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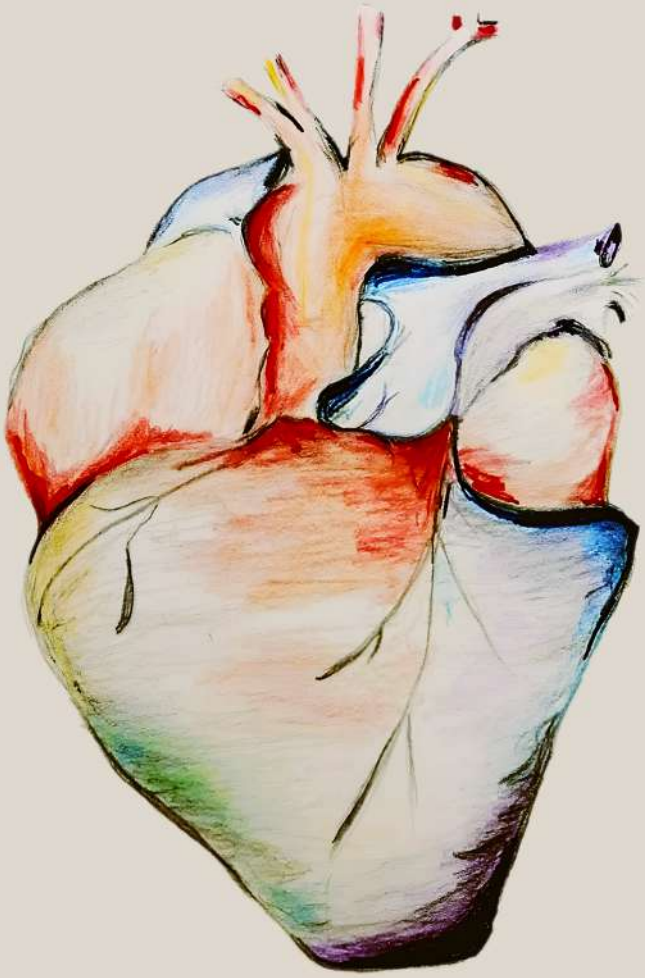
# INSIGHTS FROM CARDIAC MAGNETIC RESONANCE

**Gizem Kasa Yaglici**



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Doctoral Thesis

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**Doctoral Thesis**

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# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **ACEi:** | Angiotensin converting enzyme inhibitors |
| **ARB:** | Angiotensin receptor blockers |
| **BSA:** | Body surface area |
| **CMR:** | Cardiac magnetic resonance |
| **HF:** | Heart failure |
| **HFmrEF:** | Heart failure with mildly reduced ejection fraction |
| **HFpEF:** | Heart failure with preserved ejection fraction |
| **HFrEF:** | Heart failure with reduced ejection fraction |
| **LA:** | Left atrium |
| **LACI:** | Left atrioventricular coupling index |
| **LARS:** | Left atrial reservoir strain |
| **LGE:** | Late gadolinium enhancement |
| **LV:** | Left ventricle |
| **LVEDD:** | Left ventricular end-diastolic diameter |
| **LVEDDi:** | Left ventricular end-diastolic diameter index |
| **LVEDV:** | Left ventricular end-diastolic volume |
| **LVEDVi:** | Left ventricular end-diastolic volume index |
| **LVESD:** | Left ventricular end-systolic diameter |
| **LVESDi:** | Left ventricular end-systolic diameter index |
| **LVESV:** | Left ventricular end-systolic volume |
| **LVESVi:** | Left ventricular end-systolic volume index |
| **LVEF:** | Left ventricular ejection fraction |
| **LV GLS:** | Left ventricular global longitudinal strain |
| **LVMi:** | Left ventricular mass index |
| **MI:** | Myocardial infarction |
| **NT-proBNP:** | N-terminal pro B type natriuretic peptide |
| **2D:** | Two-dimensional |
| **3D:** | Three-dimensional |
| **SGLT2i:** | sodium-glucose cotransporter-2 inhibitors |
| **TDI:** | Tissue doppler imaging |

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# GENERAL INDEX

# ABSTRACT

Heart failure (HF) is a heterogeneous clinical syndrome, that remains a major health problem. Cardiac remodeling is the hallmark of HF.

Cardiac remodeling refers to the alteration in the geometry and function of any cardiac chamber driven by a histological basis of molecular, cellular and interstitial changes. The extent of cardiac remodeling is associated with prognosis and therefore, it is important to early diagnose and characterize cardiac remodeling with cardiac imaging.

The left ventricle (LV) has been the most widely studied cardiac chamber in HF. Both linear and volumetric measurements of LV dilatation have shown prognostic value separately. However, the correlation between LV diameter and volume measured with 3-dimensional imaging techniques has not been studied and the relative merits of each parameter to predict long-term prognosis in patients with HF has not been explored. Left atrial (LA) structure and function are important determinants of LV preload and subsequently, LV stroke volume. In addition, LA remodeling is influenced by LV remodeling and particularly by the diastolic and systolic function of the LV. Accordingly, the assessment of the LA function integrated with the LV function seems more clinically appropriate, although it is not common clinical practice. Recently, left atrioventricular coupling index (LACI) has emerged as a novel imaging marker which evaluates global LA and LV structure and function simultaneously. LACI is defined by the ratio between LA and LV volumes at end-diastole. Cardiac magnetic resonance (CMR) is a 3-dimensional imaging technique considered the reference imaging technique for volumetric and functional assessment of any cardiac chamber. Furthermore, CMR has the unique characteristic of allowing the assessment of myocardial tissue characteristics (myocardial fibrosis and scar) and therefore, it provides an holistic assessment of cardiac remodeling.

The hypothesis of this thesis is to demonstrate that comprehensive CMR evaluation of cardiac remodeling provides improved risk stratification of patients with HF.

The main objective of the thesis is to characterize cardiac remodeling in patients with HF and LVEF <50% with the use of comprehensive CMR evaluation. The secondary objectives of the thesis are:

1. To assess the agreement between CMR-derived LV linear and volumetric measures to define LV dilatation and characterize the groups of patients with concordant and discordant definitions of LV dilatation.

2. To investigate the prognostic implications of concordant and discordant definition of LV dilatation based on CMR derived LV linear and volumetric dimensions.

3. To assess the distribution of left atrio-ventricular uncoupling in patients with HF and LVEF <50% by measuring the LACI with CMR and to elucidate its prognostic implications.

In order to achieve these objectives, a large number of patients with HF and LVEF <50% who underwent CMR at the Germans Trias i Pujol University Hospital were retrospectively identified. Patients were followed-up regularly during 5 years in a specialized HF unit. CMR was performed on a 1.5 T scanner, following standardized protocol.

According to the results, we demonstrated that the CMR derived indexed LV linear dimensions showed a modest correlation with indexed LV volumes and therefore, they are not interchangeable when defining LV dilatation. Interestingly, 20% of patients displayed discordant definitions of LV dilatation. Indexed end-diastolic LV diameters and volumes were independently associated with cardiovascular outcomes (cardiovascular death or HF hospitalization). When phenogrouping the patients according to the type of LV dilatation (based only on LV linear dimension, only LV volume or both), the group of patients with both increased end-diastolic diameters and volumes presented the worst clinical outcomes suggesting that the assessment of both metrics is needed for better risk stratification.

In the study evaluating the prognostic implications of LACI in HF with LVEF <50%, patients were divided according to LACI tertiles. LACI was independently associated with the combined endpoint (all-cause death or HF hospitalization) and the patients with the most impaired left atrioventricular coupling (highest LACI values) showed the worst clinical outcomes. According to these results, we suggest that CMR-derived LACI should be considered as routine measurement for risk stratification of patients with HF and LVEF <50%.

In conclusion, this doctoral thesis highlights the incremental prognostic value of comprehensive cardiac remodeling assessment by CMR in patients with HF and LVEF <50%. Both linear and volumetric LV measurements should be assessed to accurately define LV dilatation. The integrated evaluation of both LV and LA, applying the use of LACI, should be considered for risk stratification. The cardiac remodeling process should be explored with a more holistic approach and CMR is state-of-the-art imaging modality for cardiac remodeling assessment in patients with HF and LVEF <50%.

# RESUMEN

La insuficiencia cardíaca (IC) es un síndrome clínico heterogéneo y un problema de salud importante a nivel mundial. El remodelado cardíaco es un fenómeno central en la IC.

El remodelado cardíaco se define como la alteración en la geometría y función de cualquier cavidad cardíaca e implica cambios a nivel molecular, celular e intersticial. La extensión del remodelado cardíaco se asocia con el pronóstico y es importante diagnosticarlo precozmente y caracterizarlo con imagen cardíaca.

El ventrículo izquierdo (VI) es la cavidad cardíaca más estudiada en la IC. Tanto las mediciones lineares como volumétricas de la dilatación del VI han demostrado valor pronóstico de forma independiente. Sin embargo, no se ha estudiado la correlación entre el diámetro y el volumen del VI medidos con técnicas de imagen tridimensionales, ni se han explorado el valor relativo de cada parámetro para determinar el pronóstico en pacientes con IC.

La estructura y función de la aurícula izquierda (AI) determina la precarga del VI y, en consecuencia, el volumen sistólico del VI. Además, el remodelado de la AI está relacionado por el del VI, y en particular por la función diastólica y sistólica del VI. En consecuencia, la evaluación de la función de la AI integrada con la del VI parece clínicamente más adecuada, aunque esta no forma parte de la práctica habitual en las unidades de imagen cardíaca.

El índice de acoplamiento auriculoventricular izquierdo (LACI, por su abreviatura en inglés) es un nuevo marcador de imagen que evalúa simultáneamente la estructura y función global de la AI y el VI. El LACI se define como el cociente entre los volúmenes telediastólicos de la AI y el VI.

La resonancia magnética cardíaca (RMC) es la técnica de imagen tridimensional considerada de referencia para la evaluación volumétrica y funcional de cualquier cavidad cardíaca. Además, la RMC es la única modalidad de imagen

que permite la caracterización del tejido miocárdico (fibrosis miocárdica) y, por lo tanto, proporciona una evaluación más global del remodelado cardíaco.

La hipótesis de esta tesis es demostrar que una evaluación integral del remodelado cardíaco mediante RMC mejora la estratificación del riesgo en pacientes con IC.

El objetivo principal de la tesis es caracterizar el remodelado cardíaco en pacientes con IC y fracción de eyección del ventrículo izquierdo (FEVI) <50% mediante una evaluación completa con RMC. Los objetivos secundarios son:

1. Evaluar la concordancia entre las medidas lineares y volumétricas del VI obtenidas por RMC para definir la dilatación del VI, y caracterizar los grupos de pacientes con definiciones concordantes y discordantes de dilatación VI.

2. Investigar las implicaciones pronósticas de las definiciones concordantes y discordantes de dilatación del VI basadas en las dimensiones lineares y volumétricas obtenidas por RMC.

3. Evaluar la distribución del desacoplamiento auriculoventricular izquierdo en pacientes con IC y FEVI <50% determinando el LACI con RMC, y aclarar sus implicaciones pronósticas.

Para alcanzar estos objetivos, se identificó retrospectivamente un gran número de pacientes con IC y FEVI <50% que se sometieron a RMC en el Hospital Universitari Germans Trias i Pujol. Los pacientes se siguieron de forma regular durante 5 años en una unidad especializada en IC. La RMC se realizó en un escáner de 1.5 T, siguiendo un protocolo estandarizado.

Según los resultados, demostramos que las dimensiones lineares del VI indexadas obtenidas por RMC mostraron una correlación modesta con los volúmenes indexados del VI, y por tanto, no son intercambiables a la hora de definir la dilatación del VI. Curiosamente, el 20% de los pacientes presentaban definiciones discordantes de dilatación del VI. Los diámetros y volúmenes teledi-

astólicos indexados del VI se asociaron de forma independiente con eventos cardiovasculares (muerte cardiovascular u hospitalización por IC). Al clasificar a los pacientes según el tipo de dilatación del VI (basada solo en dimensión linear, solo en volumen, o por ambas definiciones), el grupo con aumento en los diámetros y los volúmenes presentó los peores resultados clínicos, lo que sugiere que la evaluación conjunta de ambas métricas es necesaria para una mejor estratificación del riesgo.

En el estudio que evaluó las implicaciones pronósticas del LACI en pacientes con IC y FEVI <50%, los pacientes se dividieron en terciles de LACI. El LACI se asoció de forma independiente con el evento combinado (muerte por cualquier causa u hospitalización por IC), y los pacientes con mayor desacoplamiento auriculoventricular izquierdo (valores más altos de LACI) mostraron los peores resultados clínicos. Según estos resultados, sugerimos que el LACI obtenido por RMC debería considerarse como una medida rutinaria para la estratificación del riesgo en pacientes con IC y FEVI <50%.

En conclusión, esta tesis doctoral demuestra el valor pronóstico adicional que aporta la evaluación integral del remodelado cardíaco mediante RMC en pacientes con IC y FEVI <50%. Tanto las mediciones lineares como las volumétricas del VI se deben evaluar conjuntamente para definir la dilatación del VI con precisión. La valoración integrada del VI y la AI, aplicando el uso del LACI, debería considerarse para la estratificación del riesgo. El proceso de remodelado cardíaco debe explorarse con un enfoque más holístico, y la RMC representa la modalidad de imagen de referencia para la evaluación del remodelado cardíaco en pacientes con IC y FEVI <50%.

# INTRODUCTION

### 1.1. Epidemiology of HF

HF is a complex clinical syndrome. Symptoms occur when structural and/or functional abnormalities of the heart results in elevated intracardiac pressures and/or inadequate cardiac output. HF remains a major health problem worldwide despite all the diagnostic and therapeutic advances in the last decades.

Due to the population growth, aging process, and the increasing prevalence of comorbidities, the number of hospital admissions for HF is expected to increase considerably in the future (1,2). Already defined as a pandemic affecting almost 64 million people in 2017 (3), along with the expected increase in its prevalence in the future, there is growing concern about the economic burden HF might cause in healthcare systems (Figure 1). Moreover, when applying a 13.5% annual all-cause mortality rate to the estimated number of patients with diagnosis of HF, approximately 8.3 million individuals are projected to die each year globally (4).

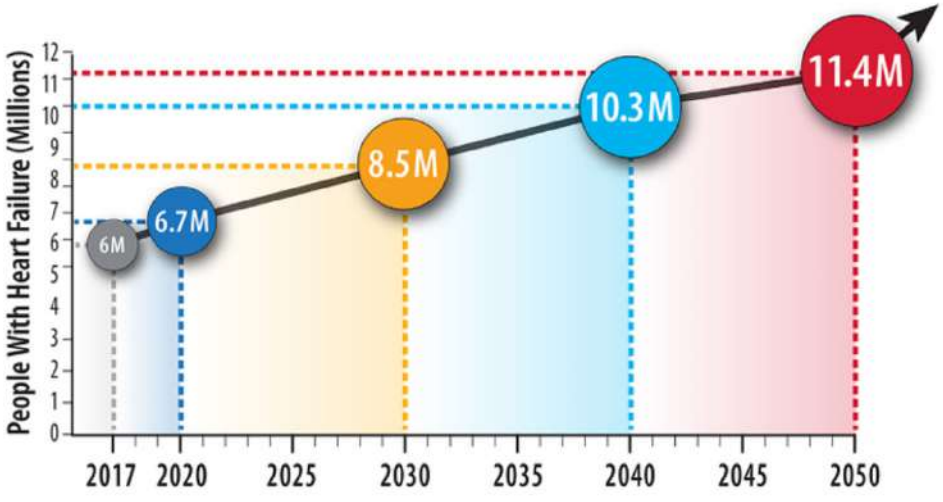


**Figure 1.** Prevalence of HF and Future Projection. Adapted from Bozkurt B et al (4), with permission

The prevalence of HF ranges between 1 and 3% in the general population in Western countries and up to almost 50% of these patients have HF with reduced LVEF (5). Importantly, the age and sex-adjusted mortality rates of this group of patients with HF and FEVI<50% is higher as compared to FEVI≥50% (6).

In conclusion, due to the high hospitalization rates, population growth, aging, and the increasing prevalence of comorbidities; HF remains one of the most important areas of economic burden and mortality in healthcare systems, in particular in those with FEVI<50%. Further research to improve risk stratification of this pathology is necessary to reduce cardiovascular mortality.

### 1.2. Cardiac Remodeling in HF

Cardiac remodeling is a fundamental process in the complex heart failure syndrome. The definition of remodeling reflects the structural and functional changes of the heart in response to different types of pathological injuries (7).

#### 1.2.1. LV remodeling

LV is the main cardiac chamber responsable for the heart's pump function. This function is achieved by providing sufficient cardiac output to maintain oxigenated blood flow to the other organ systems. Any alteration in the LV structure may result in failure of the rest of organs and cause life-threatening conditions.

Normal LV geometry has been decribed as an ellipsoid shape with its long-axis directed from apex to base (8). During a cardiac cycle, the LV wall shortens, thickens, and twists along the long axis (9). Cardiac output results from systolic contraction of the left ventricle, which is influenced by preload, afterload, and contractility. Stroke volume is the amount of blood pumped out of the heart in one cardiac cycle. Preload, also known as LV end-diastolic pressure, measures the degree of the ventricular stretch at the end of diastole. Afterload is the pressure the left ventricle must push against during each contraction.

High preload conditions such as valvular regurgitation and increased afterload observed in hypertension and aortic valve stenosis may alter LV structure and function progressively, if not treated.

LV is a remarkably plastic chamber, able to provide changes in its geometry during short periods of time (10). This adaptative response of the LV may be observed in physiological conditions such as pregnancy and rigorous athletic training. Pathological remodeling occurs when the stimuli causing these alterations perpetuates over time. The changes observed in ventricular architecture, driven by a combination of pathological alterations including myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis define remodeling (11). The activation of neuroendocrine factors such as renin-angiotensin aldosterone axis and the adrenergic nervous system, increased oxidative stress, proinflammatory cytokines, and endothelin also play a role in this process (11).

LV remodeling occurs in response to different forms of myocardial injury and increased wall stress. Ventricular wall stress is directly related to LV pressure and radius and inversely proportional to twice the LV wall thickness, according to the Law of Laplace (12) (Figure 2).

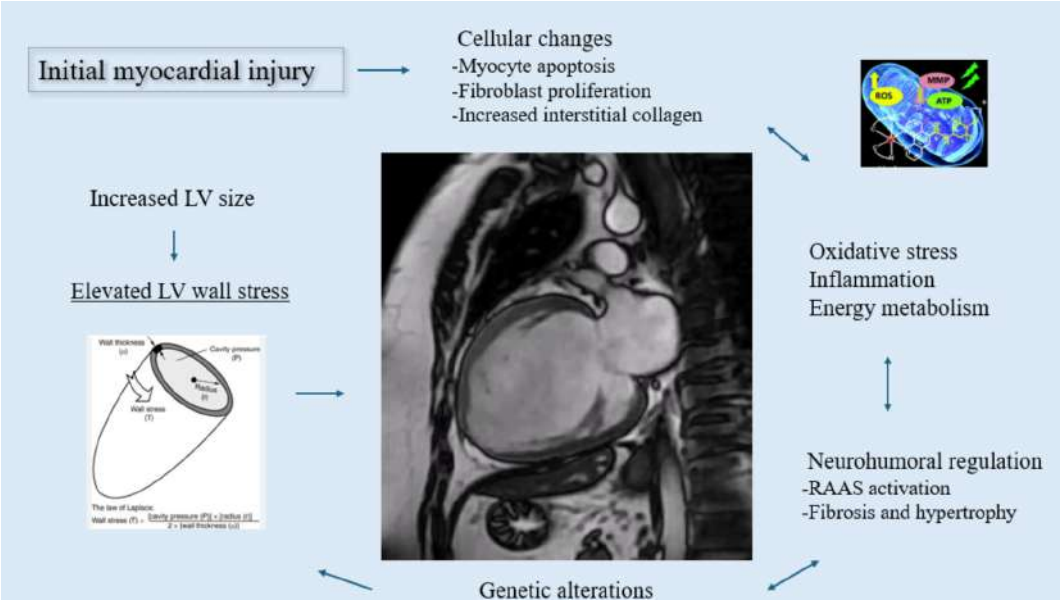


**Figure 2.** Pathophysiological changes in LV remodeling in HF.

Cardiac remodeling may occur after myocardial infarction (MI) or in response to conditions involving pressure (aortic stenosis, hypertension) or volume (valvular regurgitation) overload, inflammatory heart muscle disease (myocarditis) or idiopathic dilated cardiomyopathy (13). Independent of the type of the initial myocardial injury, an early adaptative increase is observed in LV volumes to maintain adequate LV stroke volume. The increase in LV volumes result in elevated LV wall stress and oxygen consumption.

After this stage, if uncontrolled, pathological cellular changes occur, resulting in globally increased myocardial mass and global LV chamber dilatation. Eventually the geometrical shape of the LV changes from an elliptical to a spherical shape (13, 14) (Figure 3). Finally, the alteration in LV structure result in globally reduced cardiac performance and overt HF symptoms.

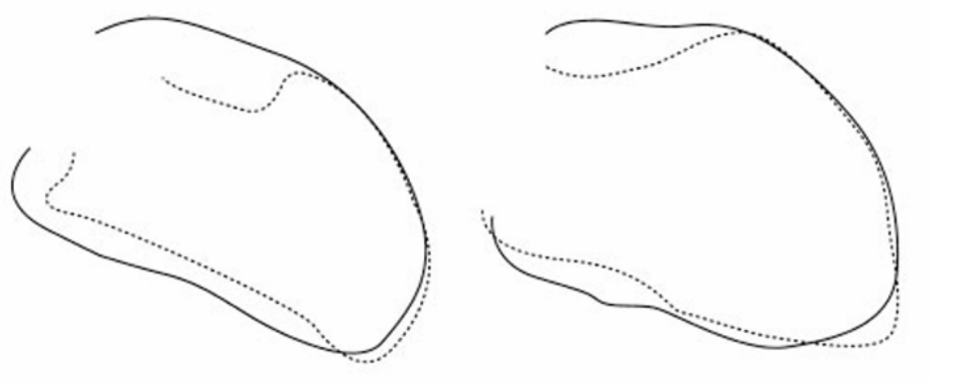

**Figure 3.** Late ventricular dilatation in patients with anterior MI. Adapted from Cohn JN et al (13), with permission.

#### 1.2.1.1. Assessment of LV dilatation by cardiac imaging

Left ventricular size and function can be evaluated by cardiac imaging techniques. Accurate definition of normal LV size is of importance to detect alterations in LV structure early in the remodeling process. Echocardiography is the initial imaging tool used in cardiac chamber size evaluation. Serial echocardiograms are commonly used in the follow-up of HF patients, due to the wide availability, easy use, lack of ionizing radiation and lower cost of this modality, when compared to others.

According to the current international guidelines on cardiac chamber quantification by echocardiography in adults, normal reference values for LV linear and volumetric measurements are stated (15). In the linear assessment of LV size by two-dimensional (2D) echocardiography, measurements are reported for end-diastole and end-systole. It is recommended to index these measurements by body surface area (BSA) to enable comparison among individuals with different body sizes. The most commonly used method for 2D echocardiographic volume measurement is the biplane method of disks summation, which is the currently recommended 2D echocardiographic method (15).

LV function is assessed by multimodal cardiac imaging. Up to date, LVEF remains the most commonly used marker to assess global left ventricular systolic function. LVEF is assessed by measuring the difference between the end-diastolic and end-systolic volume of a 2D, or three-dimensional (3D) parameter divided by its end-diastolic value. The biplane method of disks (modified Simpson's rule) is the currently recommended 2D method to assess LVEF by the latest echocardiography guidelines (15). In daily practice, LV volumes and function are mostly assessed by 2D biplanar methods. The better accuracy of real time 3D echocardiography compared to 2D methods for the evaluation of LV volumes and function has been reported (16, 17, 18).

For decades, the classification of HF has been based on LVEF measures. Currently international guidelines recommend the use of LVEF to phenotype heart failure into three categories: HF with reduced LVEF (HFrEF, LVEF ≤40%), HF with mildly reduced EF (HFmrEF, LVEF between 41 and 49%) and HF with preserved LVEF (HFpEF, LVEF ≥50%) (19, 20). However, LVEF is not a perfect parameter of LV performance since it only takes into consideration the change in volume of the LV and does not consider the effective stroke (forward) volume. The measurement of LV deformation by strain imaging has emerged as a powerful tool to accurately quantify myocardial mechanics (21, 22). Strain is a dimensionless measurement of change in length between two points, and LV global longitudinal strain (GLS) is defined as the change in the LV myocardial length of various LV myocardial segments between diastole and systole divided by the original end-diastolic length (22). LV GLS can be measured with

echocardiography, CMR and more recently ECG-gated computed tomography (23, 24, 25). The measurement of LV GLS is more reproducible than the measurement of LVEF and it is less influenced by loading conditions (21). Impairment of LV GLS occurs earlier than impairment of LVEF, thus its utility to diagnose subclinical LV systolic dysfunction, in early HF stages (26) (Figure 4). The feasibility and reproducibility of strain imaging to determine LV function has been explored, both by echocardiography and CMR ( 27, 28, 29, 30).

Although echocardiography is the imaging technique most frequently used for a first evaluation of patients with HF, multimodality imaging is key to diagnose the aetiology of HF. CMR is a 3D technique with high spatial and temporal resolution. Compared with echocardiography, CMR offers better spatial resolution in cine images and high reproducibility (31). The sharp contrast between the blood pool and myocardium enables accurate assessment of LV volume, mass and function (11). Currently CMR is considered the reference technique for the assessment of volume and function of any cardiac chamber. Reference values for LV diameters and volumes, indexed by the BSA are established according to the latest CMR studies (32). Due to its better spatial resolution as compared to echocardiography, diameters and volumes are slightly bigger and LVEF is slightly lower when measured by CMR (33, 34).

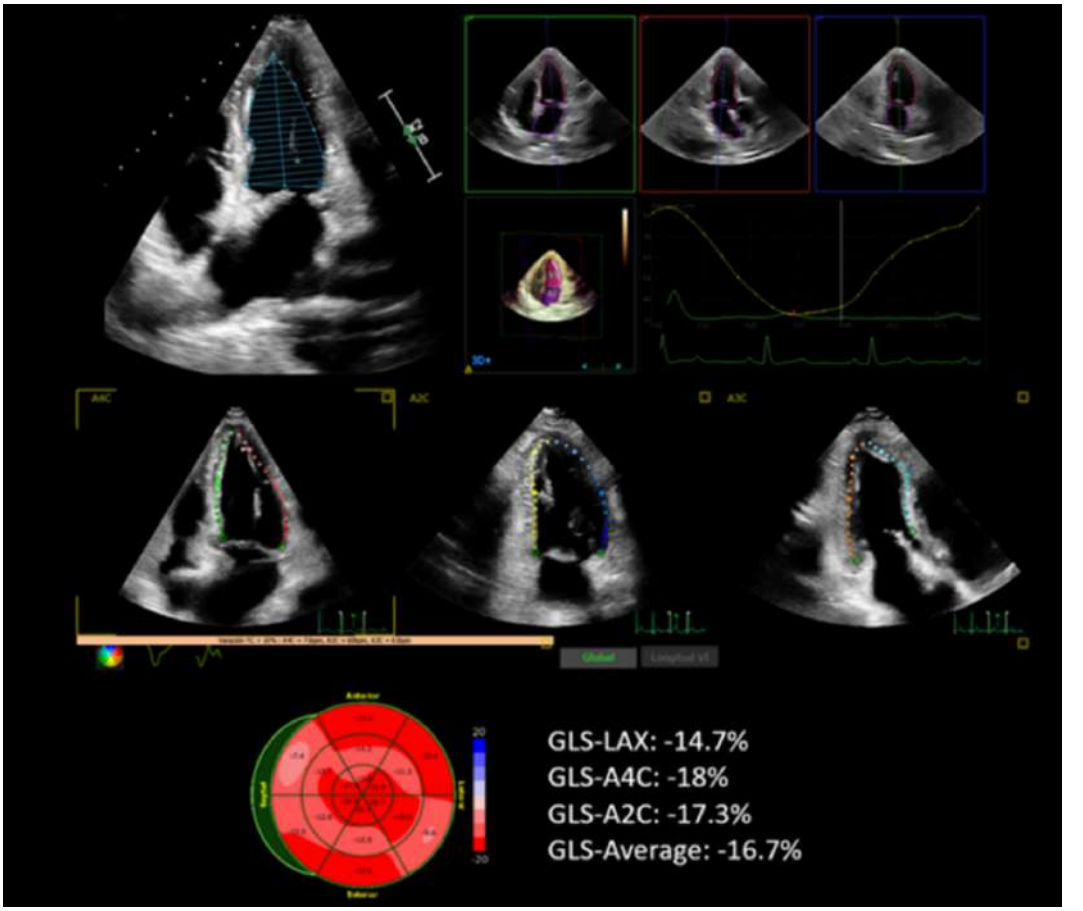


**Figure 4.** Myocardial deformation by strain imaging in echocardiography. A 60 year old patient receiving oncological therapy and showing impaired LV global longitudinal strain (GLS) despite preserved LVEF measured with biplane 2D Simpson method (65%) and 3-dimensional echocardiography (58%). Abbreviations: A2C: apical 2-chamber view; A4C; apical 4-chamber view; LAX: long-axis view. Adapted from Kasa G et al (26), with permission.

### 1.2.1.2. Prognostic implications of LV remodeling in HF

Dilatation of the LV reflects the increase in LV cavity size. Dilatation by both linear and volumetric measurements have demonstrated prognostic value in HF separately (11, 13, 14, 31, 35, 36, 42, 44, 45, 52).

#### 1.2.1.2.1. Prognostic implication of LV diameters in HF

LV dilatation was initially measured as the increase in linear internal dimensions by 2D-echocardiography in HF studies. One of the earliest studies of LV remodeling after myocardial infarction demonstrated that the extent of ventricular dilatation after infarction was related to the magnitude of the initial injury and ventricular dilatation was associated with a reduction in survival (14). Another study in advanced HF patients with LVEF <30% investigated the prognostic implications of LV dilatation using linear dimensions by 2D-echocardiography. Patients with massively dilated LV were defined by indexed LV end-diastolic diameter (LVEDDi) and LV size was found to be a significant predictor of sudden death (35). The echocardiographic data from the Valsartan HF trial showed that increasing LVEDDi was independently associated with mortality and morbidity (36). LV linear diameters have also demonstrated to be important values to define LV remodelling and to decide timing of intervention for example, in patients with severe aortic or mitral regurgitation (37, 38). In non-ischemic cardiomyopathy patients, left ventricular end-systolic diameter index (LVESDi) by 2D-echocardiography, along with LVEF were used to define LV remodeling and prognosis (39). Finally, multiple echocardiographic studies with large number of patients with HF and LVEF <50% investigated the prognostic role of reverse LV remodeling according to the changes observed in indexed left ventricular end-diastolic and end-systolic diameter measurements (40, 41).

Interestingly, only few studies have investigated the clinical and prognostic significance of LV dilatation assessed by linear dimensions on CMR in patients with HF and LVEF <50%. In the multi-ethnic study of aterosclerosis, the association of LV dilatation measured by linear CMR dimensions and the onset of HF was investigated in a large number of asymptomatic individuals with no prior history of cardiovascular disease (42). In this study, LV dilatation, defined as LV end-diastolic diameter > 52 mm, was associated with incident HF during follow-up. More recently, a reduction in LV end-systolic diameter (LVESD) measured by CMR was used as an imaging criterion to assess reverse remodeling in a cohort of patients with advanced HF and LVEF <35% who were treated with cardiac resynchronization therapy (43).

#### 1.2.1.2.2. Prognostic implication of LV volumes in HF

There is a large body of evidence relating the changes in LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF with cardiovascular outcomes in HF patients. The association between ventricular dilatation and reduced survival has been widely demonstrated, mostly using increased LV volumes by 2D-echocardiography (11, 14, 44, 45). LVESV was one of the most commonly used imaging markers associated with poor prognosis after MI (46). Established HF therapy pillars of today, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), betablockers or aldosterone receptor blockers target at reverse remodeling in HF by reducing both end-diastolic and end-systolic LV volumes by echocardiography (45, 47, 48, 49, 50, 51).

Data regarding the prognostic implication of LV dilatation as assessed by volumes using CMR are also available. Studies including both acute ischemic and chronic non-ischemic HF patients evaluated the LV remodeling, by LV end-diastolic volume changes in CMR (52, 53, 54). More recently, the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on LV remodeling in HFrEF patients has been explored, using both end-diastolic and end-systolic volume changes by CMR (55, 56, 57). Finally, both LVEDV and LVESV as assessed by CMR have provided prognostic value in predicting the need for aortic valve replacement in patients with severe aortic regurgitation and mortality in patients with mitral regurgitation (58, 59, 60).

### 1.2.1.3. Cardiac MRI-Based Tissue Characterization of LV Remodeling in HF

Importantly, LV remodeling does not only refer to macroscopic dilatation of LV, but also involves fundamental cellular alterations like myocardial fibrosis. Interstitial fibrosis and replacement fibrosis are both predictors of HF events. CMR provides the unique characteristic of non-invasive myocardial tissue characterization by T1 mapping and late gadolinium enhancement (LGE) sequences (Figure 5).

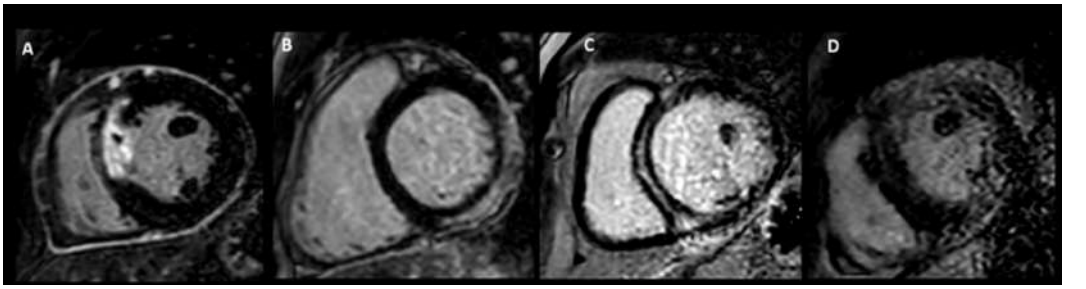


**Figure 5**. Tissue characterization by LGE in CMR. Examples of different contrast enhancement. patterns. A: Transmural MI in the anterior interventricular septum. B: Subepicardial enhancement in the lateral and posterior walls of the left ventricle due to myocarditis. C: Mid-wall fibrosis of the interventricular septum characteristic of idiopathic dilated cardiomyopathy. D: concentric left ventricular hypertrophy with diffuse late gadolinium enhancement pattern and poor differentiation of the blood pool in a patient with cardiac transthyretin amyloidosis. Adapted from Kasa G et al (26), with permission.

Concretely, the presence of LGE has been demonstrated to be associated with adverse cardiovascular outcomes in cardiomyopathies of different aetiologies (61). In ischemic cardiomyopathy, the presence and extent of LGE was shown to be strongly related to the improvement in wall motion and LVEF after coronary revascularization (62). In non-ischemic cardiomyopathy, the presence of mid-wall fibrosis by LGE showed incremental prognostic value beyond LVEF for all-cause mortality and sudden cardiac death (63, 64). Similarly, in a large cohort of 874 patients with dilated cardiomyopathy of non-ischemic origin, the presence of concomitant septal and free-wall LGE was related to higher risk of sudden cardiac death (65). Furthermore, the extent of LGE is inversely related to reverse remodeling in HF (11, 31, 66).

Non-invasive T1 mapping by CMR allows detection of diffuse interstitial myocardial disease. In 637 consecutive non-ischemic dilated cardiomyopathy patients, T1 mapping parameters (native T1 values and extracelular volume fraction) were predictive of all-cause mortality and HF, along with the presence and extent of LGE (67). Similarly, native T1 values showed a strong relationship with markers of structural and functional LV remodeling and diastolic dysfunction in patients with dilated cardiomyopathy (68).

In summary, the accurate definition of LV remodeling in HF is of vital importance. LV dilatation is a hallmark of LV remodeling. According to the robust evidence from numerous HF trials, both linear and volumetric measurements of LV dilatation have shown prognostic value separately in HF patients with LVEF <50%. However, the correlation between LV diameter and volume measured with 3D imaging techniques has not been studied and the relative merits of each parameter to predict long-term prognosis in patients with HF has not been explored.

### 1.2.2. LA remodeling

LA is the most posterior of the cardiac chambers, with a thin wall and a complex anatomy, including a venous component. From an anatomic perspective, LA is closely related to the LV through the mitral valve apparatus and includes the pulmonary veins within its border. LA acts as a frontier and conduct between the LV and pulmonary circulation and determines the right ventricular afterload. This close anatomical relationship between the two cardiac chambers are also reflected on their function. LA has a fundamental role in LV filling, providing 30% of the LV stroke volume (69). The mechanical function of the LA consists of three components. The reservoir function is during ventricular systole, when LA serves as a reservoir for the blood returning from the pulmonary veins. LA conduit function occurs during early LV diastole. During late LV diastole, LA active contraction occurs, which reflects the booster bump function (6, 70). This interplay among the atrial function and ventricular performance may be observed throughout the cardiac cycle. For example atrial conduit function not only depends on atrial compliance and atrial reservoir function, but it is also closely related to LV relaxation and compliance (71).

Apart from the mechanical functions, LA displays a remarkable neurohormonal function by producing atrial natriuretic peptide. Increased atrial volume and stretch are responsible for its release, resulting in diuresis and vasodilation (72). The regulatory function of LA depends on the atrial mechanoreceptors, which detect minor fluctuations in venous volume, and signal to the central nervous system to maintain optimal volume control (72). LA also regulates vasopressin production, which is essential for water and electrolyte balance (72).

LA remodeling refers to the pathophysiological changes in atrial structure and function that occur in response to an initial injury caused by pressure or volume overload or arrythmia. Hypertension, diabetes mellitus, obesity and sleep apnea syndrome are important conditions related to LA remodeling. LA remodeling reflect the changes in LA size, shape and architecture, involving myocardial fibrosis, electrophysiological alteration and global LA dysfunction (70) (Figure 6).

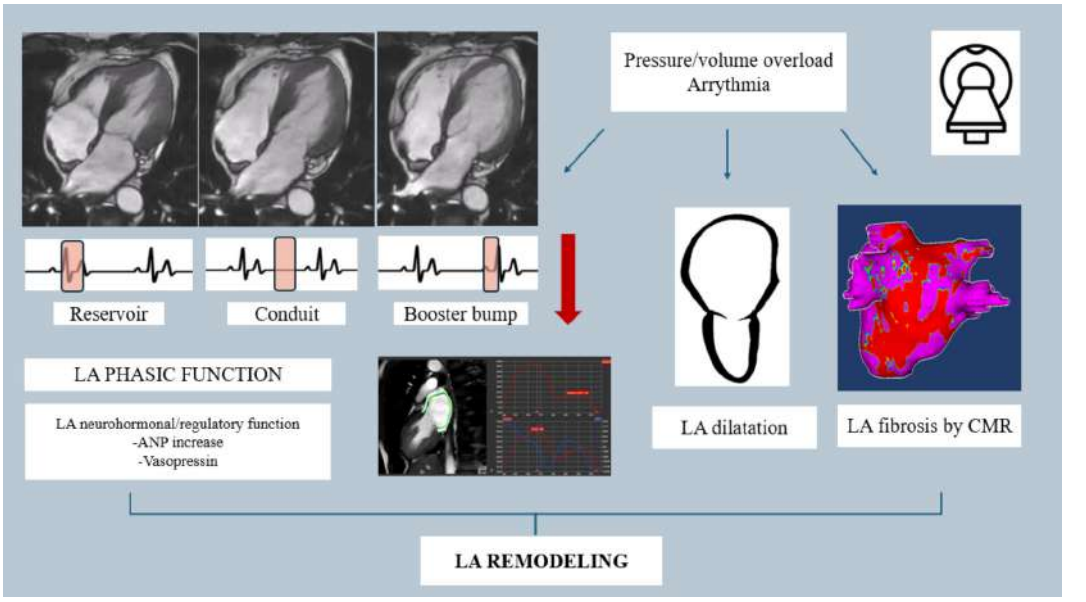


**Figure 6.** LA remodeling in heart failure.

Early detection of changes in LA size and function is crucial to prevent adverse cardiovascular outcomes. Multimodal cardiac imaging plays a key role in detection of LA remodeling.

### 1.2.2.1. Assessment of LA size and function

Assessment of LA size may be challenging, due to the left atrium's complex geometry and the variable contributions of its appendage and pulmonary veins (71, 72). LA dilatation can be assessed by linear and volumetric measurements. 2D and more recently 3D-echocardiography are the most commonly used non-invasive imaging techniques to evaluate LA size in daily practice. The most

widely used linear dimension is the LA anteroposterior measurement in the parasternal long-axis view.

However assessment of LA size using only the anteroposterior diameter is not accurate, given that when LA dilatation does not occur symmetrically in all the dimensions. The current guidelines on chamber cuantification by echocardiography recommend measurement of LA volume using the biplanar disk summation algorithm (15). LA volumes should be indexed to BSA, to enable comparison between patients with different body sizes. However, volumetric LA values may differ according to the imaging technique used. 2D echocardiography derived LA volume measurements may infraestimate LA volumes when compared to by 3D imaging techniques such as CMR and cardiac computed tomography (73).

LA function is commonly assessed by echocardiography using volumetric analysis, spectral Doppler of transmitral and pulmonary venous flows, and tissue Doppler and deformation analysis. The transmitral A wave by pulsed-wave Doppler, was commonly used to assess LA function during follow-up after cardioversion of atrial fibrillation to sinus rhythm or after catheter-based ablation (74). However there are serious limitations for its use, as the transmitral flow pattern is influenced by other factors such as heart rate, age, loading conditions, and LV diastolic properties (75). Tissue Doppler imaging (TDI) measurements with peak velocity of the mitral annulus in late diastole (a') correlates with both LA emptying fraction and LA ejection force, however this measurement is angle-dependent and can be used only in sinus rhythm.

LA strain imaging is a feasible technique to determine LA function. LA strain measurements are less load dependent compared with volumetric parameters of LA function (76). LA strain measurements can be obtained by either TDI or 2D speckle tracking echocardiography. 2D speckle tracking echocardiography is currently the preferred technique for the routine measurement of LA strain (75). Normal reference ranges of reservoir, conduit and contractile strain have been reported in a systematic review and meta analysis of 40 studies (77). Among the phasic metrics of LA function, left atrial reservoir strain (LARS) is

the most commonly used in cardiovascular research, with established prognostic value in various pathologies, including HF and atrial fibrillation (78, 79, 80, 81, 82).

Currently, CMR is considered as the most accurate modality to image any cardiac structure (83). When assessed by CMR, LA volumes are commonly calculated using the biplane area length method or Simpson's method and indexed to BSA. Linear measurements of LA diameters are taken in conventional longitudinal cine views at both end diastole and end-systole, and LA function is evaluated through volume changes across the cardiac cycle to calculate LA ejection fraction and phasic functions (reservoir, conduit, and booster bump/contractile functions) (32). Several studies have demonstrated that CMR estimates of atrial reservoir, conduit, and contractile functions predicted cardiovascular events in asymptomatic general population, in patients with cardiovascular risk factors and with ischemic heart disease (84, 85, 86, 87). Moreover, similar to LV remodeling, CMR provides additional information on LA remodeling by revealing atrial fibrosis with LGE. The presence of fibrosis on atrial myocardium has been reported to favor electrical dissociation and clinical onset of atrial fibrillation (70).

#### 1.2.2.2. Prognostic implications of LA remodeling in HF

Historically, LA was considered a passive bystander of changes occuring in LV in HF patients with reduced LVEF. The advances in multimodality imaging techniques, along with the growing interest in non-invasive treatment of atrial arrythmias, have put the focus on LA structure.

The prognostic implications of LA dilatation are well established. LA dilatation is clearly associated with adverse cardiovascular outcomes in general population and in valvular heart diseases such as aortic stenosis and mitral regurgitation (88, 89, 90, 91). In 52,639 patients remitted to imaging units for the first clinically indicated echocardiography exam, LA diameter was independently associated with all-cause mortality (88). LA dilatation is associated with increased mortality, even in asymptomatic, general population (92). Both

linear and volumetric parameters to detect LA dilatation have demonstrated prognostic value separately (88, 89, 90, 91, 92, 93). An undeniable relationship exists between LA dilatation and the incidence of atrial fibrillation and stroke (88, 89, 94, 95, 96). The prognostic implications of enlarged LA have also been demonstrated in patients with HF and MI (97, 98, 99, 100, 101, 102). LA dysfunction reflected by alteration in strain parameters have also demonstrated prognostic value in a large number of acute HF studies (77 - 81, 103). Concretely, LARS showed incremental prognostic value for risk stratification in HF patients with reduced LVEF (80, 104). The presence of fibrosis on atrial myocardium has been reported to favor electrical dissociation and clinical onset of atrial fibrillation (70). The extension of atrial fibrosis has demonstrated impact on the risk of arrhythmia recurrence at follow-up (105).

So far, most of the prognostic studies on LA size and function by CMR have targeted HF patients with preserved LVEF (106, 107, 108, 109). However, few data is available on the prognostic implications of LA remodeling in HF patients with reduced LVEF, by CMR.

### 1.2.3. Left atrioventricular coupling

The close anatomical and physiological relationship between the left cardiac chambers is reflected on global cardiac performance. When the geometry or function of either of those chambers is altered, global cardiac dysfunction occurs. Thus, the reciprocal changes involving the LA and LV structure, may accelerate the progression of HF. LA and LV are directly connected during ventricular diastole and their function and filling pressures are tightly coupled in absence of mitral valve stenosis. Left atrioventricular coupling refers to this interaction of LV and LA throughout the cardiac cycle.

One of the first studies about left atrioventricular coupling applied 2D-echocardiography, and defined left atrioventricular coupling index (LACI) using ratio between LA volume index (LAVi) and TDI myocardial velocity at atrial contraction (TDI-a'). The study cohort consisted of 4196 patients with first diagnosis of HFrEF. The authors concluded that higher LACI was strongly and

independently associated with mortality, irrespective of mitral regurgitation grade (110). The same echocardiographic LACI definition (ratio between LAVi and TDI-a') was applied to determine prognosis in a large cohort of patients with isolated floppy mitral valve in sinus rhythm. LACI was concluded to be strongly and independently determinant of survival under medical treatment (111). Despite the inital promising results in HF, tissue Doppler based LACI approach did not gain ground in daily practice in cardiac imaging units, maybe due to the limitations of tissue Doppler imaging.

In addition, the advance in cardiac imaging techniques helped identify LA structure and function more accurately in global cardiac performance. In this regard, LA volume can be measured at different times throughout the cardiac cycle. Although, LA maximal volume (measured at the end of left ventricular systole) is currently the only LA echocardiographic parameter recommended by international guidelines to grade LV diastolic dysfunction (112), LA minimal volume (measured at the end of LV diastole) has shown a stronger association with both invasively measured LV filling pressure and outcome in HF compared with maximal LA volume (113, 114, 115).

Based on this growing evidence and interest about global cardiac remodeling in HF, a novel, more feasible definition of LACI has been suggested as the ratio between LA and LV volumes at end-diastole (116) (Figure 7). This new definition of LACI was first measured by CMR in a large cohort of asymptomatic individuals with cardiovascular risk factors in the Multi-Ethnic Study of Atherosclerosis and was shown be a strong predictor for the incidence of HF, atrial fibrillation, hard cardiovascular disease, and coronary heart disease death (116).

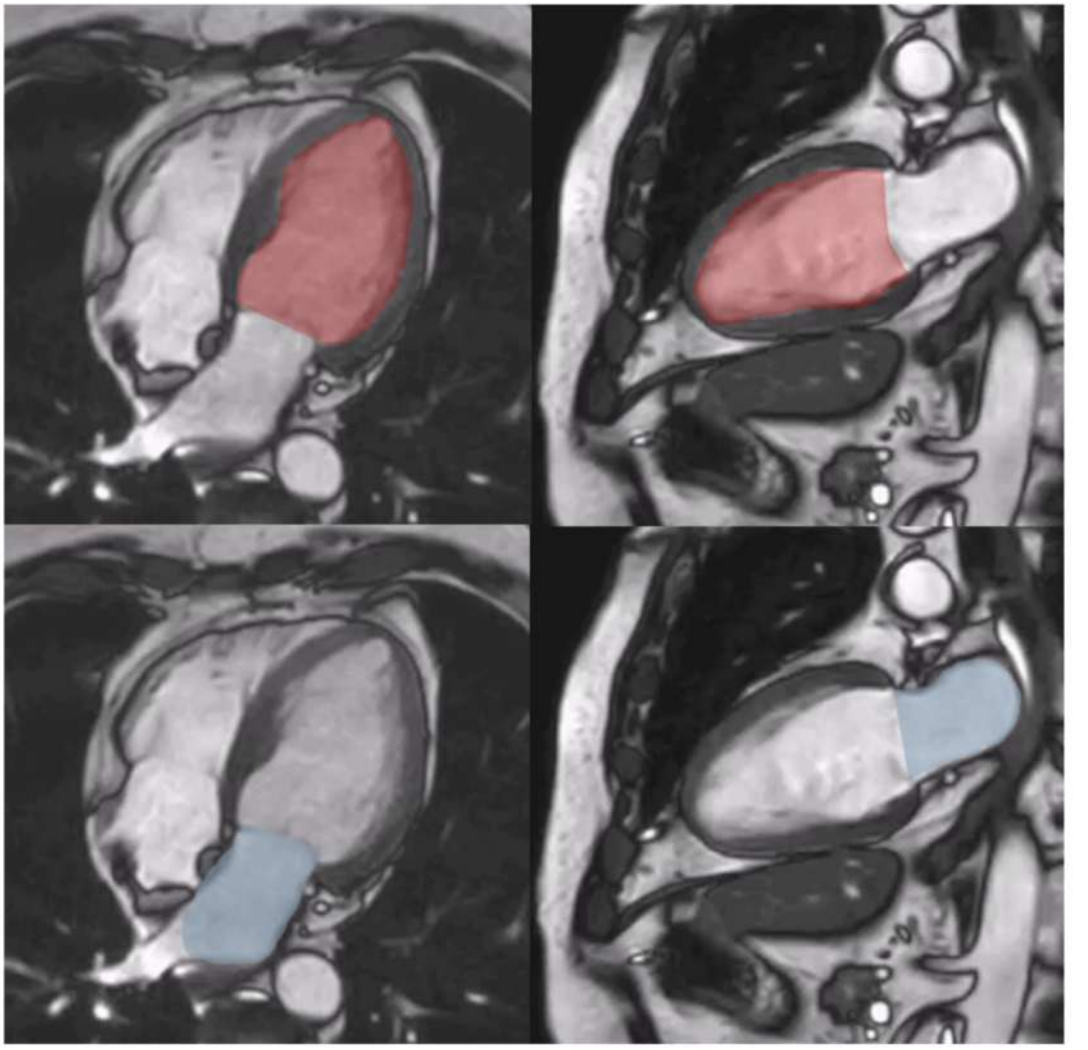

**Figure 7.** Method to assess the Left Atrio-ventricular Coupling Index (LACI) by CMR. LACI is defined by the ratio between the LA end-diastolic volume and the LV end-diastolic volume.

In a large cohort of patients with acute MI, CMR-derived LACI was reported to be a superior measure of death, reinfarction or heart failure, beyond LVEF especially in high-risk patients with LVEF ≤ 35% (117). In 2134 patients with undergoing vasodilator stress CMR, LACI measured by fully automated artificial intelligence-based method, was associated with cardiovascular death or acute HF hospitalization. Moreover, LACI showed incremental prognostic value over traditional CMR risk factors, including inducible ischemia or LGE with ischemic pattern (118). In patients with hypertrophic cardiomyopathy, LACI was measured by both echocardiography and CMR. An increase in echo-

cardiographic LACI values were related to occurrence of new-onset atrial fibrillation (119). CMR-derived LACI was superior to LGE extent in mortality risk stratification in hypertrophic cardiomyopathy (120). In a recent study including 375 patients with different LV hypertrophic phenotypes, LACI was independently correlated with LA function (121). Finally in a large cohort of patients with chronic HF, LACI measured by echocardiography was associated with the severity of diastolic dysfunction and with all-cause death or HF hospitalization at follow-up (122).

In conclusion, LACI is a promising and novel imaging marker for patients with HF. However, data on left atrioventricular coupling and its relationship with adverse clinical outcomes in patients with HF and LVEF <50% remain limited.

# HYPOTHESIS

# HYPOTHESIS

The hypothesis of this thesis is to demonstrate that comprehensive CMR evaluation of cardiac remodeling enables improved risk stratification in HF patients with LVEF<50%. The remodeling process should be assessed with a more holistic approach with CMR established as the standard imaging modality for evaluating cardiac remodeling.

## 2.1. The rationale of the doctoral thesis

HF remains a major cause of cardiovascular mortality and morbidity, causing remarkable economic burden in healthcare systems, including Spain. Cardiac remodeling is of critical importance in the progression of HF. In the majority of the HF studies, echocardiography has been the main imaging technique applied to define cardiac remodeling. Traditionally, the definition of LV dilatation was based on the increase in diameters and volumes by 2D imaging techniques. Currently CMR is considered gold standard in volumetric and functional evaluation of any cardiac chamber. However, the correlation between LV diameter and volume measured with 3-dimensional imaging techniques has not been studied and the merits of each parameter to predict long-term prognosis in patients with HF with LVEF <50% has not been explored.

LA structure and function are crucial determinants of global cardiac function. The assessment of the LA function integrated with LV function is of critical importance. Recently, LACI has emerged as a novel imaging marker which evaluates global LA and LV structure and function simultaneously. The prognostic value of LACI has been explored in a large population of asymptomatic individuals, in acute MI and HFpEF patients, however data evaluating the association of CMR-derived LACI with adverse clinical outcomes in patients with heart failure and LVEF <50% is limited.

This doctoral thesis aims to address the gaps of knowledge and provide new insights in assessment of cardiac remodeling by comprehensive CMR analysis in patients with HF and LVEF<50%.

# OBJECTIVES

# OBJECTIVES

### 3.1. Main Objective

The main objective of this project is to characterize cardiac remodeling in patients with heart failure and LVEF <50% with the use of comprehensive CMR evaluation including volumetric, geometric and strain analysis.

### 3.2. Secondary Objectives

The secondary objectives of this project are:

1. To assess the agreement between CMR derived LV linear and volumetric measures to define LV dilatation and characterize the groups of patients with concordant and discordant definitions of LV dilatation.

2. To investigate the prognostic implications of concordant and discordant definition of LV dilatation based on CMR derived LV linear and volumetric dimensions.

3. To assess the distribution ofleft atrio-ventricular uncoupling in patients with HF and LVEF <50% by measuring the LACI with CMR and to elucidate its prognostic implications.

# COMPENDIUM OF PUBLICATIONS

# COMPENDIUM OF PUBLICATIONS

This doctoral thesis is based on a compendium of two original research articles, using a comprehensive CMR evaluation to analyse cardiac remodeling parameters in patients with HF and LVEF <50%.

A third article included is a review article on the recent updates in HF imaging. This review is available as supplementary material in the annex section.

### 4.1. First Original Research Article

**Clinical and prognostic implications of left ventricular dilatation in heart failure**

Kasa G, Teis A, Juncà G, Aimo A, Lupón J, Cediel G, Santiago-Vacas E, Codina P, Ferrer-Sistach E, Vallejo-Camazón N, López-Ayerbe J, Bayés-Genis A, Delgado V.

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ESC European Society of Cardiology

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ORIGINAL PAPER

# Clinical and prognostic implications of left ventricular dilatation in heart failure

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**Aims** To assess the agreement between left ventricular end-diastolic diameter index (LVEDDi) and volume index (LVEDVi) to define LV dilatation and to investigate the respective prognostic implications in patients with heart failure (HF).

**Methods and results** Patients with HF symptoms and LV ejection fraction (LVEF) < 50% undergoing cardiac magnetic resonance were evaluated retrospectively. LV dilatation was defined as LVEDDi or LVEDVi above the upper normal limit according to published reference values. Patients were followed up for the combined endpoint of cardiovascular death or HF hospitalization during 5 years. A total of 564 patients (median age 64 years; 79% men) were included. LVEDDi had a modest correlation with LVEDVi ($r = 0.682$, $P < 0.001$). LV dilatation was noted in 84% of patients using LVEDVi-based definition and in 73% using LVEDDi-based definition, whereas 20% of patients displayed discordant definitions of LV dilatation. During a median follow-up of 2.8 years, patients with both dilated LVEDDi and LVEDVi had the highest cumulative event rate (HR 3.00, 95% CI 1.15–7.81, $P = 0.024$). Both LVEDDi and LVEDVi were independently associated with the primary outcome (hazard ratio 3.29, 95%, $P < 0.001$ and 2.8, $P = 0.009$; respectively).

**Conclusion** The majority of patients with HF and LVEF < 50% present both increased LVEDDi and LVEDVi whereas 20% show discordant linear and volumetric definitions of LV dilatation. Patients with increased LVEDDi and LVEDVi have the worst clinical outcomes suggesting that the assessment of these two metrics is needed for better risk stratification.

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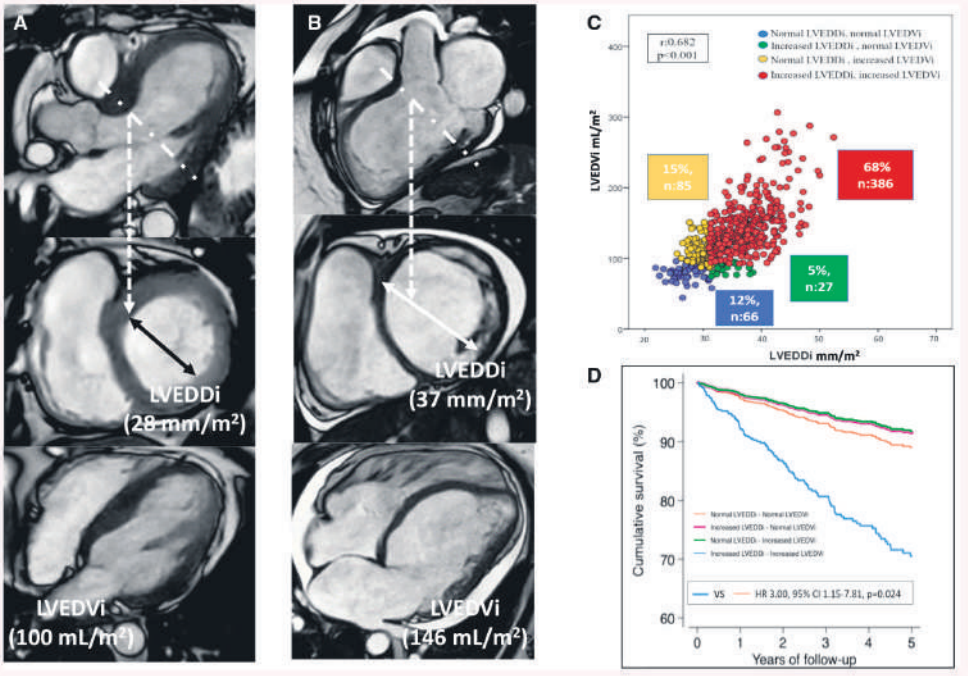
## Graphical Abstract




**Left ventricular dilatation based on linear dimension (left ventricular end-diastolic diameter) or volumetric dimension (left ventricular end-diastolic volume) vs prognosis.** Panel A shows the 3-chamber reconstruction of the left ventricle from a cardiac magnetic resonance (CMR) cine image. The dotted line demarcates the plane where the short-axis of the left ventricle is acquired and where the left ventricular endi-diastolic diameter is measured and indexed , LVEDDi). The 4-chamber view of the left ventricle is shown and the left ventricular end-diastolic volume is measured from stacks of short-axis and indexed to body surface area (LVEDVi). In this case, the LVEDDi is non-dilated whereas the LVEDVi is dilated. Panel B shows the CMR data of a patient with dilated left ventricle based on LVEDDi and LVEDVi. Panel C shows the correlation between LVEDDi and LVEDVi and the 4 groups of patients based on the dilatation of one or the other dimension or both. Panel D shows the cumulative survival curves for each group of patients.

**Keywords** heart failure • left ventricular • remodelling • dilatation • cardiac magnetic resonance

## Introduction

Heart failure (HF) is currently classified according to left ventricular ejection fraction (LVEF),[1] the most frequently used metric of left ventricular (LV) performance in clinical practice. Left ventricular dilatation, hallmark of LV remodelling, is considered an adaptive response to maintain stroke volume and normal cardiac output and has been the focus of HF therapies clinical trials.[2,3] The degree of LV remodelling is the main determinant of LVEF. However, LV volumes and mass relate more closely to the impact of therapy and prognosis than LVEF does and therefore, they will be more appropriate parameters to phenotype patients with HF.[4,5] LV dilatation is mainly assessed in clinical practice with two-dimensional echocardiography, measuring LV diameters and volumes. However, there are inherent limitations of two-dimensional echocardiography that impact on the accuracy of the measurements (i.e. foreshortened images and inaccurate plane of acquisition), particularly in dilated LV.[6] In addition, the equivalence of LV dilatation based on LV diameters and LV volumes has not been well established. Regional LV remodelling may lead to dilated LV diameter but normal LV volume and vice versa. Three-dimensional echocardiography and cardiac magnetic resonance (CMR) provide more accurate quantification of LV volumes than two-dimensional echocardiography and overcome the limitations of the geometric assumptions used by two-dimensional echocardiography. These techniques would allow the measurement of the largest LV diameter and provide a better correlation between LV diameter and volume. However, the correlation between LV diameter and volume measured with three-dimensional imaging techniques has not been studied and the relative merits of each parameter to predict long-term prognosis in patients with HF has not been explored. Accordingly, the aim of this study was two-fold: (1) to evaluate the frequency of LV dilatation when defined based on a volumetric assessment vs. a linear (diameter) measurement in a cohort of patients with HF

undergoing CMR and (2) to investigate the association between each LV dilatation definition and the occurrence of clinical outcomes at follow-up.

# Methods

## Patient population

Patients with HF symptoms who underwent clinically indicated CMR at the Hospital University Germans Trias i Pujol (Badalona, Spain) from 2009 to December 2021 were retrospectively identified. Patients were selected if LVEF at the time of CMR was <50%. Demographic data, comorbidities, renal function, and HF therapies were retrieved from clinical records. Ischaemic heart failure was defined by the presence of obstructive coronary artery disease.[7] The study complied with the personal data law protection and the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study (REGI-UNIC PI-18-037 and ICOR-2019-04-EB-IDI).

## Cardiac magnetic resonance data acquisition and analysis

Cardiac magnetic resonance scans were performed with a 1.5 Tesla magnetic resonance imaging scanner (Achieva dStream; Philips, The Netherlands) or 3 Tesla magnetic resonance imaging scanner (Verio; Siemens Medical Imaging, Erlangen, Germany), with the patient in the supine position and a 16-element phased-array coil placed over the chest. Images were acquired during breath-holds with electrocardiogram gating. A segmented k-space steady-state free-precession sequence [repetition time 44.70 ms; echo time 1.26 ms; flip angle 60–78; matrix 272; spatial resolution (1.3–1.5) × (1.3–1.5) × 8 mm depending on the field of view] was used for cine imaging in parallel short-axis (contiguous slices of 8 mm thickness, 2 mm gap, covering from base to apex) and three long-axis views of the LV. Late gadolinium enhanced (LGE) images were acquired with a segmented gradient-echo inversion-recovery sequence (repetition time 600–800 ms depending on heart rate; echo time 3.24 ms; flip angle 25; matrix 256; spatial resolution 1.3 × 1.3 × 8 mm) 10 to 20 min after intravenous gadolinium-diethylenetriaminepentaacetic acid administration (0.15 mmol/kg; Gadovist, Bayer Schering Pharma AG, Berlin, Germany) at matching cine-image slice locations.[8] The inversion time was optimized to null the normal myocardium. Adjusted views per segment and trigger delay were optimized according to the patient's heart rate. All images were reviewed and analysed off-line with a specialized post-processing software (Intellispace Portal v8, Philips, The Netherlands) blinded to the clinical data and outcome. For volumetric analysis, LV endocardial borders were manually traced on all short-axis cine images at end-diastole and the LV end-diastolic volume (LVEDV) was measured and indexed for body surface area (BSA) according to the DuBois and DuBois formula.[9] The endocardial contours excluded the papillary muscles. For linear measurements, the left ventricular end-diastolic diameter (LVEDD) was measured in a basal short-axis slice of the LV, as the distance between the anteroseptal and inferolateral walls, mimicking the echocardiographic parasternal long-axis view, and was also indexed by BSA. The LV mass was calculated by subtracting the endocardial volume from the epicardial volume at end-diastole and multiplying by the tissue density (1.05 g/mL).[10]

LV dilation based on LVEDVi was defined as an LVEDVi above the upper normal limit according to published reference values normalized by age and gender.[11] LV dilation based on LVEDDi was defined as an LVEDDi above the upper normal limit according to reference cut-off values normalized by gender and BSA of the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.[12] Based on the concordance of the volumetric and the linear definitions of LV dilation, four different groups were created: Group 1 (normal LVEDDi and LVEDVi), Group 2 (increased LVEDDi but normal LVEDVi), Group 3 (normal LVEDDi but increased LVEDVi), and Group 4 (increased both LVEDDi and LVEDVi).

## Follow-up

All patients were followed up regularly at the HF clinic. The clinical evaluation and treatment of patients were directed by the treating physician according to a unified protocol based on current clinical practice guidelines recommendations.[1,13–17] The primary endpoint of the study was the combined endpoint of cardiovascular death or HF hospitalization (whichever came first) during 5 years of follow-up. A death was considered cardiovascular if caused by HF (decompensated HF or treatment-resistant HF in the absence of another cause), sudden death (unexpected death, witnessed or not, of a previously stable patient with no evidence of worsening HF or any other cause of death), acute myocardial infarction (directly related in time with acute myocardial infarction due to mechanic, haemodynamic, or arrhythmic complications), and stroke (associated with recently appearing acute neurologic deficit). The events were identified from the clinical records of patients with HF, hospital wards, the emergency room, general practitioners, and by contacting the patient's relatives. Mortality data were verified by the databases of the Catalan and Spanish Health Systems and the Spanish National Death Registry (INDEF). Hospitalizations were identified from the clinical records of patients with HF, hospital wards, and the shared electronic health record in Catalonia. Follow-up was closed at 31 December 2021.

## Statistical analysis

Statistical analysis was performed using STATA V.13.0 (College Station, TX, USA) and IBM SPSS Statistics (version 22, 2013) software. Normal distribution of continuous variables was assessed by plotting histograms and applying the Shapiro–Wilk test. Variables with normal distribution are presented as mean ± standard deviation, while those with non-normal distribution are presented as median and interquartile range. Continuous variables were compared between groups using the unpaired Student's *t*-test, the Mann–Whitney *U* test, or the one-way ANOVA test, as appropriate. Continuous variables with non-normal distribution were compared between groups with one-way ANOVA test. Categorical variables were compared by the $\chi^2$ test with Yates correction or the Fisher exact test. Simple linear regression between LVEDDi and LVEDVi was assessed. The association between the definitions of LV dilation and the combined clinical endpoint were assessed with Cox proportional regression models. A competing risk strategy using the Fine and Gray method was adopted, considering non-cardiovascular death as competing event for the clinical endpoint. Statistically significant variables in the univariate regression analysis were included in the multivariate regression analysis applying the 'one-in-ten' rule to avoid model overfitting of the model.[18] Cumulative incidence curves were plotted. The crude incidence of HF hospitalizations was calculated. *P*-values of <0.05 were considered statistically significant.

# Results

## Patient population

A total of 564 patients were included (median age 64 years; 79% men). Patient clinical characteristics and CMR data are reported in *Tables 1* and *2*, respectively. Ischaemic HF was present in 42% of the patients whereas the remaining patients had non-ischaemic HF, being dilated cardiomyopathy the most frequent aetiology (30%).

## Concordance between linear and volumetric definitions of LV dilatation

On linear regression analysis, LVEDDi had a modest correlation with LVEDVi ($r = 0.682$, $P < 0.001$, *Figure 1*). LV dilatation based on

**Table 1 Patient characteristics**

| | All ($n = 564$) | Group 1 LVEDDi normal LVEDVi normal ($n = 66$) | Group 2 LVEDDi increased LVEDVi normal ($n = 27$) | Group 3 LVEDDi normal LVEDVi increased ($n = 85$) | Group 4 LVEDDi increased LVEDVi increased ($n = 386$) | *P*-value |
|---|---|---|---|---|---|---|
| Clinical characteristics | | | | | | |
| Age (years) | 64 ± 11.7 | 63 ± 11.1 | 66 ± 11.13 | 63 ± 12.79 | 64 ± 11.6 | 0.75 |
| Male, *n* (%) | 446 (79) | 55 (83) | 17 (63) | 71 (84) | 303 (79) | 0.11 |
| BSA (kg/m$^2$) | 1.85 ± 0.2 | 1.92 ± 0.2 | 1.72 ± 0.2 | 2.01 ± 0.2 | 1.81 ± 0.2 | <0.001 |
| Hypertension, *n* (%) | 346 (61) | 43 (65) | 18 (67) | 61 (72) | 224 (58) | 0.09 |
| DM, *n* (%) | 234 (42) | 27 (41) | 13 (48) | 37 (44) | 157 (41) | 0.86 |
| Smoker, *n* (%) | 382 (68) | 46 (70) | 15 (56) | 58 (68) | 263 (68) | 0.58 |
| Dyslipidaemia, *n* (%) | 349 (62) | 42 (64) | 12 (44) | 56 (66) | 239 (62) | 0.25 |
| Obesity, *n* (%) | 134 (24) | 26 (39) | 3 (11) | 41 (48) | 64 (17) | <0.001 |
| NYHA class II/III, *n* (%) | 432 (81)/42 (8) | 52 (84)/4 (7) | 25 (93)/2 (7) | 66 (81)/3 (4) | 289 (80)/33 (9) | 0.24 |
| LBBB, *n* (%) | 212 (38) | 12 (18) | 7 (26) | 30 (35) | 163 (42) | <0.001 |
| AF/flutter, *n* (%) | 75 (13) | 13 (20) | 5 (19) | 10 (12) | 47 (12) | 0.31 |
| Aetiology of HF, *n* (%) | | | | | | 0.05 |
| Ischaemic | 237 (42) | 29 (44) | 15 (56) | 31 (36) | 162 (42) | |
| Non-ischaemic | 327 (58) | 37 (56) | 12 (44) | 54 (64) | 224 (58) | |
| Laboratory | | | | | | |
| Haemoglobin[a] (g/dL) | 14.2 ± 12 | 17 ± 25 | 13 ± 1.3 | 14 ± 1.5 | 14 ± 10 | 0.39 |
| NT-proBNP[a] (pg/mL) | 1193 (541–2825) | 1245 (589–3013) | 1159 (729–1997) | 476 (176–1050) | 1440 (672–3367) | <0.001 |
| eGFR[a] (mL/min/1.73 m$^2$) | 68.4 ± 24 | 67 ± 24 | 65 ± 23 | 72 ± 25 | 68 ± 24 | 0.61 |
| Treatment | | | | | | |
| Betablocker, *n* (%) | 494 (88) | 58 (88) | 25 (93) | 74 (87) | 337 (87) | 0.88 |
| ACEinh/ARBs, *n* (%) | 399 (71) | 41 (62) | 18 (67) | 64 (75) | 276 (72) | 0.32 |
| ARNi, *n* (%) | 73 (13) | 10 (15) | 5 (19) | 12 (14) | 46 (12) | 0.68 |
| MRA, *n* (%) | 420 (75) | 44 (67) | 16 (59) | 62 (73) | 298 (77) | 0.07 |
| Loop diuretics, *n* (%) | 419 (74) | 49 (74) | 17 (63) | 55 (65) | 298 (77) | 0.05 |

All values are *n* (%), mean ± SD, except for NT-proBNP values that are presented as median (interquartile range).
ACE inhibitor, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; ARNi, angiotensin receptor neprilysin inhibitor; BSA, body surface area; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LBBB, left bundle branch block; LVEDDi, left ventricular end-diastolic diameter index; LVEDVi, left ventricular end-diastolic volume index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B type natriuretic peptide; NYHA, New York Heart Association.
[a]eGFR levels available only in 446 patients, haemoglobin levels in 396, and NT-proBNP levels available in 364 patients.

volumetric definition was present in the majority of the patients ($n = 471$, 84%) whereas only 73% ($n = 413$) had LV dilatation based on a linear definition. Based on the concordance of the volumetric and the linear definition of LV dilatation, 66 patients (12%) had normal LVEDVi and LVEDDi (Group 1), 27 patients (5%) had dilated LVEDDi and normal LVEDVi (Group 2), 85 patients (15%) showed dilated LVEDVi and normal LVEDDi (Group 3), and 386 (68%) showed dilated LVEDVi and LVEDDi (Group 4).

No clinical or HF treatment differences were observed across the groups. Group 4 had the highest NT-proBNP values. BSA was significantly higher and the presence of obesity was significantly more frequent in the Group 1 and Group 3. Left bundle branch block was present in 212 patients (38%) and it was more prevalent in Group 4. LVEF progressively decreased whereas LVESVi progressively increased from Group 1 to 4. LV mass index (LVMi) was higher in patients with increased LVEDVi (Group 3 and Group 4). LGE was present in the majority of the patients (82%) and it was more frequently observed in patients of the Group 2 and Group 4.

## Linear and volumetric definition of LV dilation and outcomes

Over a median follow-up of 2.8 years (IQR 1.4–5.0), cardiovascular death or first HF hospitalization occurred in 105 patients (19%). Cardiovascular death occurred in 56 patients (10%) and HF hospitalization in 85 patients (15%), respectively. The cumulative rates of the combined endpoint with the following distribution according to the four subgroups were: 5 patients in Group 1 (7.6%), 2 patients in Group 2 (7.4%), 5 patients in Group 3 (5.9%), and 93 patients in Group 4 (24.1%). Both, LV dilatation according to LVEDDi and LVEDVi, were significantly correlated with cardiovascular death or HF hospitalization after adjusting for sex, age, ischaemic HF aetiology, HF categories based on LVEF < 40% and presence of diabetes mellitus, hypertension, and LGE (HR 3.29, 95% CI 1.72–26.29, $P < 0.001$ and HR 2.80, 95% CI 1.30–6.03, $P = 0.009$; respectively) (*Table 3*). However, when analysing the survival curves according to LV dilatation groups, only patients with concordant dilatation of LV (Group 4) had a worse outcome as

**Table 2 Cardiac magnetic resonance characteristics**

| | All ($n = 564$) | Group 1 LVEDDi normal LVEDVi normal ($n = 66$) | Group 2 LVEDDi increased LVEDVi normal ($n = 27$) | Group 3 LVEDDi normal LVEDVi increased ($n = 85$) | Group 4 LVEDDi increased LVEDVi increased ($n = 386$) | *P*-value |
|---|---|---|---|---|---|---|
| LVEDDi (mm/m$^2$) | 35 ± 5 | 27 ± 2.3 | 34 ± 2.2 | 29 ± 1.3 | 37 ± 4.4 | <0.001 |
| LVEDVi (mL/m$^2$) | 130 ± 42 | 81 ± 11 | 86 ± 6.7 | 115 ± 21 | 145 ± 41 | <0.001 |
| LVESVi (mL/m$^2$) | 95 ± 41 | 50 ± 9.5 | 53 ± 7 | 79 ± 22 | 108 ± 40 | <0.001 |
| LVEF (%) | 29 ± 10 | 39 ± 7 | 38 ± 7 | 31 ± 9 | 27 ± 9 | <0.001 |
| LVMi (g/m$^2$) | 90 ± 26 | 77 ± 19 | 70 ± 18 | 89 ± 30 | 93 ± 26 | <0.001 |
| T1 mapping (ms)[a] | 1069 ± 61 | 1062 ± 90 | 1072 ± 54 | 1059 ± 63 | 1073 ± 53 | 0.40 |
| LGE, *n* (%) | 461 (82) | 53 (80) | 25 (93) | 59 (69) | 324 (84) | 0.007 |
| LV to RV ratio | 2,03 ± 0.75 | 1.5 ± 0.36 | 1.7 ± 0.39 | 1.8 ± 0.54 | 2.2 ± 0.79 | <0.001 |

LGE, late gadolinium enhancement; LV, left ventricle; LVEDDi, left ventricular end-diastolic diameter index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; RV, right ventricle.
[a]Septal native T1 mapping values available in only 305 patients.

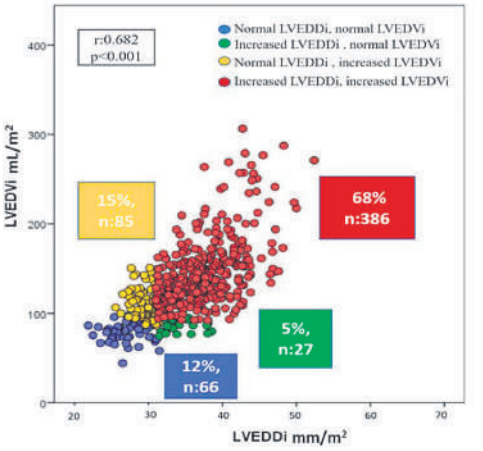



**Figure 1** Correlation between left ventricular end-diastolic diameter index (LVEDDi) and left ventricular end-diastolic volume index (LVEDVi).

compared with those with concordant non-dilatation of LV (HR 3.00, 95% CI 1.15–7.81, $P = 0.024$) (*Figure 2*).

## Discussion

The main results of the present study can be summarized as follows: LVEDDi had a modest correlation with LVEDVi when measured with CMR. The presence of discordant definition of LV dilatation based on the combination of both LVEDDi and LVEDVi was 20% of the patients with HF suggesting a significant proportion of patients that may be misclassified. Importantly, both LVEDDi and LVEDVi were independently associated with the primary outcome and those patients with concordant linear and volumetric definition for LV dilatation had worse outcomes. Changes in LV size, shape, and function are the hallmark of LV remodelling and occur in response to ischaemic or non-ischaemic injury and are partly mediated by neurohormonal and haemodynamic alterations.[19] These changes involve changes in myocardial tissue, myocardial mass, and LV volumes and non-invasive imaging techniques can currently characterize the myocardial tissue changes (predominantly with the use of CMR techniques) and LV volumes and ejection fraction. There is a large body of evidence relating the changes in LV end-systolic volume (LVESV), LVEDV and LVEF with cardiovascular outcomes,[5] particularly using radionuclide ventriculography or echocardiography. Subsequent studies using CMR have confirmed the results. In the general population for example, LVEDV measured with CMR was associated with increased risk of HF or cardiovascular death (HR 1.5, 95% CI 1.2–1.9) independently of the LV wall thickness and other

**Table 3 Univariable and multivariable Cox regression analyses**

| | LV dilatation based on LVEDVi | | LV dilatation based on LVEDDi | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Univariate | 2.43 (1.11–5.31) | 0.026 | 3.36 (1.75–6.46) | <0.001 |
| Multivariate adjustment[a] | 2.80 (1.30–6.03) | 0.009 | 3.29 (1.72–6.29) | <0.001 |

Univariate regression analysis of LV dilatation defined by increased LVEDVi or increased LVEDDi, respectively.
[a]Multivariate Cox regression analysis adjusted for sex, age, ischaemic HF aetiology, HF categories based on LVEF cut-off value, diabetes mellitus, hypertension, and presence of late gadolinium enhancement in CMR studies. Other variables that are associated with cardiovascular events are sex, age, and ischaemic HF aetiology.

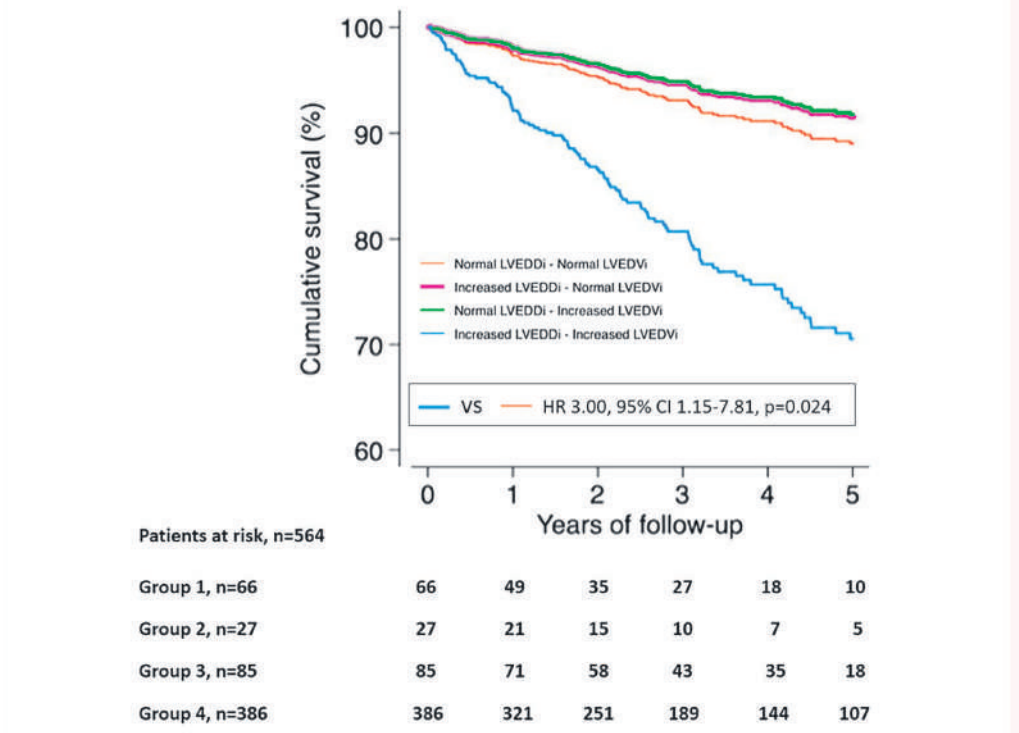



**Figure 2** Cumulative survival analysis for the combined endpoint of cardiovascular death or HF hospitalization. LVEDDi, left ventricular end-diastolic diameter index; LVEDVi, left ventricular end-diastolic volume index; VS, versus; Group 1, normal LVEDDi-normal LVEDVi; Group 2, increased LVEDDi-normal LVEDVi; Group 3, normal LVEDDi-increased LVEDVi; Group 4, increased LVEDDi-increased LVEDVi.

parameters.[20] In patients with acute myocardial infarction, increasing LVESV on baseline CMR (HR 1.02, 95% CI 1.01–1.03) and an increase in LVEDV > 15% at 6 months of follow-up was significantly associated with the occurrence of HF, ventricular arrhythmias, or cardiovascular death.[21] Similarly, among patients with ischaemic HF, LVESV, and LVEDV measured with CMR have shown to be incremental to LVEF.[22] Accordingly, LV volumes have become an important therapeutic target to demonstrate the efficacy of HF therapies to revert the adverse LV remodelling. Additionally, LV diameters are also important values to define LV remodelling and to decide timing of intervention (for example, in patients with severe aortic regurgitation).[23,24] The echocardiographic data from the Valsartan heart Failure Trial showed that increasing LV end-diastolic diameter index was independently associated with poor outcomes.[25] Furthermore, the reduction in LV end-systolic and end-diastolic diameters by various heart failure therapies (including cardiac devices such as cardiac resynchronization therapy) was directly correlated with a favourable effect on mortality as demonstrated by a recent meta-analysis including 69 766 patients.[26]

Therefore, based on this robust evidence, it could be established that both volumetric and linear dimensions of the LV would be excellent surrogates to assess the risk of adverse cardiovascular outcomes and the effects of heart failure therapies. However, there is no study so far demonstrating that this assumption is valid. In the present HF cohort, the correlation between linear and volumetric assessment of LV remodelling was moderate. Previous reports observed similar results in valvular heart disease, although those studies used transthoracic echocardiography.[27] In the present study, 20% of the patients presented a discrepancy between the definition of LV dilatation according to linear vs. volumetric assessment. Interestingly, the clinical cause of HF did not differ between those with concordant or discordant definition of LV dilatation. It could be hypothesized that in ischaemic cardiomyopathy, the discrepancy between linear and volumetric LV dilatation definitions could be explained by the infarct location that would lead to specific LV local remodelling [for example, an inferior or inferolateral myocardial infarction would result in larger linear LV dimension (LVEDDi) but still normal LVEDVi]. However, this could be also explained by the timing of the CMR imaging: in the early process of the LV remodelling, the discrepancy between linear and volumetric LV dilatation could be more prominent whereas in a much later stage of the disease, the LV remodelling is more global having consistent definitions of linear and volumetric LV dilatation. The present study cohort consisted of patients with advanced HF and therefore, the percentage of discrepant definitions of LV dilatation was relatively low. We could also suggest that LV remodelling is a complex process, and there are different stages involved, and the differentiation of those stages may not follow the order of the groups created in the study.

In terms of outcomes, both linear and volumetric definitions for LV dilatation were independently associated with outcomes in the present cohort. However, the new insight of this study is highlighted by the combination of both definitions and its association with outcomes. Patients with HF and concordant definition of LV dilation exhibited the worse outcomes as compared with the other groups. In addition, the outcome of patients with LV dilation based on volumetric definition but with normal LV linear dimension did not differ from that of patients with normal LV volume. This is an interesting finding as the group with inconsistent definition of LV dilation (dilated based on linear dimension but not on volumetric definition) may reflect a much earlier stage of the heart failure process and therefore, they may be the patients that most benefit from heart failure therapies.

## Study limitations

The present study is a single-centre, retrospective study that included patients who were imaged with CMR. Therefore, there may be a selection bias that has not been accounted for in the study. Prospective validation of the present results warrants further studies.

# Conclusions

In patients with HF and LVEF < 50%, the prevalence of LV dilatation may change according to the definition used. While the majority of patients present both increased LVEDDi and LVEDVi, 20% show discordant values. Patients with LV dilatation based on LVEDDi and LVEDVi have the worse clinical outcomes as compared with patients without LV dilatation by either measurement.

**Conflict of interest:** V.D. received speaker fees from Edwards Lifesciences, GE Healthcare, Medtronic, Philips, and Novartis and consulting fees from Edwards Lifesciences, MSD and Novo Nordisk. A.B.-G. has participated in advisory and/or lectured for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor. The remaining authors have nothing to disclose.

## Data availability

The data underlying this article could be shared on reasonable request to the corresponding author.

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### 4.2. Second Original Research Article

Prognostic value of left atrioventricular coupling index in heart failure

Kasa G, Teis A, De Raffele M, Cediel G, Juncà G, Lupón J, Santiago-Vacas E, Codina P, Bayés-Genis A, Delgado V.

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ORIGINAL PAPER

# Prognostic value of left atrioventricular coupling index in heart failure

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**Aims** To investigate the distribution of left atrioventricular coupling index (LACI) among patients with heart failure and left ventricular ejection fraction (LVEF) < 50% and to explore its association with the combined endpoint of all-cause death or HF hospitalization at long-term follow-up.

**Methods and results** Patients with HF and LVEF < 50% undergoing cardiac magnetic resonance were evaluated. Patients with atrial fibrillation or flutter were excluded. Left atrioventricular coupling index was measured as the ratio between the left atrial (LA) and the LV end-diastolic volumes. Patient population was divided according to LACI tertiles and followed up. Total of 478 patients (mean age 62 ± 12 years, 78% male) were included. The median value of LACI was 27.1% (interquartile range 19.9–34.5). Patients within the worst LACI tertile (≥30.9%) showed smaller LV volumes and larger LA volumes as compared with patients in the first or second tertile (LACI 6.2–22.2 and LACI 22.3–30.9, respectively). Left atrioventricular coupling index was significantly associated with the combined endpoint [hazard ratio (HR) 1.87, $P = 0.01$]. After adjusting for sex, age, ischaemic HF aetiology, LVEF, LA reservoir strain, diabetes mellitus, LV scar, mitral regurgitation, and LVEDVi, LACI remained significantly associated with the combined endpoint (HR 1.77, $P = 0.02$). Patients with the highest LACI values had worse outcomes compared with patients in first and second tertiles (HR 1.69, $P = 0.02$ and HR 1.77, $P = 0.02$, respectively).

**Conclusion** In patients with HF and LVEF <50%, LACI is independently associated with adverse events. Patients with most impaired left atrioventricular coupling have the worst clinical outcomes.

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† These authors contributed equally to this manuscript.

## Structured Graphical Abstract

### Key question

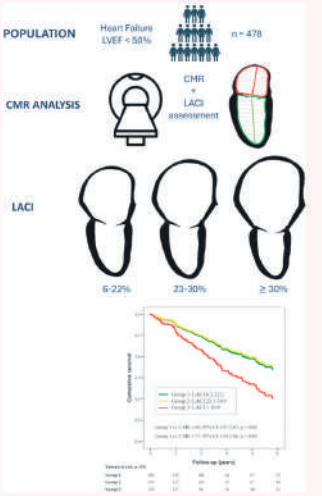
In patients with heart failure and left ventricular ejection fraction <50%, what is the distribution of left atrioventricular coupling and what is its prognostic value?

### Key finding

The most severe form of left atrioventricular uncoupling (LACI) ≥30% was present in one-third of the patients, and it was associated with increased all-cause death or heart failure hospitalization.

### Take home message

Left atrioventricular uncoupling is a valuable marker of left-sided cardiac remodelling and can help in the risk stratification of patients with heart failure and left ventricular ejection fraction <50%.




The association between left atrioventricular coupling index (LACI) and adverse outcomes in heart failure with reduced ejection fraction. Left atrioventricular coupling index was independently associated with all-cause death or heart failure (HF) hospitalization in a large HF cohort with left ventricular ejection fraction <50% without history of atrial fibrillation or flutter. According to LACI tertiles, the group 3 with the highest LACI values showed worst clinical adverse outcomes compared with the other two groups.


**Keywords** left atrioventricular coupling • cardiac magnetic resonance • heart failure

# Introduction

The assessment of left atrial (LA) dimensions and function has recently gained attention. Particularly, LA volumetric function and strain indices have been included in unsupervised machine learning algorithms leading to distinct cardiac phenogroups associated with cardiac events such as myocardial infarction, heart failure, atrial fibrillation, non-fatal stroke, and cardiovascular death.[1] The left atrium is the reservoir of blood drained by the pulmonary veins, buffers the increased left ventricular (LV) filling pressures avoiding its transmission to the pulmonary circulation and contributes to 30% of the left ventricular stroke volume.[2] These LA functions are influenced by the LA compliance, relaxation and contractility, LV end-diastolic pressures, and the pulmonary venous return. Particularly important is the assessment of the LA function integrated with the LV function.

The left atrioventricular coupling index (LACI) is a parameter that reflects the interplay between the LA function and the LV end-diastolic pressures. Left atrioventricular coupling index is measured as the ratio between the LA and LV end-diastolic volumes.[3] While atrial fibrillation is the maximum expression of left atrioventricular uncoupling, there are various clinical scenarios where left atrioventricular coupling may be impaired reflecting the inability of the LA to compensate the dysfunction of the left ventricle.[4–6] The association between impaired LACI and the occurrence of atrial fibrillation,[6,7] heart failure,[3,5,8] reinfarction,[4] and stroke[3] has been shown in various studies. However, limited data are available on the frequency of left atrioventricular uncoupling and its association with adverse clinical outcomes in patients with heart failure and LV ejection fraction <50%. Accordingly, the aim of this study was to characterize the phenotypes of patients with HF and LV ejection fraction (LVEF) < 50% and various grades of left atrioventricular

uncoupling as assessed with LACI and to investigate the association between LACI and the occurrence of clinical outcomes at follow-up.

# Methods

## Patient population

Patients ≥18 years old with heart failure symptoms who underwent clinically indicated cardiac magnetic resonance (CMR) at the Germans Trias University Hospital (Badalona, Spain) from 2009 to December 2021 were retrospectively identified. Patients were selected if LVEF at the time of CMR was <50%. The initial number of patients identified was 564. Of these 564 patients, only 550 had available LACI values. Seventy-two patients had history of atrial fibrillation or atrial flutter (13%) and were excluded from the analysis. Other exclusion criteria were patients <18 years of age and incomplete CMR studies mainly due to artefacts in the aquisition of cine sequences.

Demographic data, comorbidities, renal function, and heart failure therapies were retrieved from clinical records. Estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft–Gault formula. Ischaemic heart failure was defined by the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography.[9] The study complied with the personal data law protection and the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study (REGI-UNIC PI-18-037 and ICOR-2019-04-EB-IDI).

## Cardiac magnetic resonance data acquisition protocol

Cardiac magnetic resonance was performed on a 1.5 T scanner (Intera dSTREAM 1.5T; Philips, Best, the Netherlands) following a standardized protocol, with the patient in supine position and a 16-element phased-array coil placed over the chest. Images were acquired during breath-holds with electrocardiographic gating. Cine long-axis (2-, 3-, and 4-chamber views) and short-axis slices (contiguous slices of 8-mm thickness covering from base to apex of the ventricles) were acquired using segmented k-space steady-state free precession sequences. Delayed enhancement images were acquired with a segmented gradient-echo inversion-recovery sequence at matching cine-image slice locations 10–20 min after intravenous gadolinium-diethylenetriamine penta-acetic acid administration (Gadovist, 0.15 mmol/kg). Inversion time was optimized to achieve myocardial nulling. Pre- and post-contrast myocardial T1-mapping were acquired using the modified look-locker inversion recovery sequences. Myocardial extracellular volume (ECV) was computed considering T1 time values and haematocrit. The haematocrit to calculate ECV was assessed on the same day of the CMR data acquisition.

## Cardiac magnetic resonance data analysis

All CMR images were analysed off-line with a commercially available post-processing software (QMass-MR, v.8.1; Medis Medical Imaging Systems, Leiden, the Netherlands). The left and right ventricular volumes were obtained from the short-axis cine images tracing the endocardial borders in the end-diastolic and end-systolic frames, excluding the papillary muscles from the tracing. The LV mass was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and then multiplying by the tissue density (1.05 g/mL). Left ventricular mass and volumes were indexed to body surface area, according to current recommendations.[10] Myocardial fibrosis was assessed visually by signal intensity on late gadolinium enhancement (LGE) sequences, and the distribution, location, and extension (number of segments affected by LGE) were reported.

Long-axis 2- and 4-chamber cine images were used to evaluate the LA dimensions. Left atrial volumes were performed by manual tracing of the LA endocardial border excluding the pulmonary veins and the LA appendage. Left atrial volumes were measured both in systole and diastole using commercially available software (QStrain Version 8.1, Medis, Leiden, the Netherlands). The maximum LA volume was assessed at a ventricular end-systolic frame (LAVMax) whereas the minimum LA volume was measured at a late ventricular diastolic frame after atrial contraction (LAVMin) and both volumes were indexed to body surface area, according to current recommendations.[10] Body surface area was measured by Du Bois and Du Bois body surface area (BSA) equation.

Feature-tracking CMR-derived analysis of the LV and LA function was performed to measure LV global longitudinal strain (GLS) and LA reservoir strain (LARS) with a commercially available software (QStrain Version 8.1, Medis, Leiden, the Netherlands). Left ventricular endocardial contours were automatically drawn in the longitudinal 2, 3 and 4-chamber cine views through all cardiac cycle and adjusted if necessary. Left atrial endocardial contours were manually traced at end-diastole and end-systole in the longitudinal 2-chamber cine view, excluding LA appendage and pulmonary veins. To improve tracking accuracy, the tracking quality was visually assessed, and manual adjustments were made. LA reservoir strain was estimated from the first peak of the LA strain curve.

Left atrioventricular coupling index was calculated as the ratio between the LA and the LV end-diastolic volumes. The LA and LV volumes were measured in the same end-diastolic phase, defined by the mitral valve closure.[3,8,11]

## Follow-up

All patients were followed up at the HF clinic at established follow-up time points. The clinical evaluation and treatment of patients were directed by the treating physician according to a unified protocol based on current clinical practice guidelines recommendations.[12–17] Heart failure hospitalization was defined as hospital admission for ≥24 h in patients with a primary diagnosis of HF, with ≥1 symptom and ≥2 physical examination, laboratory, or invasive findings of heart failure, and receiving a heart failure-specific treatment.[18] The primary endpoint of the study was the combined endpoint of all-cause death or HF hospitalization (whichever came first) during 5 years of follow-up. The events were identified from the clinical records of patients with HF, hospital wards, the emergency room, general practitioners, and by contacting the patient's relatives. Mortality data were verified by the databases of the Catalan and Spanish Health Systems and the Spanish National Death Registry. Hospitalizations were identified from the clinical records of patients with HF, hospital wards, and the shared electronic health record in Catalonia.

## Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 22, 2013) software. Normal distribution of continuous variables was assessed by visualization of the histograms and applying the Shapiro–Wilk test. Variables with normal distribution are presented as mean ± standard deviation, while those with non-normal distribution are presented as median and interquartile range. The patient population was divided according to LACI tertiles: Group 1: LACI from 6.2 to 22.2%, Group 2: LACI from 22.3 to 30.9%, and Group 3: LACI ≥ 30.9%. Continuous variables were compared between groups using the unpaired one-way ANOVA test. Categorical variables were compared by the $\chi^2$ test with Yates correction or the Fisher exact test. For not normally distributed continuous variables, the Kruskal–Wallis test with Bonferroni correction was used. The association between LACI and the combined clinical endpoint was assessed with Cox proportional regression models. The proportional hazards assumptions for Cox models were tested using Schoenfeld residuals. Logarithmic transformation of the continuous variables with non-normal distribution was performed in the regression analysis. Statistically significant variables in the univariate regression analysis were included in the multivariate regression analysis applying the 'one-in-ten' rule to avoid model overfitting of the model.[19] Cumulative incidence curves of the combined endpoint were plotted according to LACI tertiles. A 2-tailed *P* value of 0.05 was considered statistically significant.

**Table 1 Patient clinical characteristics**

| | All $n = 478$ | Group 1 (LACI 6.2–22.2%) $n = 160$ | Group 2 (LACI 22.3–30.9) $n = 159$ | Group 3 (LACI ≥ 30.9%) $n = 159$ | *P*-value |
|---|---|---|---|---|---|
| Clinical characteristics | | | | | |
| Age (years) | 62 ± 12 | 61 ± 11 | 62 ± 11 | 64 ± 12 | 0.06 |
| Male, *n* (%) | 373 (78) | 121 (76) | 126 (79) | 126 (79) | 0.67 |
| BSA (kg/m$^2$) | 1.85 ± 0.2 | 1.84 ± 0.2 | 1.85 ± 0.2 | 1.85 ± 0.2 | 0.93 |
| Hypertension, *n* (%) | 289 (60) | 93 (58) | 95 (60) | 101 (64) | 0.60 |
| Diabetes mellitus, *n* (%) | 197 (41) | 57 (36) | 64 (40) | 76 (48) | 0.08 |
| Dyslipidaemia, *n* (%) | 293 (61) | 92 (58) | 106 (67) | 95 (60) | 0.22 |
| Smoker, *n* (%) | 131 (27) | 48 (30) | 46 (29) | 37 (23) | 0.35 |
| Obesity, *n* (%) | 113 (24) | 39 (24) | 36 (23) | 38 (24) | 0.92 |
| LBBB, *n* (%) | 179 (37) | 78 (49) | 58 (36) | 43 (27) | <0.001[e,f] |
| Ischaemic HF, *n* (%)[h] | 202 (42) | 66 (41) | 75 (47) | 61 (38) | 0.06 |
| NYHA class II/III, *n* (%)[a] | 364 (81)/30 (7) | 121 (76)/10 (6) | 127 (80)/7 (4) | 116 (73)/13 (8) | 0.51 |
| Mitral regurgitation (Grades I, II, III), *n* (%) | 283 (59)/115 (24)/25 (5) | 88 (55)/46 (29)/5 (3) | 100 (63)/35 (22)/10 (6) | 95 (60)/34 (21)/10 (6) | 0.23 |
| Laboratory | | | | | |
| Haemoglobin (g/dL)[b] | 13 ± 1.8 | 13 ± 1.5 | 13 ± 2 | 14 ± 1.8 | 0.38 |
| NT-proBNP (pg/mL)[c] | 1091 (466–2727) | 898 (370–1965) | 1047 (433–2748) | 1295 (599–3848) | 0.06 |
| eGFR (mL/min/1.73 m$^2$)[d] | 70 ± 25 | 73 ± 25 | 74 ± 23 | 63 ± 25 | <0.001[f,g] |
| Treatment | | | | | |
| Beta-blocker, *n* (%) | 422 (88) | 143 (89) | 144 (91) | 135 (85) | 0.25 |
| ACEinh/ARBs, *n* (%) | 343 (72) | 122 (76) | 119 (75) | 102 (64) | 0.03[f,g] |
| ARNi, *n* (%) | 56 (12) | 20 (13) | 17 (11) | 19 (12) | 0.88 |
| MRA, *n* (%) | 353 (74) | 124 (78) | 115 (72) | 114 (72) | 0.43 |
| Loop diuretics, *n* (%) | 347 (73) | 110 (69) | 115 (72) | 122 (77) | 0.28 |

All values are *n* (%), mean ± SD, except for NT-proBNP values which are presented as median (interquartile range). The chi-square test was used for categorical variables, analysis of variance for normally distributed variables, and the Kruskal-Wallis test for non-normally distributed continuous variables. Post hoc pairwise comparisons were executed with Bonferroni correction.

ACEinh/ARBs, angiotensin-converting-enzyme inhibitor/Angiotensin receptor blockers; ARNi, angiotensin receptor/neprilysin inhibitor; BSA, body surface area; eGFR, estimated glomerular filtration rate; HF, heart failure; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]NYHA class data available in 451 patients.

[b,c,d]Haemoglobin, NTproBNP and eGFR levels available in 334, 306, and 375 patients, respectively.

[e]Demonstrates statistically significant differences ($P < 0.05$) between Groups 1 and 2.

[f]Demonstrates statistically significant differences ($P < 0.05$) between Groups 1 and 3.

[g]Demonstrates statistically significant differences ($P < 0.05$) between Groups 2 and 3.

[h]Ischaemic heart failure was defined by the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography. Non-ischaemic HF involved the rest of the HF aetiologies in this cohort, the most frequent non-ischaemic HF aetiology being DCM (30% of patients). The aetiologies of the remaining HF patients in our study are as follows (in order of frequency): alcoholic cardiomyopathy, hypertensive cardiomyopathy, drug-induced cardiomyopathy, valvular heart disease, non-compaction cardiomyopathy, tachy cardiomyopathy, peripartum cardiomyopathy, hypertrophic cardiomyopathy, cardiac amyloidosis.

# Results

## Patient population

A total of 478 consecutive patients with HF and LVEF <50% (mean age 62 ± 12 years, 78% male) were included for analysis. Patient clinical characteristics and CMR data are reported in *Tables 1* and *2*, respectively. Ischaemic HF was present in 42% of the patients whereas the remaining patients had non-ischaemic HF, being dilated cardiomyopathy the most frequent aetiology (30%). The median value of LACI was 27.1% (IQR 19.9–34.5).

When comparing the groups of patients divided according to the tertiles of LACI, patients within the worst LACI tertile (≥30.9%) were older, had higher proportion of diabetes, and showed higher values of NT-proBNP and worse renal function as compared to the other groups. Patients within the worst LACI tertile received less frequently HF medication such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers but received higher doses of diuretics and presented a minor percentage of left bundle branch block. Mitral regurgitation was present in 89% of the patients ($n = 425$), of which almost 83% had mild to moderate grade of mitral regurgitation. The presence and grade of mitral regurgitation did not differ significantly across the groups.

In terms of CMR characteristics, patients within the worst LACI tertile showed statistically significant smaller LV volumes and larger LA volumes as compared with their counterparts and better LVEF (*Figure 1*), although this comparison did not reach statistical significance. ECV values were observed in patients within the worst LACI tertile

**Table 2 Cardiac magnetic resonance characteristics**

| | All $n = 478$ | Group 1 (LACI 6.2–22.2%) $n = 160$ | Group 2 (LACI 22.3–30.9%) $n = 159$ | Group 3 (LACI ≥ 30.9%) $n = 159$ | *P*-value |
|---|---|---|---|---|---|
| LVEDVi (mL/m$^2$) | 124 ± 41 | 142 ± 45 | 130 ± 38 | 122 ± 37 | <0.001[b,c] |
| LVESVi (mL/m$^2$) | 95 ± 37 | 104 ± 43 | 94 ± 37 | 87 ± 36 | 0.001[b,c] |
| LVEF (%) | 29 ± 10 | 28 ± 9 | 29 ± 9 | 30 ± 10 | 0.14 |
| LVMi (g/m$^2$) | 90 ± 26 | 94 ± 27 | 90 ± 26 | 85 ± 25 | 0.01[c] |
| LVGLS (%) | −10.3 ± 4 | −10.5 ± 5 | −10.4 ± 4 | −10.3 ± 4 | 0.93 |
| T1 mapping (ms)[a] | 1069 ± 62 | 1071 ± 67 | 1061 ± 49 | 1071 ± 60 | 0.43 |
| ECV (%)[a] | 34 ± 7 | 33 ± 6 | 33 ± 6 | 35 ± 9 | 0.05 |
| LGE, *n* (%) | 393 (82) | 130 (81) | 127 (80) | 136 (86) | 0.39 |
| LGE[e] extension | 4.8 ± 4 | 4.6 ± 4 | 4.8 ± 4 | 4.9 ± 4 | 0.38 |
| LAVMin index (mL/m$^2$) | 37 ± 19 | 24 ± 9 | 35 ± 10 | 54 ± 22 | <0.001[b,c,d] |
| LAVMax index (mL/m$^2$) | 57 ± 21 | 44 ± 13 | 57 ± 14 | 71 ± 23 | <0.001[b,c,d] |
| LARS | 20 ± 9 | 25 ± 10 | 20 ± 8 | 14 ± 7 | <0.001[b,c,d] |
| LACI (%) | 27.1 (19.9–34.5) | 17.5 (14.0–20.1) | 27.1 (24.5–28.8) | 40.5 (34.5–48.2) | <0.001[b,c,d] |

All values are *n* (%), mean ± SD, except for LACI values which are presented as median (interquartile range). The $\chi^2$ test was used for categorical variables, analysis of variance for normally distributed variables, and the Kruskal–Wallis test for non-normally distributed continuous variables. *Post hoc* pairwise comparisons were executed with Bonferroni correction.
ECV, extracellular volume; LACI, left atrioventricular coupling index; LARS, left atrial reservoir strain; LAVMin, left atrial minimum volume; LAVMax, left atrial maximum volume; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVGLS, left ventricular global longitudinal strain; LVMi, left ventricular mass index.
[a]T1 mapping and ECV data available values available in only 263 patients.
[b]Demonstrates statistically significant differences ($P < 0.05$) between Groups 1 and 2.
[c]Demonstrates statistically significant differences ($P < 0.05$) between Groups 1 and 3.
[d]Demonstrates statistically significant differences ($P < 0.05$) between Groups 2 and 3.
[e]LGE extension: myocardial fibrosis/necrosis assessed visually (not by percentage) by signal intensity on LGE sequences, and extension reported as the number of myocardial segments affected by LGE.

although there were no differences in presence or extension of LGE and T1 native time values across the groups.

## Association between left atrioventricular coupling and outcomes

Over a median follow-up of 2.8 years (IQR 1.4–5.0), all-cause death or first HF hospitalization occurred in 110 patients (23%). All-cause death occurred in 68 patients (14%) and HF hospitalization in 59 patients (12%), respectively. The causes of death in the present cohort were cardiovascular in 46%, cancer in 27%, infectious diseases in 19%, neurological in 3%, traffic accidents in 2%, respiratory in 2%, and haemorrhagic in 1% of patients. The cumulative rates of the combined endpoint according to the three study subgroups were as follows: 36 patients in Group 1 (23%), 29 patients in Group 2 (18%), and 45 patients in Group 3 (28%). Left atrioventricular coupling index was significantly associated with the combined primary endpoint (HR 1.87, 95% CI 1.17–2.99, $P = 0.01$; *Table 3*). After adjusting for sex, age, ischaemic HF aetiology, diabetes mellitus, mitral regurgitation, LV end-diastolic volume index (LVEDVi), LVEF, presence of LGE and LARS, LACI remained significantly associated with the combined primary endpoint (HR 1.77, 95% CI 1.10–0.86, $P = 0.02$; *Table 3*) together with sex, age, ischaemic HF aetiology, and LVEDVi. When analysing the survival curves according to the LACI tertiles, patients in Group 3 (LACI ≥30.9%) had worse outcome as compared with patients in Groups 1 and 2 (HR 1.69, 95% CI 1.07–2.67, $P = 0.02$ and HR 1.77, 95% CI 1.10–2.86, $P = 0.02$, respectively), whereas no statistical differences were observed between the clinical outcomes of patients in Groups 1 and 2 (*Figure 2*).

# Discussion

The main findings of the present study are summarized as follows: patients with HF and LVEF < 50% the highest LACI values (Group 3, worst left atrioventricular coupling) had remarkably worse clinical outcomes as compared with patients with better left atrioventricular coupling. Left atrioventricular coupling index was significantly associated with all-cause death or heart failure hospitalization even after adjusting for clinical and imaging prognostic parameters.

## Left atrioventricular coupling

The pathophysiology of HF is diverse and, usually, remodelling of the left ventricle is the hallmark to classify patients with HF. To maintain the stroke volume and ejection fraction, the LV remodels with dilatation and/or hypertrophy in response to volume or pressure overload and to myocardial injury such as myocardial infarction.[20] The LV filling by the left atrium is also key to maintain the LV systolic function.[2] The LV end-diastolic pressure and the compliance and contractility of the LV and LA are important determinants of the LV filling.[21] The LV remodelling leads to various grades of LA remodelling with dilatation and fibrosis.[22] However, the proportion of the LA remodelling relative to the LV remodelling in patients with HF has not been extensively evaluated.

The left atrio-ventricular coupling, measured by the LACI, is a parameter that reflects the remodelling of the LA relative to the remodelling of the LV. A high value of LACI represents an excessive LA remodelling relative to the LV dilation and indicates greater impairment of the left atrioventricular coupling. Left atrioventricular coupling index has been first explored in a large cohort of asymptomatic individuals with

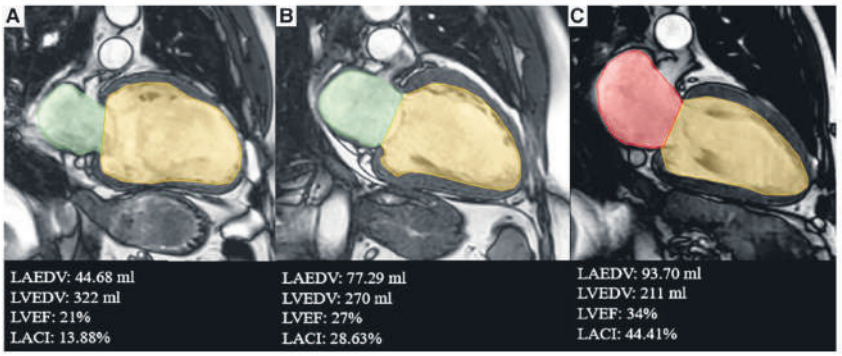



**Figure 1** Assessment of LACI with cardiac magnetic resonance. The long-axis two chamber cine images of cardiac magnetic resonance studies are shown to illustrate how LACI is calculated in three patients with heart failure and left ventricular ejection fraction <50%. (*A*) Shows a patient with the best left atrioventricular coupling (first tertile) as compared to the patients in (*B*) (second tertile) and (*C*) (third tertile). LACI, left atrioventricular coupling index; LAEDV, left atrial end-diastolic volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

**Table 3 Univariable and multivariable Cox regression analyses**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P*-value** | **HR (95%CI)** | ***P*-value** |
| Sex | 1.28 (0.83–1.98) | 0.26 | 1.59 (1.02–2.48) | 0.04 |
| Age | 1.04 (1.02–1.06) | <0.001 | 1.04 (1.02–1.06) | <0.001 |
| Ischaemic HF aetiology | 1.89 (1.29–2.77) | 0.001 | 1.83 (1.23–2.73) | 0.003 |
| Presence of diabetes mellitus | 1.46 (1.00–2.12) | 0.05 | | |
| Grades of MR | 1.29 (1.01–1.64) | 0.04 | | |
| LVEDVi | 1.01 (1.00–1.01) | 0.02 | 1.01 (1.00–1.01) | <0.001 |
| LVEF | 0.97 (0.96–0.99) | 0.01 | | |
| Presence of LGE | 1.93 (1.04–3.60) | 0.04 | | |
| LARS | 0.97 (0.94–0.99) | 0.001 | | |
| LACI | | 0.02 | | 0.02 |
| Tertile 3 vs. tertile 1 | 1.54 (0.99–2.39) | 0.06 | 1.69 (1.07–2.67) | 0.02 |
| Tertile 3 vs. tertile 2 | 1.87 (1.17–2.99) | 0.01 | 1.77 (1.10–2.86) | 0.02 |
| Tertile 1 vs. tertile 2 | 1.21 (0.74–1.98) | 0.44 | 1.05 (0.64–1.72) | 0.85 |

LACI tertile 1 (LACI 6.2–22.2%), LACI tertile 2 (LACI 22.3–30.9), LACI tertile 3 (LACI ≥ 30.9%).
HF, heart failure; HR, hazard ratio; LACI, left atrioventricular coupling index; LARS, left atrial reservoir strain; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

cardiovascular risk factors in the Multi-Ethnic Study of Atherosclerosis (MESA).[5] In those individuals, the mean value of LACI was 17.0% ± 8.0. In the present study, the median value of LACI was 27.1% (IQR 19.9–34.5), which is remarkably higher than the asymptomatic patients in the MESA study cohort, thus representing a higher risk patient population with symptomatic HF. Recently, Fortuni *et al.*[23] reported a median value of LACI 29% (IQR 19–42) in a large cohort of patients with HF. However, the study included a broad range of patients with HF (including also patients with preserved LVEF), and LACI was measured with echocardiography which could explain the differences compared with the present study. Cardiac magnetic resonance offers an accurate visualization of LA wall with high spatial resolution. Normal ranges for LA volumes relative to gender, age, and body surface area have consistently been defined.[24,25] Left atrial reservoir strain has demonstrated prognostic value for predicting cardiovascular events and has shown to be the most reproducible LA functional parameter by CMR.[25–27] The present study provides additional information on the phenotyping of patients with HF and LVEF < 50% by CMR. The patients with the worst LACI tertile showed smaller LV volumes and larger LA volumes as compared with the other groups suggesting the presence of stiffer LV causing LA remodelling disproportionate to the LV dilatation. Therefore, it could be hypothesized that patients with worst LACI could have restrictive LV

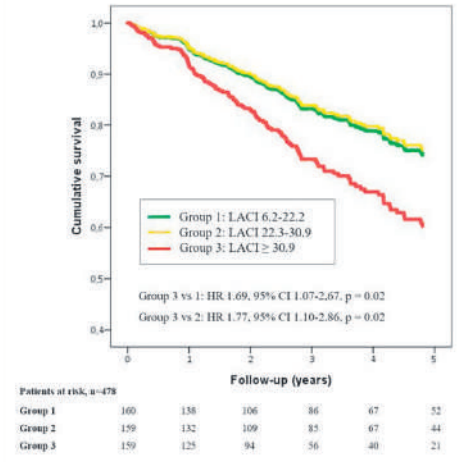



**Figure 2** Survival curves for the combined endpoint of all-cause death or heart failure hospitalization at 5 years of follow-up. Survival curves according to Cox regression analysis for LACI tertile groups; variables included in multivariate analysis are as follows: sex, age, ischaemic HF aetiology, presence of diabetes mellitus, grades of mitral regurgitation, LV end-diastolic volume index (LVEDVi), LVEF, presence of LGE, and LARS.

physiology. This is important since LACI may help guide optimal HF medical therapy in this group of patients with a different pattern of cardiac remodelling.

## Prognostic value of LACI

The prognostic value of LACI has been explored in various clinical scenarios. In a large cohort of asymptomatic individuals with traditional cardiovascular risk factors in the MESA study, LACI was independently associated with incident HF, atrial fibrillation, and cardiovascular disease over a 10-year follow-up.[3,5] In patients with hypertrophic cardiomyopathy, LACI was associated with the occurrence of new-onset AF, and the prognostic value was incremental to conventional echocardiographic parameters of LA remodelling improving the risk stratification of those patients.[6] In a large cohort of patients with acute myocardial infarction, LACI was significantly associated with major cardiovascular events during follow-up, particularly among patients with an LVEF <35%.[4] The present study provides additional evidence on the association between LACI and cardiovascular outcomes in a large cohort of patients with HF and LVEF < 50%. This association was independent of other clinical and CMR parameters that are used in isolation to characterize and risk stratify patients with HF. Therefore, LACI may become an important holistic parameter that combines the systolic and diastolic LV function.

## Study limitations

The limitations of present study relate to the single centre and retrospective design that included patients who were imaged with CMR. Therefore, we cannot exclude a selection bias and the generalizability of the results needs to be explored in further studies. In addition, data on native T1 mapping values were only available in 263 patients, which could explain why there were no differences across the groups in contrast to the significant differences in ECV values.

# Conclusions

In patients with HF and LVEF <50%, LACI was independently associated with all-cause death or HF hospitalization. Patients with the highest LACI values (most impaired left atrioventricular coupling) had remarkably worse outcomes. Left atrioventricular coupling index should be considered as an alternative and feasible imaging marker to improve risk stratification in patients with HF with LVEF < 50% in further studies.

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## Data availability

The data underlying this article could be shared on reasonable request to the corresponding author.

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# SUMMARY OF RESULTS

# SUMMARY OF RESULTS

The original articles included in the compendium of this thesis aim to explore the objectives previously described. A large cohort of patients with HF symptoms and LVEF <50% who underwent clinically indicated CMR in our terciary hospital were included.

### 5.1. Correlation and prognostic value of linear and volumetric definition of LV dilatation in patients with HF and LVEF<50% using CMR

In the first article we explored the agreement and prognostic implications of LV dilatation defined by LVEDDi and LVEDVi in a large cohort of patients with HF and LVEF <50% using CMR. The patient population consisted of a total of 564 patients (median age 64 years; 79% men). Ischemic HF was present in 42% of the patients whereas the remaining patients had non-ischemic HF, dilated cardiomyopathy being the most frequent etiology (30%). Published cut-off values for LV linear and volumetric dimensions were used to define presence of LV dilatation. Based on the concordance of the volumetric and the linear definitions of LV dilatation, 4 different groups were created: Group 1 (normal LVEDDi and LVEDVi), Group 2 (increased LVEDDi but normal LVEDVi), Group 3 (normal LVEDDi but increased LVEDVi) and Group 4 (increased both LVEDDi and LVEDVi). The distribution of the patients across these four groups are as follows: 66 patients in group 1 (12%), 27 patients in group 2 (5%), 85 patients in group 3(15%), 386 patients in group 4 (68%).

Patients with concordant definition of LV dilatation (Group 4) had the highest N-terminal pro B type natriuretic peptide (NT-proBNP) values and presence of left bundle branch block. LVEF progressively decreased and LV end-systolic volume index (LVESVi) progressively increased from Group 1 to 4. LV mass index (LVMi) was higher in patients with increased LVEDVi (Groups 3 and 4). LGE was present in the majority of the patients (82%) and it was more frequently observed in patients of the Group 2 and Group 4.

### 5.1.1. Correlation between linear and volumetric definitions of LV dilatation using CMR in patients with HF and LVEF <50%

In our cohort of patients with HF and LVEF <50%, LVEDDi had a modest correlation with LVEDVi on linear regression analysis (r=0.682, p<0.001, Figure 9). LV dilatation based on volumetric criteria was present in the majority of the patients (n=471, 84%) while only 73% (n=413) met the criteria for dilatation based on linear measurements. Notably, 20% of patients exhibited discordant classifications of LV dilatation when comparing linear and volumetric assessments.

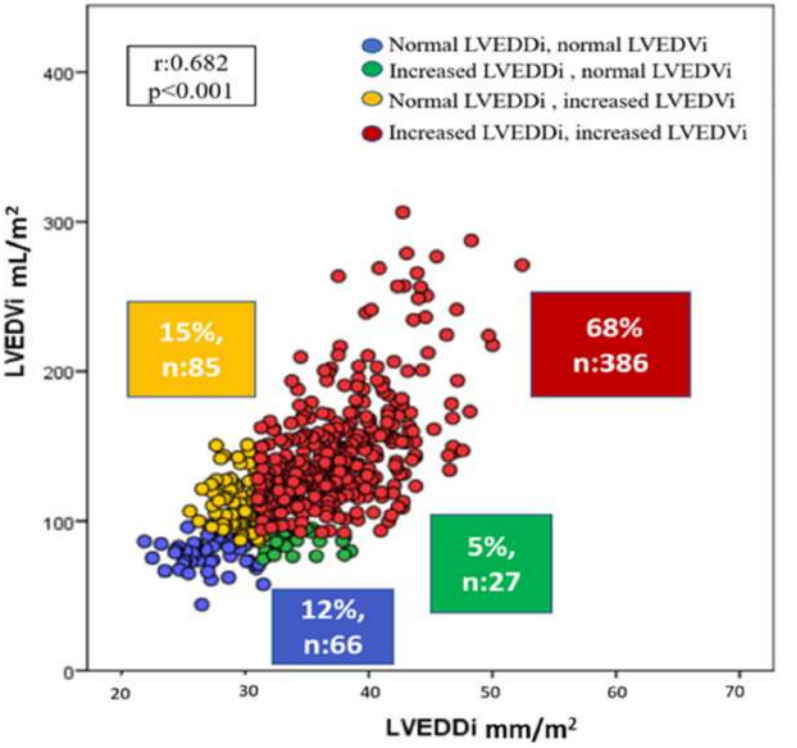


**Figure 8.** Scatter plot representing correlation between left ventricular end-diastolic diameter index (LVEDDi) and left ventricular end-diastolic volume index (LVEDVi).

### 5.1.2. Prognostic value of linear and volumetric definition of LV dilatation using CMR in patients with HF and LVEF <50%

Patients were followed-up for a period of five years to assess the combined endpoint of cardiovascular death or HF hospitalization. Over a median follow-up of 2.8 years, the combined endpoint occurred in 105 patients (19 %). Specifically, cardiovascular death occurred in 56 patients (10%), while HF hospitalization in 85 patients (15%). Based on the predefined subgroups, the cumulative incidence of the combined endpoint was as follows: 5 patients in Group 1 (7.6%), 2 patients in Group 2 (7.4%), 5 patients in Group 3 (5.9%), 93 patients in Group 4 (24.1%).

Both, LV dilatation according to LVEDDi and LVEDVi, were significantly associated with the combined endpoint of cardiovascular death or HF hospitalization after adjusting for sex, age, ischemic HF aetiology, HF categories based on LVEF and presence of diabetes mellitus, hypertension and LGE (HR 3.29, 95% CI 1.72-26.29, p<0.001 and HR 2.80, 95% CI 1.30-6.03, p=0.009; respectively). When analyzing the survival curves according to LV dilatation groups, only patients with concordant dilatation of LV (Group 4) had a worse outcome as compared to those with concordant non-dilatation of LV (HR 3.00, 95% CI 1.15-7.81, p = 0.024).

## 5.2. CMR-based LACI in patients with HF and LVEF <50%

In the second article, we explored the distribution of LACI among patients with HF and LVEF <50% and its association with the combined endpoint of all-cause death or HF hospitalization. A total of 478 patients (mean age 62±12 years, 78% male) free of atrial fibrillation or flutter were included.

### 5.2.1. Distribution of LACI in patients with HF and LVEF<50%

LACI was calculated as the ratio between the LA and the LV end-diastolic volumes, using CMR. The median value of LACI was 27.1% (interquartile range 19.9-34.5). Patient population was divided according to LACI tertiles

and followed-up. The values of LACI according to tertiles were as follows: LACI tertile 1 (LACI 6.2-22.2%), LACI tertile 2 (LACI 22.3-30.9), LACI tertile 3 (LACI≥30.9%).

Patients within the worst LACI tertile (≥30.9%) were older, had higher proportion of diabetes and showed higher values of NT-proBNP and worse renal function as compared to the other groups. Patients with the highest LACI values (worst LACI tertile) received less frequently HF medication such as ACE inhibitors or ARBs but received higher doses of diuretics and presented a minor percentage of left bundle branch block. Mitral regurgitation was present in 89% of the patients (n=425) in the entire cohort, of which almost 83% had mild to moderate grade of mitral regurgitation. However, the presence and grade of mitral regurgitation did not differ significantly across the groups. In terms of CMR characteristics, patients within the worst LACI tertile showed smaller LV volumes and larger LA volumes as compared to their counterparts and better LVEF, although this comparison did not reach statistical significance (Figure 10).

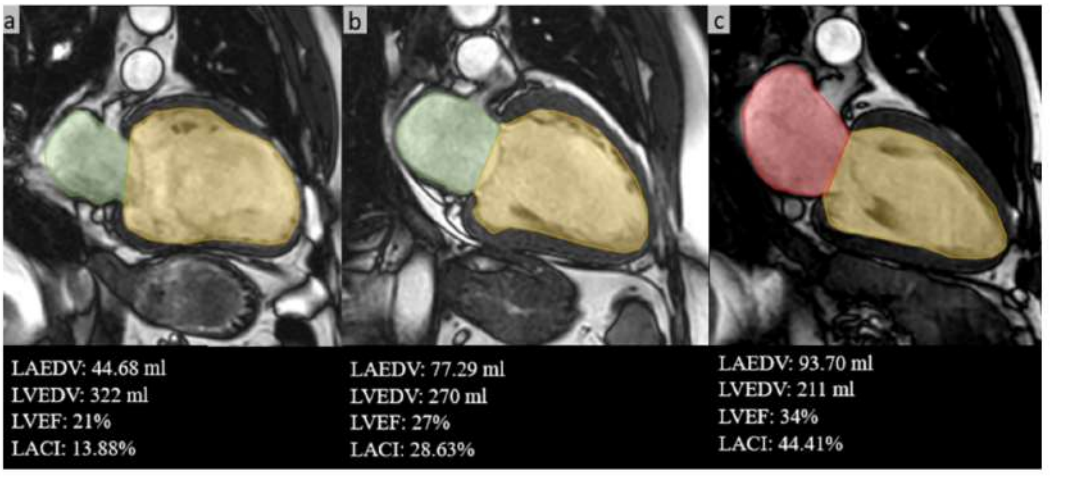


**Figure 9.** Assessment of LACI with CMR. Panel a shows a patient with the best left atrioventricular coupling (first tertile) as compared to the patients in panels b (second tertile) and c (third tertile).

There were no differences in presence or extension of LGE and T1 native time values across the groups. However, higher extracelular volume values were observed in patients within the worst LACI tertile.

### 5.2.2. Prognostic value of LACI in patients with HF and LVEF <50%

Over a median follow-up of 2.8 years (IQR 1.4-5.0), all-cause death or first HF hospitalization occurred in 110 patients (23%).

All-cause death occurred in 68 patients (14%) and HF hospitalization in 59 patients (12%). The cumulative rates of the combined endpoint according to the three study subgroups were as follows: 36 patients in Group 1 (23%), 29 patients in Group 2 (18%), 45 patients in Group 3 (28%).

LACI was significantly associated with the combined primary endpoint (HR 1.87, 95% CI 1.17-2.99, p=0.01). After adjusting for sex, age, ischemic HF aetiology, diabetes mellitus, mitral regurgitation, LVEDVi, LVEF, presence of LGE and LARS, LACI remained significantly associated with the combined primary endpoint (HR 1.77, 95% CI 1.10-.86, p=0.02) together with sex, age, ischemic HF aetiology and LVEDVi.

When analyzing the survival curves according to the LACI tertiles, patients in Group 3 (LACI ≥30.9%), had worse outcome as compared to patients in Groups 1 and 2 (HR 1.69, 95% CI 1.07-2.67, p=0.02 and HR 1.77, 95% CI 1.10-2.86, p=0.02 respectively), whereas no statistical differences were observed between the clinical outcomes of patients in groups 1 and 2.

# SUMMARY OF DISCUSSION

# SUMMARY OF DISCUSSION

This doctoral thesis aims to address the objectives outlined at the beginning of the project. Comprehensive CMR analysis techniques were employed to assess LV and LA structure and function in patients with HF and LVEF <50%. The results from both articles included in this compendium underscore the prognostic significance of CMR-based remodeling markers, emphasizing the value of a holistic approach to the assessment of cardiac remodeling.

### 6.1. LV dilatation by CMR in patients with HF and LVEF <50%

According to the results of the first article, LVEDDi had a modest correlation with LVEDVi when measured with CMR. The presence of discordant definition of LV dilatation based on the combination of both LVEDDi and LVEDVi was 20% of the patients with HF suggesting a significant proportion of patients that may be misclassified. Both LVEDDi and LVEDVi were independently associated with the primary outcome (the combined endpoint of cardiovascular death or HF hospitalization) and those patients with concordant linear and volumetric definition for LV dilatation had worse outcomes.

Many studies have demonstrated the prognostic value of LV diameters or volumes in HF setting. There is a large body of evidence relating the changes in LVESV, LVEDV and LVEF with cardiovascular outcomes (11). In patients with acute MI, increasing LVESV on baseline CMR and an increase in LVEDV>15% at 6 months of follow-up was significantly associated with the occurrence of heart failure, ventricular arrhythmias or cardiovascular death (52). Similarly, among patients with HF of ischemic origin, LVESV and LVEDV measured with CMR have shown to be incremental to LVEF (123). Additionally, LV diameters are also important values to define LV remodelling and to decide timing of intervention, for example in valvular heart disease (37, 38). The echocardiographic data from the Valsartan heart Failure Trial showed that increasing LVEDDi was independently associated with poor outcomes (36). The reduction in LV end-systolic and end-diastolic diameters by various heart failure therapies was directly correlated with a favourable effect on mortality as demonstrated by a

recent meta-analysis (124). Based on this evidence, it could be established that both volumetric and linear dimensions of the LV would be excellent surrogates to assess the risk of adverse cardiovascular outcomes and the effects of heart failure therapies. However, there is no study so far demonstrating that this assumption is valid.

In the present cohort of patients with HF and LVEF <50%, the correlation between linear and volumetric assessment of LV remodelling was moderate, with 20% of patients presenting discrepancies between the definition of LV dilatation according to linear versus volumetric assessment. It could be hypothesized that in ischemic cardiomyopathy, the discrepancy between linear and volumetric LV dilatation definitions could be explained by the infarct location that would lead to specific LV local remodeling (for example, an inferior or inferolateral myocardial infarction would result in larger linear LVEDDi but still normal LVEDVi). However, the clinical cause of HF did not differ between those with concordant or discordant definition of LV dilatation. The discrepancies observed could also be explained by the timing of the CMR imaging: in the early process of the LV remodeling, the discrepancy between linear and volumetric LV dilatation could be more prominent whereas in a much later stage of the disease, the LV remodeling is more global having consistent definitions of linear and volumetric LV dilatation. We could also suggest that LV remodeling is a complex process, with different stages involved, and the differentiation of those stages may not follow the order of the groups created in the study.

In terms of outcomes, both linear and volumetric definitions for LV dilatation were independently associated with adverse events in this cohort. However, the key insight of this study lies in the combined assessment of both definitions and its association with outcomes. Patients with HF who exhibited concordant definition of LV dilatation based on both linear and volumetric criteria, experienced the worse outcomes as compared to the other groups. Notably, patients with LV dilatation defined only by volumetric criteria but with normal linear dimensions, had similar outcomes to those with normal LV volumes. This is particularly relevant, as the subgroup with discordant LV dilatation defined only by linear dimensions may represent an earlier stage in the HF continuum.

Therefore, these patients could potentially derive the greatest benefit from timely iniciation of HF therapies.

### 6.2. LACI in patients with HF and LVEF <50%

The main findings of the second article are summarized as follows: patients with HF and LVEF<50% and worst left atrioventricular coupling had remarkably worse clinical outcomes as compared to patients with better left atrioventricular coupling. LACI was significantly associated with all-cause death or heart failure hospitalization even after adjusting for clinical and imaging prognostic parameters.

LV remodels with dilatation and/or hypertrophy in response to volume or pressure overload and to myocardial injury, to maintain stroke volume and LVEF. The LV filling by the LA is essential to maintain the LV systolic function (70). The LV remodeling leads to various grades of LA remodeling with dilatation and fibrosis (125). However, the proportion of the LA remodeling relative to the LV remodeling in patients with HF has not been extensively evaluated.

The left atrioventricular coupling, measured by LACI, is a parameter that reflects the remodeling of the LA relative to the remodeling of the LV. A high value of LACI represents an excessive LA remodeling relative to the LV dilation and indicates greater impairment of the left atrio-ventricular coupling. LACI has been first explored in a large cohort of asymptomatic individuals with cardiovascular risk factors in the Multi-Ethnic Study of Atherosclerosis (116). In those individuals, the mean value of LACI was 17.0% ± 8.0. In the present study with patients with HF and LVEF<50%, the median value of LACI was 27.1% (IQR 19.9–34.5) which is remarkably higher than the asymptomatic patients in the Multi-Ethnic Study of Atherosclerosis cohort, thus representing a higher risk patient population with symptomatic HF.

Recently, a large HF study including 1158 patients with chronic HF, reported a median value of LACI 29% (IQR 19-42) and demonstrated that LACI was associated with severity of LV diastolic dysfunction and all-cause death or HF

hospitalization (122). However, the study included a broad range of patients with HF (including also patients with preserved LVEF) and LACI was measured with echocardiography.

The present study provides additional information on the phenotyping of patients with HF and LVEF<50% by CMR. The patients with the worst LACI tertile showed smaller LV volumes and larger LA volumes as compared to the other groups suggesting the presence of stiffer LV causing LA remodeling disproportionate to the LV dilatation. We hypothesize that patients with worst LACI could have a more restrictive LV physiology and LACI may help guide optimal HF medical therapy in this group of patients with a different pattern of cardiac remodeling.

### 6.2.1. Prognostic value of LACI in patients with HF and LVEF <50%

The prognostic value of LACI has been explored in different clinical scenarios. In a large cohort of asymptomatic individuals with traditional cardiovascular risk factors in the Multi-Ethnic Study of Atherosclerosis, LACI was independently associated with incident HF, atrial fibrillation and cardiovascular disease over a 10-year follow-up (116, 126). In patients with hypertrophic cardiomyopathy, LACI was associated with the occurrence of new-onset atrial fibrillation and the prognostic value was incremental to conventional echocardiographic parameters of LA remodeling improving the risk stratification of those patients (119). In a large cohort of patients with acute MI, LACI was significantly associated with major cardiovascular events during follow-up, particularly among patients with an LVEF <35% (117).

The present study provides additional evidence on the association between LACI and cardiovascular outcomes in a large cohort of patients with HF and LVEF<50%. This association was independent of other clinical and CMR parameters that are used in isolation to characterize and risk stratify patients with HF. Therefore, LACI may become an important holistic parameter that combines the systolic and diastolic LV function.

### 6.3. Limitations

In both original research articles of the doctoral thesis, the limitations relate to the single-center and retrospective design of the studies that included patients who were imaged with CMR. Therefore, we cannot exclude a selection bias and the generalizability of the results needs to be explored in further studies. In reference to the second article on LACI, data on native T1 mapping values were only available in 263 patients which could explain why there were no differences across the groups in contrast to the significant differences in ECV values. Prospective validation of the present results of both articles warrants further studies.

# CONCLUSIONS

# CONCLUSIONS

The conclusions derived from this thesis project are:

1. Comprehensive CMR evaluation provides extensive characterization of cardiac remodeling and allows risk stratification in HF patients with LVEF <50%.

2. In patients with HF and LVEF<50%, LVEDDi has a modest correlation with LVEDVi when measured by CMR. 20% of patients display discordant definition of LV dilatation based on the combination of both LVEDDi and LVEDVi.

3. In patients with HF and LVEF<50%, both LVEDDi and LVEDVi are independently associated with cardiovascular death or HF hospitalization and those patients with concordant linear and volumetric definition for LV dilatation have worse clinical outcomes.

4. In patients with HF and LVEF <50%, LACI is significantly associated with all-cause death or heart failure hospitalization even after adjusting for clinical and imaging prognostic parameters. Patients with HF and LVEF <50% and the most impaired left atrioventricular coupling have remarkably the worse outcomes.

# FUTURE RESEARCH DIRECTIONS

# FUTURE RESEARCH DIRECTIONS

The original research articles included in the compendium of this doctoral thesis provide new insights from CMR on cardiac remodeling in HF patients with LVEF <50%. In agreement with the results of both articles, we may suggest the following research directions in the future:

1. Assessment of cardiac remodeling in HF patients with reduced and preserved LVEF, including evaluation of both linear and volumetric parameters of LV dilatation using CMR in a larger number of patients with prospective design.

2. Application of artificial intelligence in detection of cardiac remodeling in HF patients with LVEF <50% in multimodal cardiac imaging.

3. Defining the association of CMR measured LACI with new-onset atrial fibrillation, stroke, HF hospitalization and cardiovascular death, in prospective studies, including HFrEF and HFpEF patients.

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# ANNEX

# ANNEX

## 10.1 Review Article

**Latest Updates in Heart Failure Imaging**

Kasa G, Bayes-Genis A, Delgado V.

Heart Fail Clin. 2023 Oct;19(4):407-418. English.

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# Latest Updates in Heart Failure Imaging

Gizem Kasa, MD, Antoni Bayes-Genis, MD, PhD, Victoria Delgado, MD, PhD*

**KEYWORDS**

• Multimodality imaging • Heart failure • Echocardiography • Cardiac magnetic resonance

**KEY POINTS**

- Cardiac imaging plays a crucial role in the accurate diagnosis of heart failure (HF).
- Echocardiography is commonly used as the initial imaging technique, with left ventricular ejection fraction (LVEF) being the main parameter for classification of HF and risk stratification.
- LVEF alone is not sufficient to diagnose the HF etiology and personalize the decision-making. In the most contemporary HF guidelines, the need to integrate novel cardiac function measurements, such as evaluation of left ventricular diastolic function and myocardial deformation, has been highlighted.
- Multimodality imaging, especially cardiac magnetic resonance with myocardial tissue characterization, is key to diagnose etiology of HF and provides incremental prognostic value.

## INTRODUCTION

Heart failure (HF) is a complex clinical syndrome. Symptoms occur when structural and/or functional abnormality of the heart results in elevated intracardiac pressures and/or inadequate cardiac output. Despite major therapeutical advances, HF remains a major public health problem. Due to the population growth, aging, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future.[1,2] Identifying the cause of HF is important because each cause may require specific treatment. Cardiac imaging has a crucial role in the classification of HF and the accurate diagnosis of the underlying cause.

Phenotyping of HF is the first approach to classify patients with HF symptoms and initiate treatment. For decades, this classification has been based on left ventricular ejection fraction (LVEF) measures. Although randomized clinical trials have shown efficacy of HF medical and device-based therapies in patients with LVEF 40% or lesser,[3] the efficacy of new specific medical therapies in patients with mildly reduced or preserved LVEF has not been demonstrated until recently.[4,5] Participant-level data analysis from recent randomized clinical trials has shown that the benefits of combining mineralocorticoid receptor antagonists, angiotensin-receptor neprilysin inhibitor, and sodium-glucose cotransporter 2 inhibitors extended up to an LVEF of 65%, questioning the usefulness of HF classification based on this functional parameter.[6] In addition, phenotyping HF with LVEF may not be enough, particularly if we aim to detect subclinical left ventricular (LV) systolic dysfunction in population at risk of HF (Stages A and B) and prevent the occurrence of clinically symptomatic HF.

The latest American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines maintain the LVEF-based HF classification; however, there is clear emphasis on adding new objective measures such as the evidence of increased LV filling pressures in patients with HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF). In this regard, exercise stress testing and echocardiographic evaluation of diastolic parameters are of importance. Furthermore, the

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incremental value of myocardial deformation parameters, such as global longitudinal strain (GLS), to predict the risk of developing HF or recurrent HF hospitalizations is also highlighted. The use of natriuretic peptides is also recommended in the most contemporary HF guidelines[3,7] but they will not be discussed in this review, which is focused on imaging.

Although echocardiography is the imaging technique most frequently used for a first evaluation of patients with HF, multimodality imaging is key to diagnose the etiology of HF and provides incremental prognostic value. Cardiac magnetic resonance (CMR) provides the unique characteristic of noninvasive myocardial tissue characterization, key aspect in differential diagnosis of cardiomyopathies.[8,9] Coronary computed tomography angiography is increasingly used to rule out the presence of ischemic heart disease (particularly in patients with low-to-intermediate pretest probability for coronary artery disease). In addition, nuclear cardiology techniques permit visualization of cellular metabolism and diagnosis of inflammatory causes of HF.

In this review article, an overview of the latest advances in multimodality imaging for diagnosis and risk stratification of patients with HF will be appraised. New diagnostic and prognostic imaging insights will be discussed.

## PHENOTYPING HEART FAILURE

Currently international guidelines advocate the use of LVEF to phenotype HF into 3 categories: HF with reduced EF (LVEF $\leq$40%), HFmrEF (LVEF between 41% and 49%), and HFpEF (LVEF $\geq$50%).[3,7] The management and outcomes of the patients may vary significantly based on this LVEF-based classification. A recent meta-analysis including more than 120,000 patients with HF showed that patients with HFmrEF had better prognosis as compared with patients with HFrEF but similar prognosis as compared with patients with HFpEF.[10]

Furthermore, in the latest ACC/AHA guidelines, a new category of HF is highlighted: HF with improved EF including patients with HF and an initial LVEF less than 40% that improves to greater than 40% at follow-up.[7] Although improvement in LVEF is associated with better outcomes, it does not mean full myocardial recovery or normalization of LV function. In most patients, cardiac structural abnormalities, such as LV chamber dilatation and ventricular systolic and diastolic dysfunction, may persist, and most importantly, LVEF can decrease after withdrawal of pharmacological treatment. LVEF is an imperfect parameter of LV performance because it only considers the change in volume of the LV and does not consider the effective stroke (forward) volume (eg, in patients with HF and severe mitral regurgitation). In addition, LVEF does not accurately reflect the structural changes that precede overt LV systolic dysfunction. The measurement of LV deformation by strain imaging has emerged as a powerful tool to accurately quantify myocardial mechanics, including longitudinal, circumferential, and radial deformation.[11] Strain is a dimensionless measurement of change in length between 2 points,[12] and LV GLS is defined as the change in the LV myocardial length of various LV myocardial segments between diastole and systole divided by the original end-diastolic length.[13] The measurement of LV GLS is more reproducible than the measurement of LVEF, and it is less influenced by loading conditions (**Fig. 1**).[11]

Impairment of LV GLS occurs earlier than impairment of LVEF. Several studies have demonstrated impaired LV GLS among asymptomatic patients with risk factors such as hypertension[14] and diabetes[15] and have normal LVEF. The underlying mechanism that explains the preservation of LVEF while LV GLS is impaired is the fact that LV circumferential shortening (determined by the midmyocardial layers) increases to compensate the impairment of LV GLS. The LV myocardium has specific disposition of the myocardial fibers: the subendocardial fibers are oriented as a right-handed helix while the subepicardial fibers show a left-handed helix orientation. The transition from the subendocardium to the subepicardium leads to the circumferentially oriented midwall fibers. Although the shortening of the subendocardial and subepicardial layers determine mainly the LV GLS, the shortening of the midmyocardial layers determines the circumferential strain. The LV subendocardium is often the first layer affected in a myocardial injury (ie, ischemia, pressure, or volume overload). Therefore, LV GLS impairs earlier than the circumferential strain, which tries to compensate and keep LV stroke volume and LVEF preserved. In individuals without HF and normal LVEF, LV GLS may be impaired in as much as 17% as shown in general population studies, probably reflecting the effects of aging on LV function,[16] and between 35% and 45% among individuals with diabetes.[17,18]

Among patients with HFpEF, the subanalysis of the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial showed that 66% of the patients had impaired LV GLS despite having an LVEF greater than 50% and 50% of the patients had an LV GLS less than 15.8%,[14] which is rather low considering

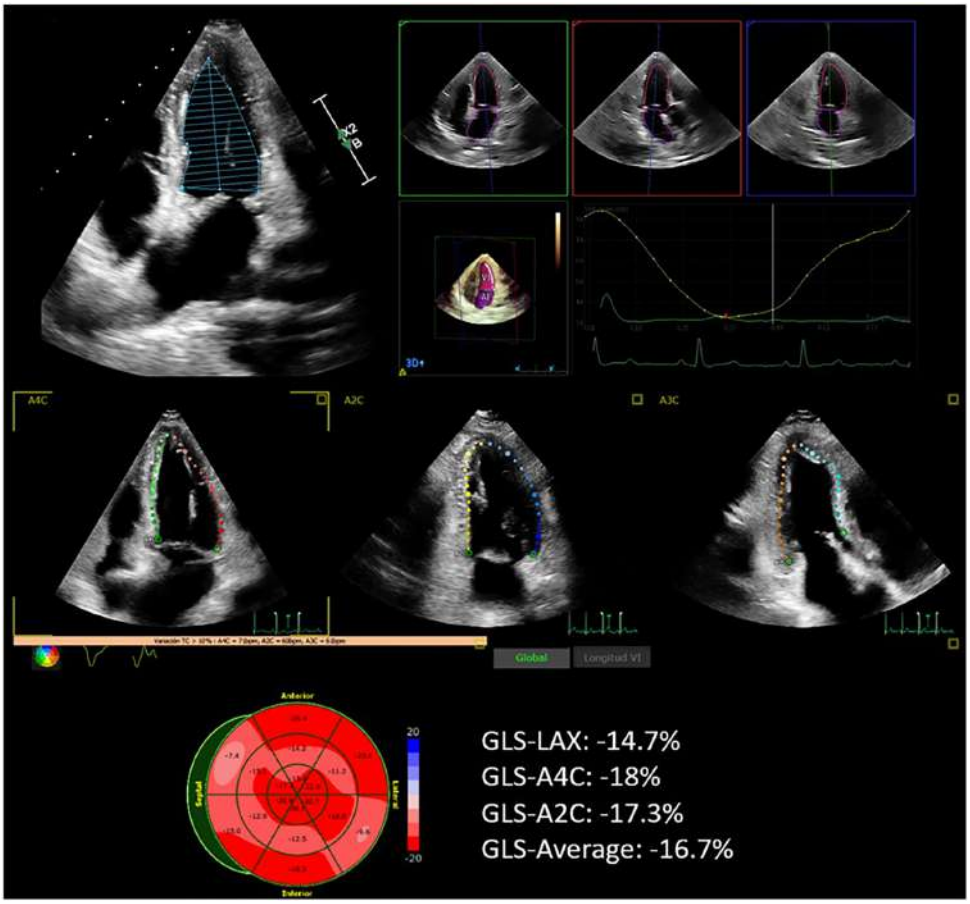


**Fig. 1.** *Speckle tracking GLS of the left ventricle to detect subclinical left ventricular dysfunction.* Example of a 60-year-old woman receiving oncological therapy and showing impaired left ventricular GLS despite preserved LVEF measured with biplane 2D Simpson method (65%) and 3-dimensional echocardiography (58%). A2C, apical 2-chamber view; A4C, apical 4-chamber view; LAX, long-axis view.

that the lower limit of a normal value is 18%.[19] Importantly, each 1% decrease in LV GLS was associated with 14% increase in the risk of the primary composite outcome, HF hospitalization alone, and cardiovascular death alone.

Fig. 2 illustrates the underlying pathophysiological mechanisms explaining the discrepancy between LVEF and LV GLS. Any mechanical, ischemic, or metabolic myocardial injury leads to structural changes that consist of diffuse deposition of highly cross-linked collagen fibers and myocyte apoptosis and replacement fibrosis.[20] These structural derangements result in increased cardiomyocyte afterload and preload due to the collagen stiffening, impaired perfusion reserve due to perivascular fibrosis and capillary rarefaction, and abnormal electrical conduction.[21] The extent and chronicity of these structural derangements will influence LV systolic and diastolic function that will be detected with LVEF and other parameters of diastolic function. However, LV GLS can reflect these structural changes at an earlier stage. LV GLS can be measured with echocardiography, CMR, and more recently ECG-gated computed tomography.[19–23] However, myocardial fibrosis is more frequently detected with CMR tissue characterization techniques. Particularly, diffuse reactive myocardial fibrosis is detected with T1 mapping, a quantitative method that tracks the recovery of the longitudinal magnetization of the tissue (Fig. 3). In native myocardium (without use of gadolinium), T1 relaxation time prolongs

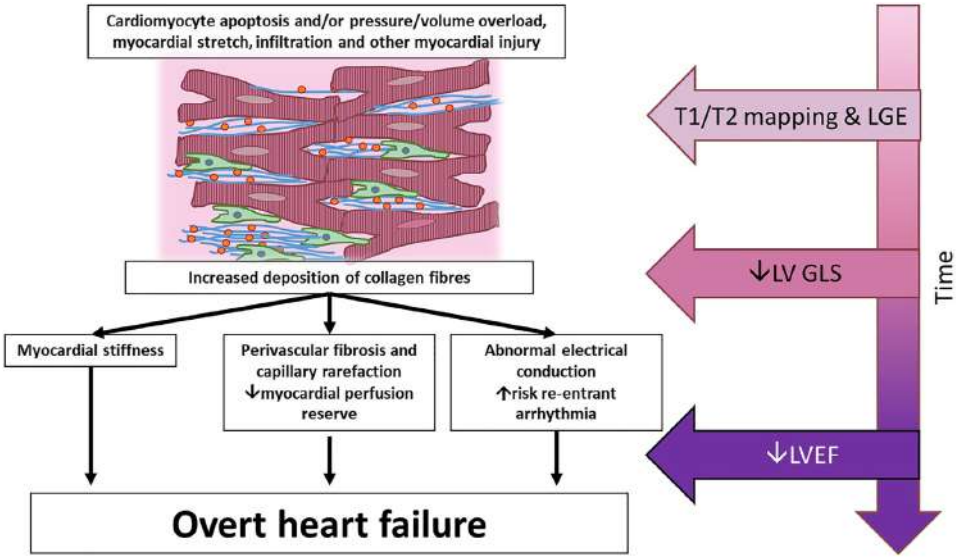


**Fig. 2.** *Time course of structural derangements of the myocardium and functional consequences evaluated with imaging techniques.* In response to myocardial injury and cardiomyocyte death, the extracellular matrix presents an increased deposition of collagen fibers and other cells that are profibrotic. At this time point, T1 and T2 mapping as well as LGE CMR can detect these early anatomical changes. The functional consequences can be detected with decreased left ventricular GLS while LVEF may remain normal. The initial deposition of collagen fibers leads to increased myocardial stiffness, perivascular fibrosis, and reduced myocardial perfusion and abnormal conduction increasing the risk of arrhythmias. Over time, these changes lead to overt HF when LVEF is reduced.

along with the amount of fibrosis of the myocardium, whereas the administration of gadolinium shortens the T1 relaxation time because the gadolinium accumulates in the increased interstitial space.[24] The extracellular volume (ECV) fraction can be calculated from the measurement of the T1 relaxation times pregadolinium and postgadolinium administration and has an excellent

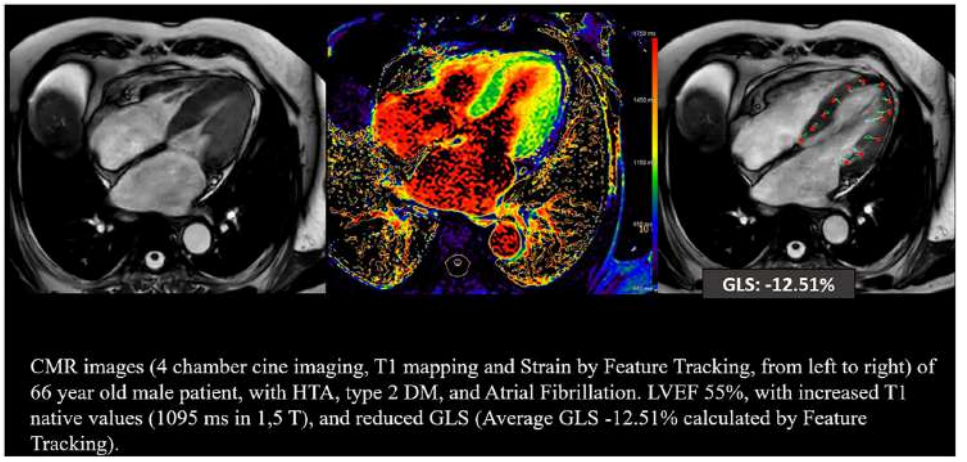


**Fig. 3.** *Assessment of reactive myocardial fibrosis with T1 mapping CMR.* Example of a 66-year-old patient with arterial hypertension, diabetes mellitus, and atrial fibrillation. Left panel shows the cine image of the 4-chamber view. Note the dilated atria and thickened left ventricular myocardium. The central panel shows the T1 mapping sequence with an increased native T1 time of 1095 milliseconds. The panel on the right shows the assessment of GLS of the left ventricle with feature tracking, which results in an impaired value.

correlation with the ECV measured on histological samples. T1 mapping techniques have shown useful to identify and risk stratify patients with HFpEF.[24] In a prospective study of 112 individuals (62 with HFpEF, 22 with hypertension, and 28 healthy control subjects), an ECV fraction greater than 31.2% measured on CMR identified the patients with HFpEF with 100% sensitivity and 75% specificity.[25] In addition, together with LV GLS, ECV fraction was significantly associated with reduced exercise capacity. The hemodynamic consequences of increased ECV fraction were evaluated in an invasive study including 24 patients with HFpEF and 12 patients without HF who underwent pressure-volume loop analysis with conductance catheter.[24] Patients with more ECV fraction had stiffer LV and longer time of active LV relaxation, which was associated with hypertensive exercise response.

The structural changes that lead to LV dysfunction may cause as well alterations of the cardiac metabolism, which in turn may impair LV function. Phosphorus (31P)-magnetic resonance spectroscopy (MRS) offers a unique window into the assessment of high-energy phosphate metabolism. High-energy phosphates occupy a central position in cardiac metabolism, coupling oxygen, and substrate fuel delivery to the myocardium with contractile work. A reduction in the phosphocreatine (PCr)/adenosine triphosphate (ATP) ratio is an energetic sign common to numerous conditions that can predispose to HF.[26] Human cardiac 31P-MRS studies have documented reductions in myocardial PCr/ATP ratio in nonischemic cardiomyopathy,[27–29] HFpEF,[30] hypertrophic cardiomyopathy,[31,32] hypertensive hypertrophy with or without HF,[33,34] severe aortic stenosis with or without HF,[35–37] among others. A reduction in the PCr/ATP ratio predicts prognosis in nonischemic cardiomyopathy,[38] and may improve with trimetazidine in HF,[39] after aortic valve replacement,[37–40] after weight loss,[41] suggesting that reduced PCr/ATP ratio is not necessarily simply an age-related phenomenon, and that energetics may be central to disease pathogenesis.[26] Although this technique seems promising in the characterization of patients with HF, the feasibility in routine clinical practice is limited to centers with high expertise in this imaging technique.

## CAUSE OF HEART FAILURE

Diagnosis of the underlying cause of HF is key to a personalized treatment. Ischemic heart disease is the most frequent cause of HF. A systematic review of multicenter HF treatment trials involving more than 40,000 patients during the past 30 years, coronary artery disease was the underlying cause of HF in nearly 65% of the patients.[42] This percentage is probably underestimated since the cause was not evaluated in a systemic manner in many trials (invasive coronary angiography was not systematically performed), and patients with a recent myocardial infarction, angina, or objective evidence of active ischemia were excluded.[42] The presence of significant coronary artery lesions in patients with HF is independently associated with a worse long-term outcome.[43] Therefore, an accurate diagnosis is important to implement secondary prevention measures to improve the outcomes. Noninvasive imaging tests, either anatomical or functional, are recommended in patients with an intermediate probability of coronary artery disease and an LVEF greater than 50%.[44] In patients with high probability of coronary artery disease, invasive coronary angiography is recommended and fractional flow reserve test is indicated to decide the need of revascularization. Recently, the 2021 ESC Practice Guidelines for the management of patients with HF upgraded the recommendation of performing a noninvasive computed tomography coronary angiography (CTCA) in patients with HF and an LVEF less than 50% while invasive coronary angiography is recommended in symptomatic patients who do not respond to treatment or have symptomatic ventricular arrhythmias and may be considered in patients with low-to-intermediate pretest probability of coronary artery disease.[3] CTCA provides information on coronary artery stenosis severity, as invasive coronary angiography does, and on characteristics of the arterial wall as well as coronary plaque features associated with an increased risk of ischemic events and plaque burden.[45] Furthermore, technological advances allow the assessment of the fractional flow reserve on computed tomography providing information on the hemodynamic consequences of the coronary stenosis.[46]

Nonischemic HF causes pose a greater diagnostic challenge than ischemic HF. Several causes of nonischemic HF have different pathophysiologic mechanisms that lead to LV dysfunction, and in addition, they may coincide with the presence of significant coronary artery disease. The 2021 ESC Practice Guidelines for the management of patients with HF proposed a new classification of the nonischemic cardiomyopathies[3]: valvular heart disease, hypertensive cardiomyopathy, infiltrative cardiomyopathy (sarcoid, hemochromatosis), familial/genetic cardiomyopathy, stress cardiomyopathy (Tako-tsubo), myocarditis (infectious, toxin or medication, immunological, hypersensitivity), and acquired diseases such as immuno-mediated diseases, cardiotoxicity,

peripartum cardiomyopathy neuromuscular disorders, and heart rhythm–related and endocrine or metabolic diseases. These different causes lead to different patterns of LV (and right ventricular) remodeling and myocardial structural changes that are better appreciated with imaging techniques that provide information on the tissue characteristics. Accordingly, CMR with the use of late gadolinium contrast-enhanced (LGE) images and other quantitative parameters such as T1-mapping and T2-mapping, and T2*-mapping is the most frequently used technique to first approach the nonischemic causes (**Fig. 4**). The presence of subendocardial or transmural LGE in a territory that follows the supply of a coronary artery suggests the presence of significant coronary artery disease and previous myocardial infarction. In contrast, nonischemic causes show more focal, patchy or midwall, and subepicardial location of the LGE. For example, midwall septal LGE is characteristic of idiopathic dilated cardiomyopathy, whereas inferolateral basal midwall LGE is observed in Andersen-Fabry disease and focal epicardial LGE is characteristic of cardiac sarcoidosis. Patchy, multifocal distribution in the hypertrophied regions or the junctions between the right and left ventricle are observed in hypertrophic cardiomyopathy, whereas diffuse LGE pattern with poor differentiation between the myocardium and the blood pool is characteristic of cardiac amyloidosis.[47]

The presence of myocardial edema detected with T2-weighted CMR sequences suggests the diagnosis of acute myocarditis, and it is one of the Lake Louise Criteria. The combination of altered T2 mapping and subepicardial or midwall LGE in patients with symptoms and increased troponin has a median area under the curve to diagnose myocarditis of 0.90.[48] T2 mapping is also useful in infiltrative cardiomyopathies such as cardiac amyloidosis and Fabry disease. Myocardial iron deposition in primary hemochromatosis can lead to dilated cardiomyopathy that is characteristically detected with T2* mapping. In addition, the timing of chelation therapy and its effectiveness can be monitored with T2* mapping.

Positron emission tomography (PET) imaging with 18 F-fluorodeoxyglucose (FDG) is being increasingly recognized as a valuable tool in the detection and monitoring of inflammatory diseases. Increased FDG uptake is a hallmark of inflammation. Compared with CMR, FDG-PET represents a different and more direct visualization of myocarditis by quantifying the metabolic activity of inflammatory cell infiltrates. Several case reports and studies have highlighted the utility of hybrid FDG-PET/CMR in the assessment of inflammatory conditions of the heart such as viral myocarditis,[49,50] cardiac sarcoidosis,[51,52] and Loeffler endocarditis.[53] In patients with unexplained increased LV wall thickness, HFpEF, familial amyloid polyneuropathy, family history of amyloidosis, calcific aortic stenosis with low flow low gradient in the elderly, and a history of bilateral carpal tunnel syndrome, $^{99m}$Technetium-bisphosphonate derivates scintigraphy facilitates the diagnosis of amyloid transthyretin (ATTR) cardiac amyloidosis.[54] The ratio of heart-to-contralateral lung uptake, heart-to-whole-body retention, and heart-to-bone ratio (visual grade) assessed at 1 and 3 hours after intravenous administration of bone-avid tracers are diagnostic parameters of cardiac amyloidosis on cardiac scintigraphy (**Fig. 5**). Perugini and colleagues demonstrated that a visual grade of 2 or greater on $^{99m}$Technetium-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD) cardiac scintigraphy had a 100% sensitivity to identify ATTR cardiac amyloidosis and 100% specificity to differentiate from amyloid immunoglobulin light chain

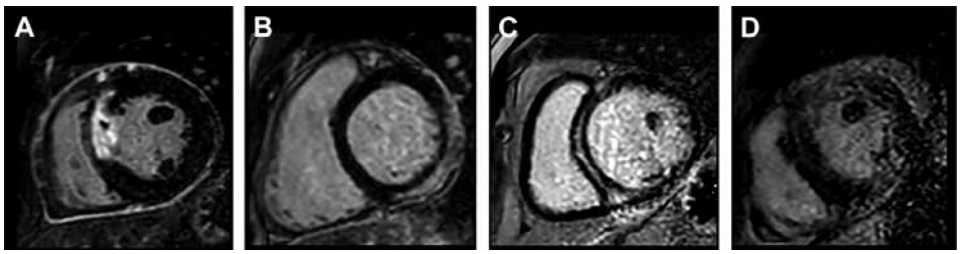


**Fig. 4.** *Late gadolinium-enhanced CMR to diagnose cause of HF.* Panel A shows an example of transmural myocardial infarction in the anterior interventricular septum. Subepicardial enhancement in the lateral and posterior walls of the left ventricle due to myocarditis is shown in panel B. Midwall fibrosis of the interventricular septum characteristic of idiopathic dilated cardiomyopathy is presented in panel C. Panel D shows concentric left ventricular hypertrophy with diffuse late gadolinium enhancement pattern and poor differentiation of the blood pool in a patient with cardiac transthyretin amyloidosis.

(AL) cardiac amyloidosis and controls.[55] It is important to emphasize that serum/urine immunofixation and serum free light chain assay excluding monoclonal process should be performed in all patients with suspected amyloidosis. In case of plasma cell dyscrasia, endomyocardial biopsy for histological diagnosis is still needed because 20% of patients with AL cardiac amyloidosis may show substantial uptake on cardiac scintigraphy.[56]

This extensive evidence highlights the key role of multimodality imaging in the etiologic diagnosis of nonischemic cardiomyopathies.

## EXERCISE IMAGING

In many patients with HF symptoms, LV systolic function may be preserved and the hemodynamic evaluation at rest may not show the underlying pathophysiology of fluid accumulation in the systemic and pulmonary circulation. Congestion is the hallmark of HF and is influenced by various hemodynamic and nonhemodynamic factors. Exercise induces changes in loading conditions that may unmask LV diastolic dysfunction that leads to high left-sided filling pressures and transient pulmonary transcapillary transudation.[57] In patients with dyspnea and preserved LVEF, invasive hemodynamic exercise testing demonstrating a pulmonary capillary wedge pressure of 25 mm Hg or greater confirms the diagnosis of HFpEF.[58] Noninvasive imaging exercise testing has shown feasibility and accuracy in diagnosing HF. Exercise stress echocardiography allows the assessment of LV diastolic function, presence of LV wall motion abnormalities, and impairment of mitral and tricuspid regurgitation, which can cause lung congestion. In addition, during the same exercise stress echocardiography, lung ultrasound can be performed and the presence of B-lines, which have been associated with cardiovascular outcomes, can be detected.[59] The presence of an average E/e' ratio during exercise 15 mm Hg or greater and a peak tricuspid regurgitation velocity of greater than 3.4 m/s suggests the presence of HFpEF.[58] More recently, combined cardiopulmonary and exercise echocardiography stress testing has shown the value of additional echocardiographic parameters to predict peak oxygen consumption ($VO_2$). In 357 patients (113 at risk of developing HF and 244 with HFpEF or HFrEF), Pugliese and colleagues[60] showed that peak LV systolic annulus tissue velocity (S'), peak tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure ratio (right ventricular-pulmonary arterial coupling) and left atrial compliance (measured as the ratio between left atrial reservoir strain and E/e' ratio) were independent predictors of $VO_2$. Using exercise-CMR, Backhaus and colleagues[61] demonstrated in 75 patients with echocardiographic signs of LV diastolic dysfunction and dyspnea on exertion that left atrial longitudinal strain during peak exercise was the most accurate parameter to detect HFpEF. Besides the structural changes that may underpin these functional abnormalities, it has been hypothesized that there may be an abnormal cardiac energetic state that impairs the active phase of the LV diastolic relaxation and leads to increased LV filling pressures and transient pulmonary congestion. This was demonstrated by Burrage and colleagues using phosphorous MRS and proton-density MRI sequence.[57] Across the spectrum of LV diastolic function (including 11

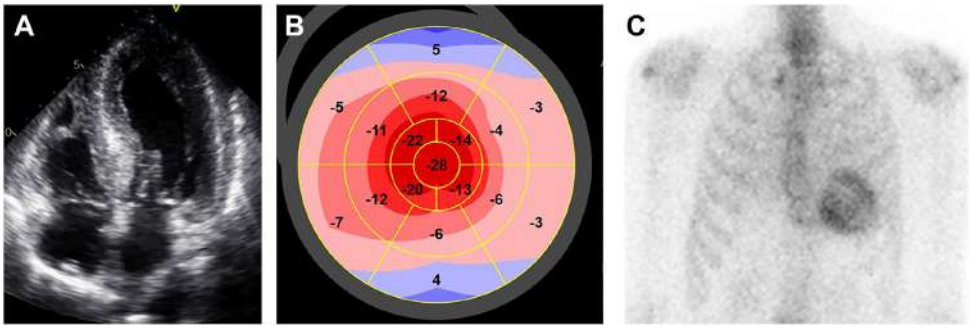


**Fig. 5.** *Diagnosis of transthyretin cardiac amyloidosis with scintigraphy.* Example of a 78-year-old patient with HF symptoms, bilateral tunnel carpal syndrome, and polyneuropathy symptoms in both legs. Panel A shows severe hypertrophy of the left and right ventricle. On speckle tracking analysis of left ventricular GLS, the typical apical cherry pattern with preserved shortening of the apical segments and impaired longitudinal strain of the mid and basal left ventricular segments can be observed (*B*). On $^{99m}$Tc-DPD cardiac scintigraphy, the uptake of the tracer is clearly shown in panel C.

healthy controls, 9 patients with type 2 diabetes mellitus, 14 patients with HFpEF, and 9 patients with cardiac amyloidosis), there was a progressive reduction in PCr/ATP ratio (measure of cardiac energetic state) along with increasing E/e' ratio. In addition, impaired cardiac energetic state was associated with lower LV diastolic filling rates and diastolic reserve, more left and right atrial dilation and worse right ventricular contractile reserve during low-intensity exercise. Furthermore, transient pulmonary congestion was observed in patients with HFpEF and cardiac amyloidosis while it was not observed in healthy controls and patients with type 2 diabetes mellitus.

## IMAGING FOR RISK STRATIFICATION OF HEART FAILURE

In recent trials including patients with HFrEF, advances in HF therapy have reduced significantly the proportion of deaths from a cardiac cause, whereas the proportion of noncardiovascular deaths has increased.[62] In patients with HFpEF, the mortality burden is also substantial and 50% to 70% of them are cardiovascular deaths, particularly driven by sudden cardiac death and HF death.[63] Compared with HFrEF, the proportions of cardiovascular deaths, sudden death and HF deaths are lower in HFpEF, whereas the proportion of noncardiovascular deaths in HFpEF exceeds that of HFrEF.[64] The majority of the studies evaluating the role of imaging for risk stratification of patients with HF have used as endpoint all-cause mortality. However, using cardiovascular death or HF-related death as endpoints may be more relevant. LVEF is the main parameter for risk stratification of HF regardless of the imaging technique used to measure it. However, it has been shown that 30% of patients with ischemic HF receiving an implantable cardiac defibrillator as primary prevention based on the presence of HF symptoms and an LVEF less than 35% do not benefit during follow-up.[65] Characterization of the arrhythmogenic substrate considering specific myocardial scar tissue features, the heterogeneous electrical activation and the interaction with myocardial sympathetic innervation is key to identify the patients at higher risk of sudden cardiac death.

Several large studies have demonstrated the association between LGE extent (myocardial scar/fibrosis) on CMR and the occurrence of sudden cardiac death in ischemic and nonischemic cardiomyopathies.[66–68] In addition, specific features of myocardial scar have been associated with ventricular arrhythmias. For example, a ringlike pattern of scar (involving at least 3 contiguous segments in the same short-axis slice) has shown to be independently associated with the composite endpoint of all-cause death and cardiac arrest due to ventricular fibrillation or hemodynamically unstable ventricular tachyarrhythmia and appropriate implantable cardioverter defibrillator shock.[69] Furthermore, in patients with ischemic HF, the so-called periinfarct zone (border zone consisting of bundles of collagen intermingled with viable myocardial tissue) has been shown to have specific corridors where reentrant ventricular arrhythmias can occur.[70]

This anatomical substrate may become unstable with the alteration of the milieu due to ischemia, altered sympathetic innervation, or electrolytes for example. PET and single photon computed tomography can detect denervated, viable myocardium, which is associated with an

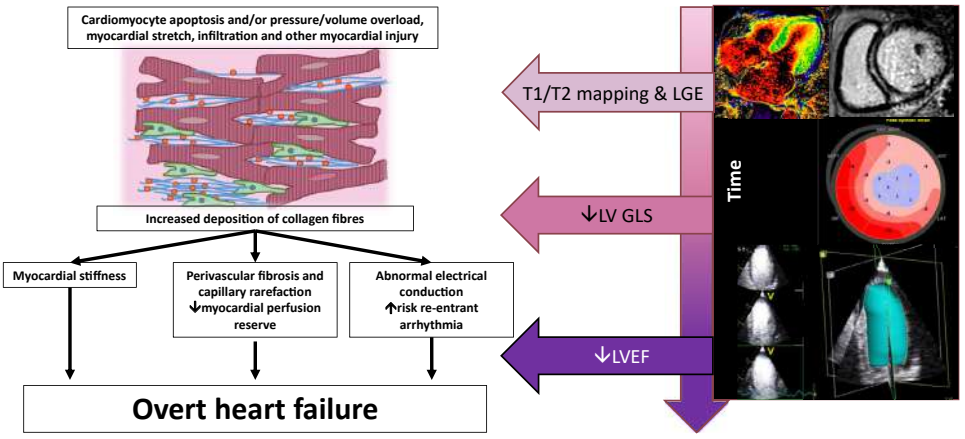


**Fig. 6.** Use of multimodality imaging to evaluate cardiac remodeling and function in patients with HF.

increased risk of ventricular arrhythmias. $^{123}$Iodine-metaiodobenzylguanidine scintigraphy is the most frequently used imaging technique to detect cardiac sympathetic innervation. On planar imaging, a low heart-to-mediastinum uptake ratio of this radiotracer, indicating myocardial denervation, has been associated with an increased risk of ventricular arrhythmias and sudden cardiac death.[71]

This accumulating evidence showing the importance of characterizing the myocardial substrate for risk stratification in patients with HF has been underscore in recent ESC guidelines on the management of ventricular arrhythmias where a significant number of recommendations for the use of multimodality imaging have been included.[72]

## SUMMARY

Multimodality imaging is key in the diagnosis of patients with HF symptoms (**Fig. 6**). Assessment of cardiac structure and function has increased in sophistication with the use of novel technologies such as strain imaging and assessment of cardiac energetics. Importantly, accurate diagnosis of cause of HF is key to provide a personalized treatment, and this requires the assessment of the myocardial tissue characteristics. Although endomyocardial biopsy remains the reference standard to define the cause, tissue characterization with noninvasive imaging modalities has become the first approach to diagnose the HF etiology.

## CLINICS CARE POINTS

- HF is a heterogeneous clinical syndrome. Diagnosis of the underlying cause of HF by multimodality imaging is key to a personalized treatment.
- Phenotyping HF with LVEF is not sensitive enough to detect subclinical left ventricular systolic dysfunction in population at risk of HF (Stages A and B). Novel parameters of cardiac function, specially left ventricular GLS, have emerged as powerful tools to detect an early impairment of left ventricular function.
- Noninvasive exercise testing (with echocardiography and/or CMR imaging) may be helpful to unmask the underlying mechanisms of HF with preserved left ventricular ejection fraction (HFpEF). Myocardial energetic state may also play a role in the worsening of left ventricular diastolic function and transient lung congestion during exercise in patients with HFpEF.

## DISCLOSURE

V. Delgado received speaker fees from Abbott Vascular, Edwards Lifesciences, GE Healthcare, Medtronic, Novartis, and Philips and consulting fees from Edwards Lifesciences and Novo Nordisk (heart failure).

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