen, S. Piechnik, S. Neubauer, B. Glocker, and D. Rueckert. Automated cardiovascular magnetic resonance image analysis with fully convolutional networks. Journal of Cardiovascular Magnetic Resonance, 20, 2018.
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ABOUT ME

Cardiologist, MD. Expert in Advanced Cardiovascular Imaging (transthoracic and transesophageal echocardiography, CMR, Cardio-CT) : ESC/EACVI certification ffor TTE (full certified), TOE (full certified), CMR (level III), CMR CHD (written part) and CCT (written part). PhD Student at "Federico II" University of Naples (Italy) - International PhD Programme in Cardiovascular Pathophysiology and Therapeutics from 2019. Research Fellow in Cardiovascular Imaging at "Vall d'Hebron" Barcelona Hospital Campus (Spain) from 2018. Head of Cardiovascular Imaging laboratory (Echo-CMR-CCT) of "Centro Medico Ascione"- Torre del Greco (Italy) from 2020. Member of the CMR, CCT and echocardiography working groups of the Italian Society of Cardiology.

WORK EXPERIENCE

01/06/2020 – CURRENT – Torre del Greco, Italy

Head of cardiovascular imaging laboratory

Centro Medico Ascione

CMR

CCT

Echocardiography

06/2021 – CURRENT – Salerno, Italy

Cardiovascular Magnetic Resonance Consultant

Cardiologia Medica Salernitana srl

01/02/2021 – 30/04/2021 – Italy

Cardiovascular Magnetic Resonance Consultant

CASA DI CURA "SAN MICHELE" SRL – VIA APPIA 190, 81024 MADDALONI (CE)

01/09/2018 – 30/03/2020 – Barcelona

Fellowship in Cardiovascular Imaging

Hospital Universitari "Vall d'Hebron"

Training period in Advanced Cardiovascular Imaging: Transthoracic echocardiography (3D, speckle tracking, stress echocardiography, contrast echocardiography), transesophageal echocardiography (including interventional procedures), Cardiac MRI (including congenital heart diseases, stress-CMR, T mapping), Cardiac-CT.

01/11/2015 – 29/10/2019 – Napoli, Italy

Cardiology Resident

University of Naples "Federico II"

01/04/2015 – 30/10/2015 – Scafati, Italy

Voluntary Doctor - Cardiology Department

Hospital "M. Scarlato"

EDUCATION AND TRAINING

01/11/2019 – CURRENT – Napoli, Italy

PhD in Cardiovascular Pathophysiology and Therapeutics (CardioPaTh)

University of Naples "Federico II"

Cardiovascular Imaging

Address Napoli, Italy

01/09/2018 – 01/11/2022 – Barcelona, Spain

Research Fellow in Cardiovascular Imaging

Hospital Universitari "Vall d'Hebron"

Address Barcelona, Spain

02/2020 – CURRENT

EACVI Certification in Adult Transoesophageal Echocardiography (TOE) - full certified

European Association of CardioVascular Imaging (EACVI)

08/2019 – CURRENT

EACVI Certification in Adult Transthoracic Echocardiography (TTE) - full certified

European Association of CardioVascular Imaging (EACVI)

09/2021 – CURRENT

EACVI Certification in Cardiovascular Magnetic Resonance (CMR) - Level 3

European Association of CardioVascular Imaging (EACVI)

11/2020 – CURRENT

EACVI Certification in Cardiovascular Magnetic Resonance Congenital Heart Disease- written part (level II – III)

European Association of CardioVascular Imaging (EACVI)

11/2020 – CURRENT

EACVI Certification in Cardiac Computed Tomography - written part (level II – III)

European Association of CardioVascular Imaging (EACVI)

02/11/2022 – CURRENT – Naples, Italy

Radiologist (Radiology Residence)

University of Naples "Federico II"

Address Naples, Italy

01/11/2015 – 29/10/2019 – Napoli, Italy

Cardiologist (Cardiology Residence)

University of Naples "Federico II"

Thesis: "Assessment of Chronic Aortic Regurgitation by Cardiovascular Magnetic Resonance: identifying additional parameters " (Supervisor: prof. M. Galderisi; co-supervisor: prof. JF Rodriguez-Palomares)

Address Napoli, Italy | **Final grade** 50/50 cum laude | **Thesis** Assessment of Chronic Aortic Regurgitation by Cardiovascular Magnetic Resonance

10/04/2021 – CURRENT

ADVANCED LIFE SUPPORT
ITALIAN RESUSCITATION COUNCIL

11/2015 – 11/2016 – Napoli, Italy

Diploma course in Phlebology
University of Naples "Federico II"
Address Napoli, Italy

02/2015 – 05/2016

Diploma course in Peripheral Vascular EchocolorDoppler
Società Italiana di Ultrasonografia in Medicina e Biologia (SIUMB) (Italy)

09/2008 – 24/07/2014

Master Degree in Medicine and Surgery
University of Naples "Federico II"
Thesis: "Valutazione della funzione endoteliale e della riserva di flusso coronarico in pazienti affetti da psoriasi" (Supervisor: prof. Pasquale Perrone Filardi)
Final grade 110/110 cum laude

09/2003 – 09/07/2008 – Angri, Italy

Classic High School Diploma
"La Mura" High School
Address Angri, Italy | **Final grade** 100/100 cum laude

05/2015 – CURRENT

Diploma de Español como Lengua Extranjera (DELE)- Nivel C1
Instituto Cervantes

06/2008 – CURRENT

Grade 9 (Graded Examination in Spoken English - Level B2.3 of CEFR)
Trinity College of London

12/2017 – CURRENT

ECDL – European Computer Driving Licence
European Computer Driving Licence

LANGUAGE SKILLS

MOTHER TONGUE(S): Italian

OTHER LANGUAGE(S):

Spanish

Listening	Reading	Spoken production	Spoken interaction	Writing
C2	C2	C2	C2	C2

English

Listening	Reading	Spoken production	Spoken interaction	Writing
C1	C1	C1	C1	C1

Catalan

Listening	Reading	Spoken production	Spoken interaction	Writing
B1	B1	B1	B1	B1

NETWORKS AND MEMBERSHIPS

2022 – CURRENT

Member of the Journal Editorial - Frontiers in Cardiovascular Medicine

2022 – CURRENT

Member of the Journal Editorial - Journal of Clinical Cardiology and Cardiovascular Diagnosis

2016 – CURRENT

European Association of CardioVascular Imaging (EACVI) - Silver member

2019 – CURRENT

European Society of Cardiology - ESC

2019 – CURRENT

Italian Society of cardiology - Echocardiography Working Group

2019 – CURRENT

Italian Society of cardiology - CMR Working Group

2020 – CURRENT

Italian Society of cardiology - CCT Working Group

2020 – CURRENT

Society for Cardiovascular Magnetic Resonance (SCMR) -Regular Member

HONOURS AND AWARDS

01/11/2019

Research Grant – the Cardiopath PhD program

09/2015

Reconocimiento de Titulo de Medico – Ministerio de Sanidad, Servicios Sociales e Igualidad - Spain

03/2016

Homologación de Titulo Universitario de Medico – Ministerio de Educación, Cultura y Deporte - Spain

COMMUNICATION AND INTERPERSONAL SKILLS

Speaker at the webinar of the CCT working group of the "Italian society of Cardiology" - June 2021

“Utilizzo della CardioTC nella diagnosi delle disfunzioni protesiche” (Cardiac CT utility about diagnosis of Valvular Prosthesic dysfunction)

Speaker at the webinar of the CMR working group of the "Italian society of Cardiology" - May 2021

“La Risonanza Magnetica nelle patologie dell’aorta: ruolo dell’imaging avanzato nella diagnosi e nel Follow-up.” - Webinar about the role of CMR in aortic disease.

Speaker at "Society for Cardiovascular Magnetic Resonance - scientific sessions 2021"

3 original works:

- "Evaluation of aortic distensibility in aortic regurgitation patients by CMR. Is there a difference depending on valve anatomy?”;
- “Assessment of Chronic Aortic Regurgitation by Cardiovascular Magnetic Resonance: identifying additional parameters.”;
- “Bicuspid valve patients: assessment of aortic regurgitation severity grade by echocardiography and cardiovascular magnetic resonance. Which difference?”

Speaker at "81° Congresso Nazionale della Società Italiana di Cardiologia", Roma – december 2020

“Evaluation of aortic regurgitation severity grade in bicuspid valve patients: differences between echocardiography and CMR.”

Teacher at “ XV Curso Teorico-Practico de Ecocardiografia Basica” of the “Sociedad Española de Cardiología”- Barcelona (Spain) – 25-29 of march of 2019.

Speaker at "ESC Congress 2020" - Clinical case session

“Late Complication After Tevar Surgery In A Chronic Aortic Dissection Patient: A Rare Case Of Secundary Aortoesophageal Fistula”.

Speaker at "ESC Congress 2020" - ePoster Session

“Relationship Between Aortic Distensibility And Aortic Regurgitation depending on aortic valve anatomy. A CMR study”

Speaker at "ESC Congress 2020" - ePoster Session

“The Role Of Descending Aorta Diastolic Reverse Flow In The Quantification Of Aortic Regurgitation By CMR.”

Speaker at ANMCO National Conference 2020

“Unusual case of heart failure in young woman”

Speaker at ANMCO National Conference 2020

“A rare case of cardiac involvement in Gaucher disease”

Speaker at "EuroEcho-Imaging 2019"

“Relationship between aortic distensibility and aortic regurgitation assessed by CMR in bicuspid valve patients”.

Speaker at "80° Congresso Nazionale della Società Italiana di Cardiologia", Roma – december 2019

“Relationship between aortic distensibility and aortic regurgitation assessed by CMR in bicuspid valve patients”.

List of all publications (pubmed format)

- **L. La Mura,** M. Lembo, F. Musella, M. D'Amato, R. Izzo. "Aortic regurgitation in bicuspid aortic valve: the role of multimodality imaging". *Under peer review.*
- F. Perone, M. Guglielmo, M.A. Coceani, **L. La Mura**, I. Dentamaro, J. Sabatino, A. Gimelli. "The role of Multimodality Imaging approach in acute aortic syndromes: diagnosis, complications, and clinical management". *Under peer review.*
- F. Musella, A. Azzu, A.S. Antonopoulos, **L. La Mura**, R.H. Mohiaddin. "Comprehensive mitral valve prolapse assessment by cardiovascular MRI". Clinical Radiology,Volume 77, Issue 2,2022,Pages e120-e129,ISSN 0009-9260, https://doi.org/10.1016/j.crad.2021.11.004.
- Casas G, Limeres J, Oristrell G, Gutierrez-Garcia L, Andreini D, Borregan M, Larrañaga-Moreira JM, Lopez-Sainz A, Codina-Solà M, Teixido-Tura G, Sorolla-Romero JA, Fernández-Álvarez P, González-Carrillo J, Guala A, **La Mura L**, Soler-Fernández R, Sao Avilés A, Santos-Mateo JJ, Marsal JR, Ribera A, de la Pompa JL, Villacorta E, Jiménez-Jáimez J, Ripoll-Vera T, Bayes-Genis A, Garcia-Pinilla JM, Palomino-Doza J, Tiron C, Pontone G, Bogaert J, Aquaro GD, Gimeno-Blanes JR, Zorio E, Garcia-Pavia P, Barriales-Villa R, Evangelista A, Masci PG, Ferreira-González I, Rodríguez-Palomares JF. Clinical Risk Prediction in Patients With Left Ventricular Myocardial Noncompaction. J Am Coll Cardiol. 2021 Aug 17;78(7):643-662. doi: 10.1016/j.jacc.2021.06.016. PMID: 34384546.
- **La Mura L**, Valente FX, Servato ML, Barrabes JA, Rodriguez-Lecoq R, Constenla I, et al. (2021) Hematemsis as a Late Complication after Tevar in a Stanford Type-B Chronic Aortic Dissection. J Clin Exp Cardiolog.12: 682.
- Guala A, Evangelista A, Teixido-Tura G, **La Mura L**, Dux-Santoy L, Ruiz-Muñoz A, Valente F, Galian-Gay L, Gutiérrez L, González-Alujas T, Dentamaro I, Johnson KM, Wieben O, Sao Avilés A, Ferreira-Gonzalez I, Rodríguez-Palomares JF. Leaflet fusion length is associated with aortic dilation and flow alterations in non-dysfunctional bicuspid aortic valve. Eur Radiol. 2021 May 12. doi: 10.1007/s00330-021-08016-3. Epub ahead of print. PMID: 33977309.
- Campello VM, Gkontra P, Izquierdo C, Martin-Isla C, Sojoudi A, Full PM, Maier-Hein K, Zhang Y, He Z, Ma J, Parreno M, Albiol A, Kong F, Shadden SC, Acero JC, Sundaresan V, Saber M, Elattar M, Li H, Menze B, Khader F, Haarburger C, Scannell CM, Veta M, Carscadden A, Punithakumar K, Liu X, Tsaftaris SA, Huang X, Yang X, Li L, Zhuang X, Vilades D, Descalzo ML, Guala A, **La Mura L**, Friedrich MG, Garg R, Lebel J, Henriques F, Karakas M, Cavus E, Petersen SE, Escalera S, Segui S, Rodriguez-Palomares JF, Lekadir K. Multi-Centre, Multi-Vendor and Multi-Disease Cardiac Segmentation: The M&Ms Challenge. IEEE Trans Med Imaging. 2021 Jun 17;PP. doi: 10.1109/TMI.2021.3090082. Epub ahead of print. PMID: 34138702.
- Ruiz-Muñoz A, Guala A, Rodriguez-Palomares J, Dux-Santoy L, Servato L, Lopez-Sainz A, **La Mura L**, Granato C, Limeres J, Gonzalez-Alujas T, Galián-Gay L,

Gutiérrez L, Johnson K, Wieben O, Sao-Aviles A, Ferreira-Gonzalez I, Evangelista A, Teixido-Tura G. Aortic flow dynamics and stiffness in Loeys-Dietz syndrome patients: a comparison with healthy volunteers and Marfan syndrome patients. Eur Heart J Cardiovasc Imaging. 2021 Jun 9:jeab069. doi: 10.1093/ehjci/jeab069. Epub ahead of print. PMID: 34104946.

- Lopez-Sainz A, Mila L, Rodriguez-Palomares J, Limeres J, Granato C, **La Mura L**, Sabaté A, Guala A, Gutiérrez L, Galian-Gay L, Sao-Aviles A, Bellmunt S, Rodriguez R, Cuellar-Calabria H, Roque A, Ferreira-González I, Evangelista A, Teixido-Tura G. Aortic Branch Aneurysms and Vascular Risk in Patients With Marfan Syndrome. J Am Coll Cardiol. 2021 Jun 22;77(24):3005-3012. doi: 10.1016/j.jacc.2021.04.054. PMID: 34140103; PMCID: PMC8091372.
- Esposito, R.; Santoro, C.; Mandoli, G.E.; Cuomo, V.; Sorrentino, R.; **La Mura, L.;** Pastore, M.C.; Bandera, F.; D'Ascenzi, F.; Malagoli, A.; et al. Cardiac Imaging in Anderson-Fabry Disease: Past,Present and Future. J. Clin. Med. 2021,10, 1994. https://doi.org/10.3390/jcm10091994
- Galderisi M, Esposito R, Sorrentino R, **La Mura L**, Santoro C, Tufano A. Atrial fibrillation, cancer and echocardiography. J Cardiovasc Echography 2020;30:S33-7.
- Gargiulo P., Paolillo S., Ferrazzano F., Prastaro M, **La Mura L**, De Roberto AM, Diana G, Dell´Aversana S, Contiello C, Vozzella MC, Bardi L, Marsico F. "Prognostic Value of Hormonal Abnormalities in Heart Failure Patients". Elsevier Inc. (2019), Heart Failure Clin 15 (2019) 371–375.
- Petitto M, Esposito R, Sorrentino R, Lembo M, Luciano F, De Roberto AM, **La Mura L**, Pezzullo E, Maffei S, Galderisi M, Lancellotti P. "Gender specific echocardiographic reference values: the female's point of view". Journal of Cardiovascular Medicine (2018), JCM-D- 2018 Oct;19(10):527-535
- C. D'Amore, P. Gargiulo, S. Paolillo, A. M. Pellegrino, T. Formisano, A. Mariniello, G. Della Ratta, E. Iardino, M. D'Amato, **L. La Mura**, I. Fabiani, F. Fusco, P. Perrone Filardi. "Nuclear imaging in detection and monitoring of cardiotoxicity", World Journal of Radiology 2014, July 28; 6(7): 486-492
- Paola Gargiulo, Santo Dellegrottaglie, Annapaola Cirillo, Irma Fabiani, Pietro Riello, **Lucia La Mura**, Marianna Amato, Tiziana Formisano, Elisabetta Iardino, Andrea Soricelli, Alberto Cuocolo, Pasquale Perrone Filardi. "Advances in Molecular Imaging: Cardiac Regeneration".Curr Cardiovasc Imaging Rep (2013) 6:354–357

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Finally, I thank my husband and my family, for having always supported and patiently understood me in my journey.