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Characterization of heart failure with preserved ejection fraction in the outpatient setting: improvement in prognosis assessment and applicability of new echocardiographic techniques

Laura Sanchis Ruiz

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CHARACTERIZATION OF HEART FAILURE WITH PRESERVED EJECTION FRACTION IN THE OUTPATIENT SETTING: IMPROVEMENT IN PROGNOSIS ASSESSMENT AND APPLICABILITY OF NEW ECHOCARDIOGRAPHIC TECHNIQUES

UNIVERSITAT DE BARCELONA

Tesis para la obtención el título de Doctor en Medicina por la Universidad de Barcelona, elaborada y presentada por

Laura Sanchis Ruiz

Dirigida por la Dra. **Marta Sitges Carreño** y el Dr. **Carlos Falces Salvador**

Barcelona Octubre 2016

A mis padres

Marta Sitges Carreño, MD, PhD and **Carles Falces Salvador, MD, pHD.** Hospital Clínic de Barcelona, Universitat de Barcelona

They declare that **Laura Sanchis Ruiz** has performed under their supervision the studies presented in the Dissertation **"Characterization of heart failure with preserved ejection fraction in the outpatient setting: improvement in prognosis assessment and applicability of new echocardiographic techniques"**. This Dissertation has been structured following the normative for PhD Thesis as a compendium of publications to obtain the degree of **International Doctor of Medicine** and the mentioned studies are ready to be presented to a Tribunal.

Director
Marta Sitges Carreño

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Carlos Falces Salvador

Barcelona, September 2016

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RESUMEN

La insuficiencia cardiaca con fracción de eyección preservada (ICFEP) es el tipo más frecuente de insuficiencia cardiaca (IC) a nivel ambulatorio, pese a ello no existe un tratamiento eficaz de la misma. Dado que la función ventricular es aparentemente normal, su diagnóstico es difícil requiriendo un alto nivel de sospecha. En nuestro estudio hemos analizado los mecanismos implicados en las fases iniciales de la ICFEP, objetivando la existencia de disfunción auricular izquierda de similar magnitud a la objetivada en pacientes con IC y fracción de eyección reducida (ICFER), pero con una función ventricular izquierda (fracción de eyección y strain) normal en los pacientes con ICFEP. En esta población con debut de ICFEP también hemos podido objetivar la presencia de disincronía interauricular. Ambos mecanismos de disfunción auricular parecen estar presentes en el momento del debut clínico de ICFEP precediendo al inicio de la disfunción ventricular. El conocimiento de dichos mecanismos podría ser útil para la realización de un diagnóstico precoz y en el desarrollo de tratamientos específicos, como podría ser aquellos basados en un enfoque agresivo sobre la arritmia auricular (ablación) para mantener la función contráctil auricular o la electroestimulación para resincronizar la función auricular.

Por otro lado, estudios previos, realizados en población con diagnóstico hospitalario de IC, sugirieron un pronóstico similar entre los pacientes con ICFEP o ICFER. En nuestro estudio con

pacientes con debut ambulatorio de IC, los pacientes con ICFEP también presentaron un pronóstico cardiovascular comparable a aquellos con ICFER. Mediante la aplicación de un análisis discriminante se determinó una conjunto de parámetros clínicos, ecocardiográficos y analíticos que mediante su combinación podrían ser útiles para predecir el pronóstico cardiovascular a medio plazo de pacientes con debut de IC: sexo masculino, hipertensión arterial, fibrilación auricular, índice E/e', Troponina I ultrasensible, metaloproteinasas MMP2 y TIMP1, hemoglobina, volumen auricular izquierdo y BNP. Así mismo, en una fase más tardía del seguimiento, se identificó la función auricular evaluada mediante strain (especialmente la onda A del strain-rate indicadora de la función contráctil de la aurícula izquierda) como un importante marcador pronóstico en esta cohorte de pacientes.

El trabajo presentado muestra como diferentes alteraciones (disfunción de la aurícula izquierda o la disincronía interauricular) pueden desembocar en una presentación clínica común de insuficiencia cardiaca en pacientes con fracción de eyección preservada. La presencia de estos hallazgos puede permitir el desarrollo de nuevos tratamientos para este síndrome. Así mismo, se han demostrado las implicaciones pronósticas de diversos biomarcadores y de la disfunción auricular, identificando de manera temprana los pacientes de alto riesgo permitiendo realizar un seguimiento y tratamiento más intensivo de dichos pacientes.

ABSTRACT

Heart failure with preserved left ventricular ejection fraction (HFPEF) is the most prevalent type of heart failure (HF) in the outpatient setting. Left ventricular ejection fraction values (considered as a surrogate of systolic function measured by standard echocardiography) are normal in HFPEF, making its diagnosis more challenging. In the present project, the underlying mechanisms involved in the early stages of HFPEF were analysed in outpatients with new onset HF and healthy controls. We observed that left atrial dysfunction was similar in HF patients with preserved or reduced left ventricular ejection fraction, but left ventricular function of HFPEF patients showed normal left ventricular ejection fraction and strain analysis similar values to that observed in a control group of patients without HF. Interatrial dyssynchrony was also observed in patients with new HFPEF onset. Both mechanisms seem to be present at the moment of symptoms onset, before ventricular dysfunction occurs. The study of these earliest alterations may be useful to achieve an early diagnosis and develop specific treatments, such as stepwise intensive management of atrial fibrillation or electrostimulation to resynchronizing the atria.

On the other hand, previous studies in patients diagnosed with HF as the cause of a hospital admission

indicated a similar prognosis for patients with HFPEF and those with reduced ejection fraction (HFREF). In our study, outpatients with new-onset HFPEF and HFREF also showed similar midterm cardiovascular prognosis. We performed a discriminant analysis to identify the best combination of clinical, echocadiographic and analytical variables to determine the cardiovascular outcome of our cohort. Several biomarkers showed prognostic value, including high-sensitivity troponine I, matrix metalloprotease type 2, tissue inhibitor of metalloprotease-1, haemoglobin, left atrial volume and brain natriuretic peptide type B. The status of atrial function, analysed by the mean left atrial deformation, was also identified as an important prognostic marker.

The present project demonstrates that the presence of underlying abnormalities such as atrial contractile dysfunction and dyssynchrony may contribute to the common clinical presentation of HF in patients with preserved left ventricular ejection fraction. These findings suggest the potential for alternative treatments in this syndrome. Additionally, the prognostic implications of several biomarkers and atrial dysfunction were demonstrated, allowing for the early identification of high-risk patients who should receive close follow-up and intensive treatment.

ABBREVIATIONS

BNP: brain natriuretic peptide type B

ECG: electrocardiogram

HF: heart failure

HFPEF: heart failure with preserved ejection fraction

HFREF: heart failure with reduced ejection fraction

LA: left atria

LAEF: left atrial ejection fraction

LV: left ventricle

LVEF: left ventricle ejection fraction

MMP: matrix metalloproteasse

TIMP: tissue inhibitor of metalloprotease 1

INTRODUCTION

1. HEART FAILURE WITH PRESERVED EJECTION FRACTION: DEFINITION AND EPIDEMIOLOGY

The term *diastolic heart failure* (HF) emerged at the beginning of the nineties. It referred to those patients with congestive HF but preserved left ventricular (LV) ejection fraction (LVEF) shown by echocardiography[1-3].

The first expert consensus for diastolic HF diagnosis was presented in 1998[4]. The criteria, depicted in Table1, had to be present for the diagnosis of *diastolic HF*. The initial term, *diastolic HF,* was selected because this type of HF was considered to be only secondary to LV diastolic dysfunction, compared to systolic HF, where the most important mechanism was the impairment of LV systolic function.

The term *HF with preserved ejection fraction* (HFPEF) was introduced in 2003[5]. In the beginning this term was controversial[6]; however, even though most patients with HFPEF have diastolic dysfunction, other factors were emerging, making it necessary to change the nomenclature.

1. Signs or symptoms of congestive heart failure

- Exertional dyspnoea
- Orthopnoea
- Gallop sounds
- Lung crepitation
- Pulmonary oedema

2. Normal or mildly reduced left ventricular systolic function

- LVEF>45%
- LV end-diastolic internal dimension index<3.2 cm/m^2 or LV end-diastolic volume index <102 ml/m^2

3. Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness

- Slow isovolumic LV relaxation
  - LVdP/dtmin<1100 mmHg /s
  - and/or isovolumic relaxation time indexed by age group:
    <30years old >92 ms
    30–50years old >100 ms
    >50years old>105 ms
  - and/or time constant of LV pressure decay >48 ms
- And/or slow early LV filling:
  - Peak LV filling rate
    - <160 ml.s^{-1} .m^{-2}
    - and/or indexed for age groups:
      - <30y <2.0 end-diastolic volume. s^{-1}
      - 30–50y <1.8 end-diastolic volume. s^{-1}
      - >50y <1.6 end-diastolic volume. s^{-1}
  - and/or E/A<50y<1.0 and DT<50y >220 ms, E/A>50y<0.5 and DT>50y >280 ms
  - and/or S/D (pulmonary vein) <50y>1.5, S/D>50y>2.5
- And/or reduced left ventricular diastolic distensibility:
  - LV end-diastolic pressure >16 mmHg or mean pulmonary capillary wedge pressure >12 mmHg
  - and/or PV A Flow >35 cm.s^{-1}
  - and/or pulmonary venous atrial flow velocity> mitral atrial flow velocity duration +30 ms
  - and/or A/H (ratio of atrial wave to total signal excursion on the apexcardiogram)>0.20
- And/or increased LV chamber or muscle stiffness.
  - B (constant of LV chamber stiffness)>0·27 and/or b* (constant of muscle stiffness)>16

Table1:Diastolic HF diagnosis based on expert consensus of 1998. Adapted from reference[4]

A: A-wave mitral inflow (PW); DT: deceleration time mitral valve; E: A- wave mitral inflow (PW); LVEF: left ventricular ejection fraction; LV: left ventricle.

The clinical presentation of HFPEF and HF with reduced ejection fraction (HFREF) is quite similar. The clinical suspicion is based on the Framingham criteria[7]. Two major criteria or one major criterion and two minor criteria are needed for HF diagnosis [Table2].

	Framingham criteria for HF diagnosis
Major	Paroxysmal nocturnal dyspnoea Neck vein distention Rales Radiographic cardiomegaly (on chest radiography) Acute pulmonary oedema S3 gallop Increased central venous pressure (>16 cm H2O at right atrium) Hepatojugular reflux Weight loss >4.5 kg in 5 days in response to treatment
Minor	Bilateral ankle oedema Nocturnal cough Dyspnoea on ordinary exertion Hepatomegaly Pleural effusion Decrease in vital capacity by one third from maximum recorded Tachycardia (heart rate>120 beats/min)

Table2: Framingham criteria for HF diagnosis. Adapted from McKee et al[7].

The prevalence of HF in general population has been estimated as 1-2% and the incidence approaches 5-10 per 1000 persons per year[8]. HF is more prevalent in persons older than 50 years and the incidence increases progressively with age, reaching 8.4% prevalence in patients ≥ 75 years old[9]. The increasing prevalence of HFPEF is concomitant with

increased comorbidities such as hypertension, atrial fibrillation and diabetes[10]. Despite the difficulty of estimating the true prevalence of HFPEF due to the lack of standardization in diagnostic criteria and the inherent difficulties in the diagnosis, half of all patients with HF have HFPEF[11] (LVEF>50%[12]), and it has been reported in up to two thirds of outpatients with HF onset[13]. Therefore, the aging of the population and the increase on comorbidities in the developed countries will result in a gradual increase in the prevalence of HF, especially HFPEF[10].

Despite a similar clinical presentation, HFPEF is more prevalent in very elderly women with high body mass index while HFREF is more prevalent in younger patients, especially men, with ischemic heart disease and usually associated to peripheral vascular disease[13, 14]. Noncardiac comorbidities are highly frequent in HF patients and worsen their prognosis. Renal disease and sleep-disordered breathing are highly frequent in both types of HF, but HFPEF patients have an increased burden of diabetes, chronic obstructive pulmonary disease, anaemia and obesity[15].

HFREF is easily diagnosed with standard two-dimensional (2D) echocardiography. By contrast, the diagnosis of HFPEF is more difficult, as LVEF values (considered as a surrogate of systolic function measured by

standard echocardiography) are within the normal range. Diagnosis of HFPEF is currently based on a combination of clinical suspicion, echocardiographic measurements and B-type natriuretic peptide (BNP) determination[12, 16]. Several diagnostic algorithms have been proposed, such as the one proposed by de Paulus et al.[16] [Figure 1] included in the previous HF guidelines of the European Society of Cardiology[17].

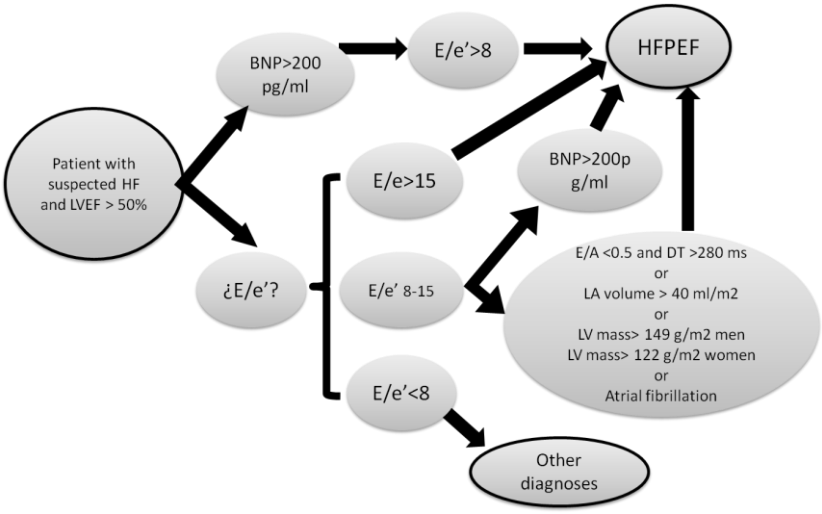

Figure1: Algorithm for HFPEF diagnosis. Adapted from de Paulus et al [16].
A: A wave mitral inflow (PW);BNP: B-type natriuretic peptide; DT: deceleration time mitral valve; E: E wave mitral inflow (PW); e': e wave lateral mitral annulus (TDI); HF: heart failure; LVEF: left ventricular ejection fraction; LA: left atrium, LV: left ventricle.

The new 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and

chronic heart failure[12] maintain the cut-off value of LVEF≥ 50% for HFPEF as in the previous guidelines[17], but a new terminology for those patients with HF and LVEF 40-49% has been included. Some studies have labeled patients in this grey area as HFPEF and other studies as HFREF. The new guidelines[12] also include a lower cut-off value of BNP (35 ng/ml) to rule-out HF diagnosis in the non-acute onset. Figure 2 summarizes the new algorithm for HF diagnosis; HFPEF diagnosis requires LVEF ≥ 50% and an objective demonstration of structural and/or functional alteration of the heart as the underlying cause for the clinical presentation. The cut-off values for LA indexed volume and LV indexed mass, e' and E/e´ratio are lower now, as compared to de Paulus algorithm[16].

It is not always possible to have all the required parameters to achieve the diagnosis of HFPEF in the ambulatory setting. Thus, many outpatients with HFPEF are not being diagnosed. In addition to a more challenging diagnosis, several studies have demonstrated poor outcomes of HFPEF, especially after an episode of hospitalization for HF[10, 14]. The improved treatment of HFREF and increased prevalence of HFPEF is leading to an increase in the proportion of patients hospitalized with HFPEF and a simultaneous decline in those with HFREF[18]. Thus, an early diagnosis of HFPEF is important to enable close follow-up of

the patients and an early detection of complications that may avoid hospital admission.

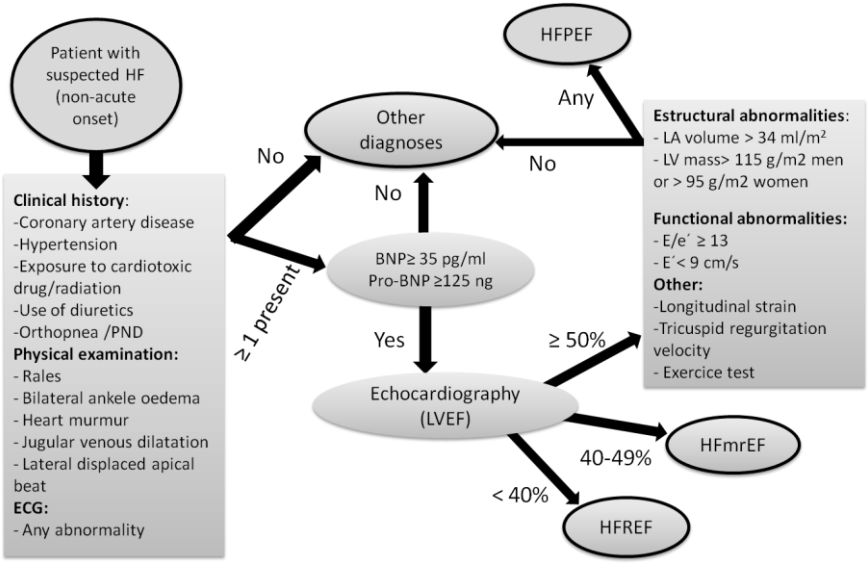

Figure 2: Algorithm for HF diagnosis. Based on 2016 European Society Guidelines for diagnosis and treatment of acute and chronic heart failure[12].
BNP: B-type natriuretic peptide; E: E wave mitral inflow (PW); e': e wave lateral mitral annulus (TDI); HF: heart failure; HFmrEF: HF with mild reduction of ejection fraction; HFPEF: HF with preserved ejection fraction; HFREF: HF with reduced ejection fraction; LVEF: left ventricular ejection fraction; LA: left atrium; LV: left ventricle.

In recent years, HFPEF has been proposed as a heterogeneous syndrome, with several underlying aetiologic and pathophysiologic factors[19, 20]. The understanding of the heterogeneity of the underlying pathophysiology of this syndrome may allow for more targeted management of

HFPEF patients that might, in turn, improve their treatment and prognosis.

To summarize, HF is an important public health problem that is increasing in prevalence due to the increase in life expectancy and population aging. HFPEF seems to be the most prevalent type of HF in the outpatient setting and will rise to a higher proportion as the population ages. The challenging diagnosis of HFPEF and the heterogeneity and lack of knowledge about the underlying pathophysiological mechanisms makes it difficult to develop specific treatments for this entity. Due to the expected increase in the prevalence of HFPEF, the need of a therapeutic option and a better understanding of this syndrome are critical.

2. PATHOPHYSIOLOGY OF HFPEF: INSIGHTS FROM IMAGING

The most widely used imaging technique for the diagnosis and follow-up of patient with HF is 2D echocardiography. It has several advantages as compared to other techniques, which mainly include its low cost, easy access and no radiation. With 2D echocardiography, it is possible to estimate LV global contractility by determining LVEF. With LVEF estimation, it is easy to diagnose HFREF. Sometimes, it is also possible to determine the aetiology of LV dysfunction (segmental wall motion abnormality, non-compaction, hypertrophy, etc.) with 2D echocardiography.

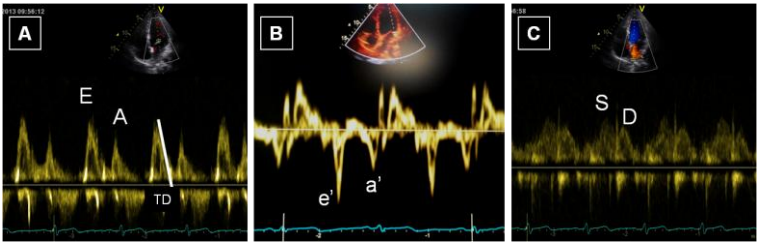

Figure 3: Echocardiographic parameters used for assessing left ventricle diastolic function. *Pulsed Doppler of mitral inflow (A), mitral annulus (B) and pulmonary vein flow (C).*

The assessment of diastolic function also can be performed with Doppler echocardiography. In the previous recommendations for the evaluation of LV diastolic function by echocardiography[21], the degree of diastolic dysfunction in

patients with abnormal diastolic function was assessed by the combination of LV inflow (early [E wave] and late [A wave] maximum diastolic velocities, E/A ratio and E wave deceleration time [DT]), diastolic velocities (tissue Doppler) in the mitral annulus (e´, a´) and pulmonary vein inflow (systolic [S] and diastolic [D] peak velocity) [Figure 3].

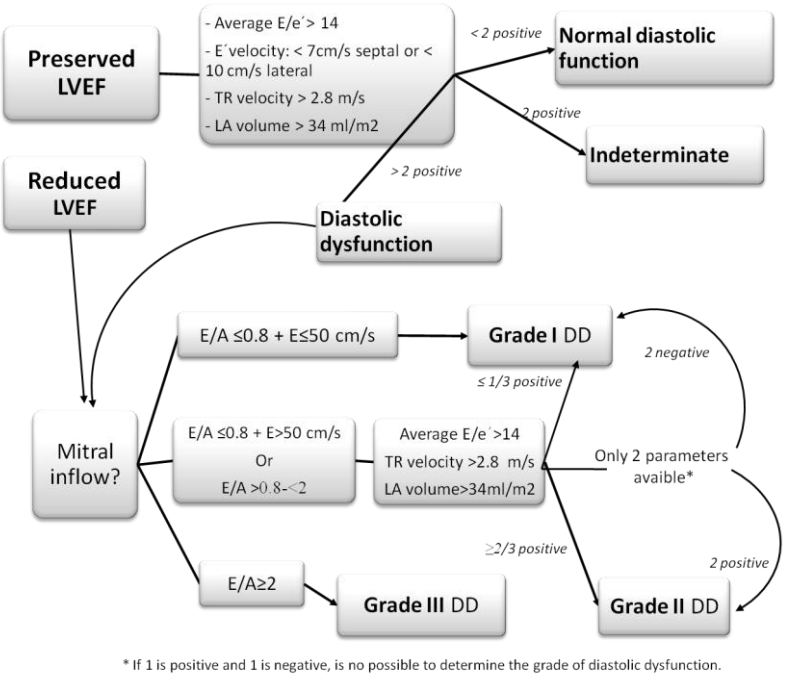

Figure 4: Algorithm for diastolic dysfunction assessment. Adapted from Nagueh et. al[22].
DD: diastolic dysfunction; LA: left atrium; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation

The recently published new recommendations for the evaluation of LV diastolic function by echocardiography[22] propose starting the evaluation in patients with normal LVEF with 4 parameters: average E/e´> 14, e´ velocity (septal < 7cm/s or lateral < 10 cm/s), tricuspid regurgitation velocity > 2.8 m/s and LA volume indexed > 34 ml/m2. If more than 2 parameters are positive, then diastolic dysfunction is present. In patients with preserved LVEF and diastolic dysfunction or in those with reduced LVEF, the recommendations propose a new algorithm to determine the grade of diastolic dysfunction [Figure 4].

As previously discussed, HFREF can be easily diagnosed using standard echocardiography (LVEF). However, LVEF is normal in HFPEF patients, so a combination of clinical, biochemical (BNP) and echocardiographic parameters is needed to perform the diagnosis of HFPEF [Figure 1 and 2][12, 16, 17]. In recent years, new non-invasive echocardiographic techniques, such as myocardial strain based on tissue Doppler or speckle-tracking, have been developed. The evaluation and quantification of global and regional myocardial systolic function is possible using these techniques[23]. With them, small changes in myocardial contractility that are impossible to detect with standard 2D echocardiography can be ruled out[24]. Therefore, it is possible to detect myocardial dysfunction in earlier stages of the

disease using these techniques. Strain imaging has also been successfully applied for in the study of LV function in patients with heart valve disease[25], hypertrophic myocardiophaty[26], Fabry disease[27], ischemic heart disease[28] and HF[29-31].

HFPEF is a heterogeneous syndrome. Several clinical risk factors for the development of HFPEF have been proposed including age, diabetes, obesity and hypertension[32, 33]. Despite the importance of comorbidities[34], the development of HFPEF is probably a consequence of a combination of pathophysiologic mechanisms including diastolic dysfunction, subclinical LV dysfunction, pulmonary hypertension, abnormal exercise induced vasodilatation, abnormal ventriculo-arterial coupling, chronotropic incompetence, extracardiac volume overload and (perhaps) atrial dysfunction. As discussed below, many of these factors can be studied with imaging, particularly echocardiography. A better understanding of these factors may allow for the discovery of mechanistically targeted therapies in this disease[35].

2.1 SUBCLINICAL SYSTOLIC DYSFUNCTION OF THE LEFT VENTRICLE

Initial studies[36, 37] demonstrated the presence of longitudinal LV systolic dysfunction analysing the mitral inflow and annular motion patterns. They proposed that HFPEF could be an early stage of HFREF[38].

With the advent of speckle-tracking echocardiography, some studies applied it to assess LV myocardial deformation (longitudinal, circumferential and radial strain) in patients with HFPEF, with controversial results[29-31, 39]. Two studies included patients admitted to hospital due to acute HF and compared patients with HFREF, HFPEF and a control group with non-HF[29, 31]. Both studies observed a reduction in longitudinal and radial LV strain in HF patients, with a greater reduction in the HFREF group. Radial strain analysis was normal in one study[29] and reduced in the other one[31]. Phan et al. compared outpatients with HFPEF to 2 control groups (young and elderly), but only found a higher circumferential strain in patients with HFPEF[30].

More recently, Kraigher-Krainer et al. studied a larger population of outpatients with HFPEF (LVEF >45%), observing a reduction in longitudinal and circumferential LV strain as compared to a healthy control group and to a group of

patients with hypertension. They also reported a significant correlation between the strain values and LVEF[39].

Otherwise, the lack of longitudinal contractile reserve during exercise was proposed as a potential pathophysiologic mechanism of the HFPEF syndrome. In this sense, Lee et al. reported that dobutamine impairs longitudinal strain during stress echocardiography in patients with HFPEF[40].

2.2 ISOLATED DIASTOLIC DYSFUNCTION

Diastolic dysfunction of the LV is the mechanism most often associated to the HFPEF syndrome[38, 41]. Nevertheless, the methodology used for the study of LV diastolic dysfunction is still controversial. Indeed, it is unknown why patients with the same grade of diastolic dysfunction (such as impaired relaxation) have clinical HF and others do not have it[9, 42].

Diastolic wall strain (the change in the thickness of the posterior LV wall during diastole) has been proposed as a marker of diastolic function[43, 44]. Aizawa et al. compared a group of patients with HFPEF to a healthy control group and a group of patients with hypertension. A smaller e' (pulsed Doppler of the lateral mitral annulus) and reduced diastolic

wall strain were observed in HFPEF group as compared to the hypertensive group[43]. A lower diastolic wall strain was also observed in a study that compared patients with HFPEF and a healthy control group and was related to worse outcomes during follow-up[44].

2.3 ABNORMAL VENTRICULO-ARTERIAL COUPLING

Ventriculo-arterial coupling measures the efficiency of the mechanical energy transfer from the heart to the arteries. It is calculated as the ratio of effective arterial elastance to end-systolic elastance. Several studies have related ventriculo-arterial coupling to the pathophysiology and symptoms onset in HFPEF[45-48].

Although ventriculo-arterial coupling is difficult to measure using echocardiography, it can be measured in a single beat[45]. Its calculation requires the following values: systolic blood pressure (SBP), diastolic blood pressure (DBP), ejection volume (EV), LVEF and estimated normalized ventricular elastance at arterial end-diastole (E(Nd)).

- Ventricular elastance at arterial end-diastole (Ees) is calculated as follows:
  - $Ees = \frac{\text{DBP} - (\text{E(Nd)} \text{ x SBP x } 0.9)}{\text{E(Nd)} \text{ x EV}}$

(E(Nd) was estimated from a group averaged value adjusted for individual contractile/loading)

- The arterial elastance (Ea) is the ratio of end-systolic blood pressure (approx: $\frac{\text{SBPx } 2}{3} + \frac{\text{DBPx } 1}{3}$) to the value of the ejection volume.
- An Ea/Ees> 1.2 is considered an abnormal ventriculo-arterial coupling (normal 0.6)

A reduced end-systolic ventricular elastance decreases the contractile reserve of the LV. Accordingly, limited response to positive ionotropism exists; as a consequence, the increase in LV ejection fraction is limited and onset of exertional dyspnoea occurs. If both arterial and end-systolic ventricular elastance are increased, the circuit may have a hypertensive response to exercise and redistribute blood to the pulmonary circuit (more compliant vasculature). As a consequence of an abnormal ventriculo-arterial coupling, the myocardial energetic consumption increases and contributes to delay of myocardial relaxation, limiting LV filling and increasing diastolic pressure[49].

Borlaug et al. studied the end-systolic ventricular and arterial elastance with echocardiography in three groups: patients with HFPEF, patients with hypertension and healthy subjects. Both parameters (end-systolic ventricular and

arterial elastance) were increased in the groups of patients with HFPEF or hypertension; patients with hypertension showed an increase in LV contractility to cope with arterial load, but a reduction in LV contractility was observed in patients with HFPEF[48].

2.4 LEFT ATRIAL DYSFUNCTION

In recent years, the presence of LA dysfunction has been proposed as one of the factors that may be related to subclinical LV systolic dysfunction or diastolic dysfunction[50, 51]. Likewise, atrial dysfunction has been related to symptoms onset and worsening of previous symptoms by inducing atrial arrhythmias[52, 53].

Initially, LA volume was related to cardiovascular outcomes[54]. Then, strain imaging was applied to evaluate LA function of HF patients, with controversial results. Early studies determined LA strain using pulsed tissue Doppler in patients with HFREF, HFPEF, LV hypertrophy with diastolic dysfunction and healthy controls; patients with HFREF showed lower LA strain, but the only difference between patients with HFPEF and those with hypertrophy and diastolic dysfunction was atrial reservoir function as determined by the S wave of LA strain-rate[50]. Morris et al.

compared patients with HFPEF and patients with diastolic dysfunction without HF, finding lower LA global strain and reduced LA strain-rate A wave (a surrogate of atrial contractile function) in patients with HFPEF; in that study, the presence of reduced LA strain was related to a higher grade of diastolic dysfunction and worse functional class[51]. Subsequent studies confirmed the relationship of atrial dysfunction (measured as global strain) and exercise capacity[55]. Similarly, Cameli et al. described a greater prognostic value of LA global strain as compared to atrial volume or LA ejection fraction to predict cardiovascular outcomes[56].

2.5 INTERATRIAL DYSSYNCHRONY

The presence of interatrial dyssynchrony may affect ventriculo-arterial coupling by reducing LA emptying (loss of coordination between the active LA contraction and the LV diastole), increasing LA afterload and LA filling pressure. This abnormality can be enhanced in situations with high heart rate, as occurs during exercise. Likewise, the increase of volume and pressure results in progressive LA dilatation, fibrosis and atrial dysfunction.

Eicher et al. demonstrated the presence of interatrial dyssynchrony in a small group of patients with HFPEF using echocardiography (pulsed tissue Doppler) and in the electrophysiological study[57]. The same group performed a pilot study implanting a bi-atrial pacemaker in patients with HFPEF and severe interatrial dyssynchrony. They observed an improvement of functional class and a reduction in the number of hospital admissions due to HF after the pacemaker implantation[58]. These findings have not been confirmed in larger studies.

2.6 GLOBAL ECHOCARDIOGRAPHIC APPROACH TO HFPEF

As previously discussed, most of the underlying pathophysiological mechanisms proposed to explain the clinical features of HFPEF can be assessed using echocardiography. These abnormalities have been demonstrated in various cohorts of HFPEF patients using different echocardiographic techniques, but the contribution of each mechanism to HFPEF syndrome development has not been explored. Each abnormality may have a different specific treatment, and thus its identification could have clinical and prognostic implications. On the other hand, as a consequence of a determined pathology (such as hypertension), an abnormal myocardial substrate can be

developed, and this substrate could produce functional alterations that contribute to the HFPEF syndrome. Consequently, the identification of specific HFPEF phenotypes may represent one way to differentiate subgroups of HFPEF patients with specific therapeutic targets.

3. PROGNOSIS OF HEART FAILURE

3.1 OVERVIEW

As previously discussed, HFPEF has a high prevalence in the general population[8] that is increasing with the aging of the population and the growing number of comorbidities (e.g., hypertension, atrial fibrillation, diabetes)[10]. The "normality" of the LVEF in HFPEF patients makes the diagnosis more challenging; however, despite being an underdiagnosed disease, several studies performed in patients with hospital admission due to HFPEF have shown a similar morbidity and mortality as compared to patients with HFREF[5, 11, 14, 59-61]. In recent years, the pharmacological and non-pharmacological treatments for HFREF have significantly improved, but there is no effective pharmacological treatment for HFPEF[62, 63]. The heterogeneity of the HFPEF syndrome may be one of the reasons why clinical trials have failed to find an effective treatment. Small studies have shown slight improvement in symptoms and prognosis of HFPEF patients with non-pharmacological therapies such as physical training[64, 65] or the use of CPAP[66]. More recently, use of an artificial interatrial shunt has been proposed for patients with severe HFPEF as a method to decompress the LA[67]. Although only a pilot study with a short (one-month)

follow-up, the first results showed an improvement in pulmonary pressure and exercise capacity.

Most of the studies of HFPEF prognosis have been based on retrospective registries[10, 59] or included patients after hospital admission due to HF[11, 14, 61, 68]. The causes of mortality in HFPEF patients, as in the patients with HFREF, are mostly secondary to cardiovascular reasons (up to 60%)[69]. Early studies described a better prognosis of HFPEF patients as compared to HFREF[70, 71]; however, most of the recent studies show a similar prognosis in both types of HF (HFPEF or HFREF)[11, 14, 59-61]. Two studies, both including only patients with HF diagnosis after hospital admission, still describe a better prognosis in patients with HFPEF[10, 68].

The worse prognosis of patients with HFREF reported in the early studies could be secondary to the absence of optimum pharmacological treatment; the use of beta-blockers or ACE inhibitors was not implemented at that time. Regarding the two recent studies that indicate a better prognosis in HFPEF patients, limitations include a very short follow-up (3 months)[68] and the lack of fully optimized pharmacological treatment (patients were included at the end of the eighties)[10]. It is unknown if the outcome of outpatients with new-onset HF is similar to those with HFPEF or HFREF.

Various classical clinical parameters have been proposed as predictors of HF outcomes. The parameters related to worse prognosis in the HFPEF patients were the presence of hypertension or atrial fibrillation and male gender. On the other hand, factors related to worse prognosis in patients with HFREF were previous ischemic heart disease or left bundle branch block in an ECG[59]. More recently, in patients with HFPEF, the presence of chronic kidney disease was also related to abnormal cardiac mechanics and adverse outcomes during follow-up[72].

3.2 ECHOCARDIOGRAPHIC PARAMETERS AND PROGNOSIS

Numerous echocardiographic parameters have been proposed to stratify the prognosis of HF: LV dimensions[73], LA volume[54], LV filling pattern[74, 75], restrictive diastolic function of the LV[76], RV systolic dysfunction[77]and the presence of pulmonary hypertension[78].

Parameters derived from the study of myocardial deformation also have been related to cardiovascular prognosis. The LV longitudinal strain was initially related to prognosis in patients with aortic stenosis and preserved LVEF[79], and then to cardiovascular prognosis in patients with suspected HF[80]. Likewise, the LA reservoir function

(determined with LA strain) has been related to prognosis in patients with mitral regurgitation[81] or myocardial infarction[82], but also to cardiovascular prognosis in the general population[56]. Similarly, LA function determined using magnetic resonance has been related to cardiovascular prognosis in the general population[83] as well as in patients with early stages of HF, being an independent prognostic factor with respect to other measures of cardiac dysfunction[84]. More recently, a study including patients with HFPEF diagnosis after a hospital admission due to HF suggested the reduction of LA strain (reservoir function) as an important factor related to adverse outcomes[85].

3.3 BIOMARKERS AND PROGNOSIS

In addition to clinical and echocardiographic variables, biomarkers have an important role to evaluate the prognosis of HF patients. BNP is the most common biomarker used to define the HF prognosis. It is often introduced in clinical practice to determine general HF diagnosis[11, 86-88] and prognosis[89, 90]. High-sensitivity troponin I also has been related to HF onset[91] and outcomes[86], being included as a recommended way to perform a cardiovascular prognostic stratification in the most recent American guidelines on HF management[92].

Increased myocardial stiffness has been reported in the heart specimen of patients with HFPEF; this is not only secondary to the presence of collagen in the extracellular matrix, but also to greater stiffness of their cardiomyocytes[93, 94]. Titin, a molecule found inside the sarcomere of the cardiomyocyte, seems to be expressed in HFPEF patients as isoforms of increased stiffness, causing an impaired elasticity of the cardiomyocyte and, consequently, HFPEF symptoms[95, 96]. One current theory proposes that comorbidities could induce a systemic pro-inflammatory state that causes coronary microvascular and generalized endothelial inflammation leading to increased diastolic LV stiffness, and these changes trigger LV hypertrophy and raise resting LV tension due to hypophosphorylation of titin[97]. In a pilot study, the use of anakinra to block interleukin-1 in HFPEF patients led to a significant reduction of the systemic inflammatory response, improved aerobic exercise capacity and reduced plasma C-reactive protein levels[98].

On the other hand, extracellular collagen (fibrosis) also contributes to the increase in ventricular stiffness. Matrix metalloproteases (MMPs) are tissue protease enzymes related to the process of replacing the extracellular medium and are therefore related to the development of fibrosis[99]. The study of the MMPs showed the presence of active fibrosis in patients with diastolic dysfunction and in patients

with HFPEF[100-103]; these alterations were more marked in patients with more severe diastolic dysfunction[100, 102]. Some studies have found MMP2 more useful than BNP determination for HFPEF diagnosis, being in those studies more useful than BNP determination[100, 102]. The relation of these biomarkers to prognosis has been studied only in patients with HFREF diagnosed after hospital admission; MMP9 was a predictor of mortality[104]. Other new biomarkers of myocardial fibrosis, such as Galectin-3 and soluble ST2, have been proposed as prognostic markers in HF patients. The presence of elevated levels of plasma Galectin-3 in patients with HFPEF was associated with worse prognosis, independent of natriuretic peptide levels[105]. The results with ST2 were more controversial, with some studies showing a good prognostic value in HF patients with acute decompensation[106], and others that did not find any association between soluble ST2 and prognosis[107]. More recently, the determination of a panel with multiple biomarkers has been proposed to try to identify different HFPEF phenotypes that may have different prognosis and therapeutic approaches[20].

4. MYOCARDIAL DEFORMATION ECHOCARDIOGRAPHY: Definition and application in the assessment of ventricular and atrial function.

4.1 LEFT VENTRICULAR FUNCTION

Although LV function is complex, it is typically assessed by using 2D echocardiography with to determine LVEF, which has some important limitations. Usually, LVEF is determined by the Simpson method that calculates LV volume (as the summation of a stack of elliptical disks) in systole and diastole and then estimates the LVEF as a percentage change. With this method, only volumetric changes are evaluated, being an indirect measure of global myocardial contractility [Figure 5].

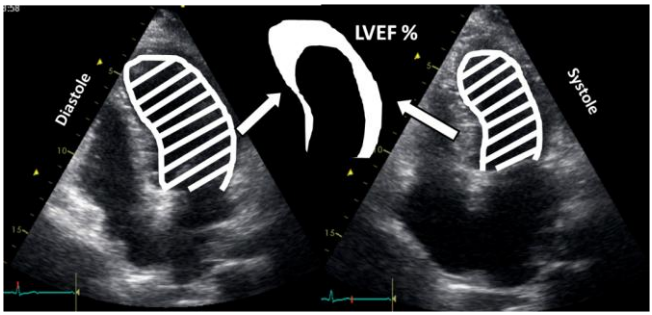

Figure 5: Simpson method for LVEF determination (4- chamber apical view)

Nevertheless, myocardial function is more complex than simple volumetric changes. First, myocardial fibres have no linear distribution along the myocardium; their orientation in space changes according to the area of the myocardial wall where they are placed. In the epicardial section, fibres have a longitudinal disposition; in the mesocardium, they are mostly circular and finally, in the endocardium they again have a longitudinal disposition[108]. Therefore, the final deformation of each myocardial segment is a composite of 3 different components: longitudinal, circumferential and the resulting composition of both into a radial deformation. The addition of the 3 myocardial components determines wall deformation and consequently the change in the LV volume[24, 108] [Figure 6].

On the other hand, the motion of each myocardial segment depends on more than its own deformation. Other factors involved include[24]:

- Interaction with adjacent segments. A segment with normal contractility can pull in an akinetic neighbouring segment, so the pulled akinetic segment will have an apparent motion despite no intrinsic deformation.
- Ventricular global geometry (curvature, wall thickness).

- Cavity pressure. This generates a passive load over each myocardial segment (wall stress) that can change the segmental motion. It depends on both LV afterload and preload.
- Tissue elasticity. It depends on the fibre structure and extracellular fibrosis and affects the elastic recoil.

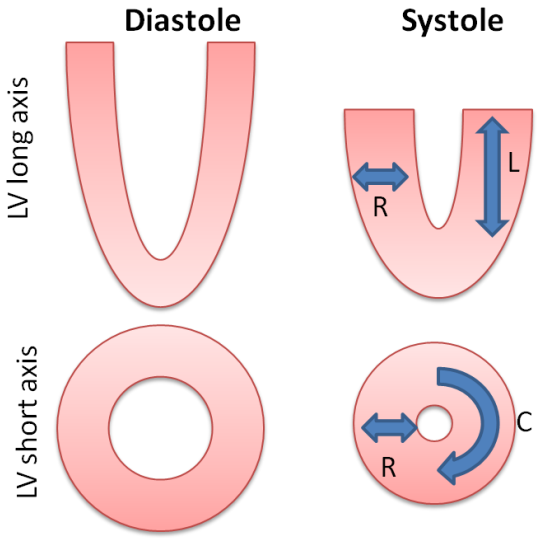

Figure 6: Change in the of left ventricle (LV) morphology: *R=radial, L=longitudinal, C=circumferential.* Modified from Bijnens et al [24]

As we have seen, many factors having a complex interaction are involved in the final motion of the myocardium, so the estimation of systolic LV function by measuring only LVEF seems to be a simplistic approach.

4.2 LEFT VENTRICULAR MYOCARDIAL DEFORMATION STUDY

The study of myocardial deformation (strain and strain rate) to determine LV systolic function has been widely tested and validated[109]. The main concepts during the study of the myocardial deformation are the following[110]:

- Distance: amount of space between two points.
- Velocity: distance per unit of time
- Strain: percentage of change in the length of a myocardial segment during a given period of time (%)
- Strain-rate: rate at which deformation or fibre shortening is taking place (s^{-1})

The development of Doppler tissue imaging (DTI) raised the possibility of non-invasive determination of myocardial deformation by producing images of the velocity of myocardial motion[111]. DTI is based on Doppler and consequently is dependent on the angle of ultrasound beam interrogation on the tissue (an angle of acquisition < 15º is required); pulsed wave DTI provides traces of longitudinal velocities throughout the cardiac cycle of a given myocardial segment and the data cannot be further processed [Figure 7A]. Conversely, colour-coded DTI can be post processed to obtain the distance (temporal integral of tissue velocity),

strain-rate ($\frac{Velocity\ \ 1-velocity\ \ 2}{distance}$) and strain (temporal integral of strain-rate)[112] [Figure 7B].

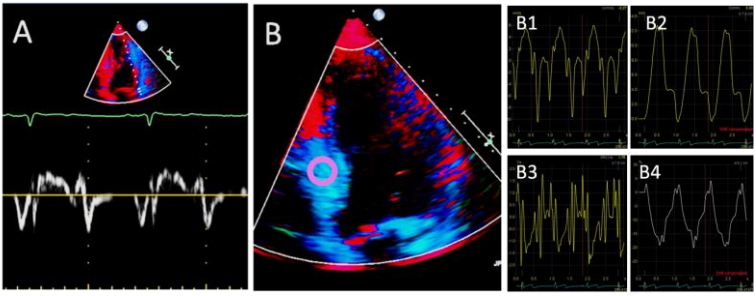

Figure 7. A: Myocardial velocities derived from Doppler tissue imaging (TDI) spectral pulse wave (PW) Doppler. B: DTI colour; B1 velocity curve; B2 displacement curve; B3 strain-rate curve; B4 strain curve.

More recently, 2D speckle-tracking echocardiography has been developed. The study of the myocardial strain using this technology is non-invasive, angle-independent and more reproducible than the strain based on TDI[109]. The myocardial wall does not appear homogeneous in 2D echocardiography. The irregularities (myocardial "speckles") are located over the entire wall (natural acoustic markers) and are similar to the pixels of a digital picture when it is magnified [Figure 8]. These acoustic markers have a random distribution that is always unique (like a finger print). In 2D echocardiography, it is possible to track the movement of these speckles along the cardiac cycle with specific software ("speckle-tracking echocardiography"). By tracking the speckles it is possible to quantify the deformation of the myocardium (strain).

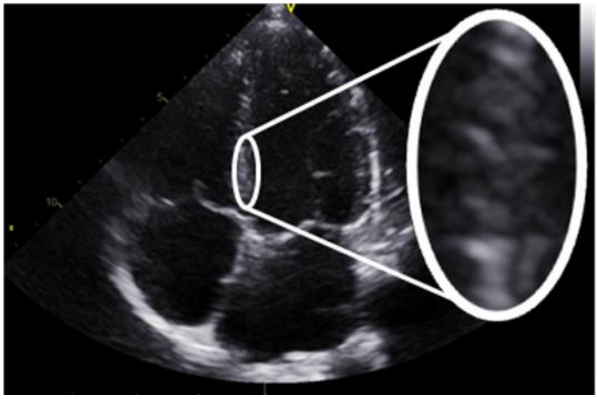

Figure 8: Zoom of the interventricular septum (2D echocardiography, 4-chamber view) where myocardial speckles can be observed.

With speckle-tracking echocardiography, it is possible to quantify the 3 different components of the LV myocardial strain: longitudinal, radial and circumferential [Figure 9].

The strain rate can also be determined with speckle tracking echocardiography based on strain values. Strain rate quantifies not only the magnitude of myocardial deformation but also the velocity of myocardial deformation. It has the same direction as the strain (negative during contraction and positive during expansion of the myocardium) and is expressed in s^{-1} [23]. While strain is more related to the systolic volume and therefore can be, influenced by heart rate and load (not only by the internal contractility), strain-rate seems to better reflect the changes in intrinsic contractility[113].

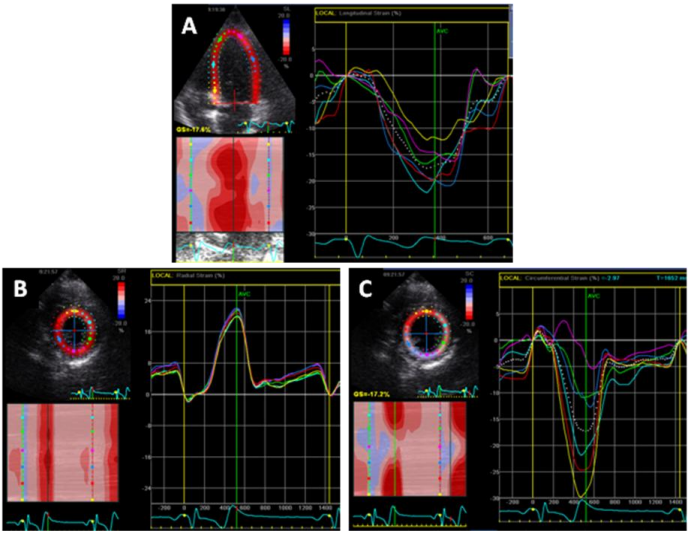

Figure 9: Left ventricular strain curves. A: longitudinal strain (4-chamber apical view); B: radial strain (parasternal short axis view, papillary muscle level); C: circumferential strain (parasternal short axis view, papillary muscle level)

4.3 ATRIAL FUNCTION

LA function has several particularities, compared to LV function. First, atrial function consists of 3 different phases (not only systole and diastole) during the cardiac cycle[114]:

- Reservoir: ventricular systole. The atrioventricular (AV) valve (mitral or tricuspid) valve is closed and blood enters and stays in the atria.

- Conduit: early ventricular diastole. Blood enters in the atria and goes to the ventricle through the opened AV valve
- Booster pump: active contraction of LA that augments ventricular filling during late ventricular diastole.

LA function was initially assessed by measuring the changes in atrial volume[115] [Figure 10].

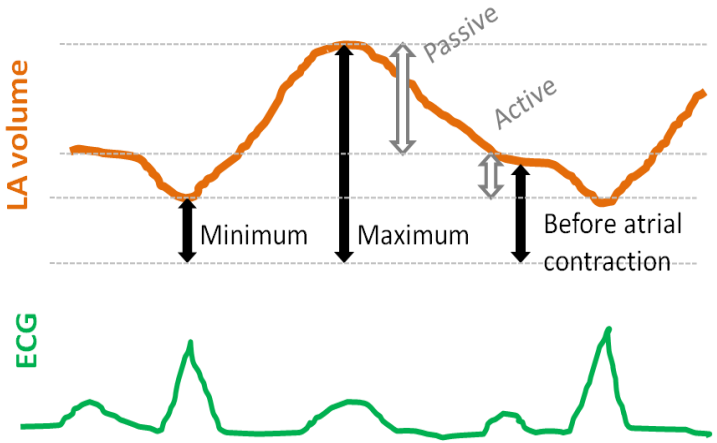

Figure 10: Left atrial volumes and ECG. Maximum volume as surrogate of reservoir function, passive volume as surrogate of conduit function and active volume as surrogate of booster pump function.

Using the atrial volumes, it is also possible to determine the LV diastolic function[116]. Usually, the atrial volumes used for these calculations are:

- Maximum volume (atrial diastole)
- Volume before the atrial contraction (before the beginning of the P-wave)
- Minimum volume (atrial systole)

Combining the previous volumes, it is possible to determine the following parameters [Figure 10]:

- *LA ejection fraction*

$$= \frac{\text{Maximum LA volume} - \text{minimum LA volume}}{\text{Maximum LA volume}} \text{x}100$$

- *Active atrial volume*:

  Volume before atrial contraction – Minimum LA volume

- *Passive atrial volume:*

  Maximum LA volume – Volume before atrial contraction

Although LA volume has been related to cardiovascular prognosis[54] and atrial fibrillation onset[117], the LA is of normal size in up to 30% of patients with diastolic dysfunction[118].

4.4 ATRIAL MYOCARDIAL DEFORMATION STUDY

In recent years, speckle-strain echocardiography has been also successfully applied to the study of the LA[119-121].

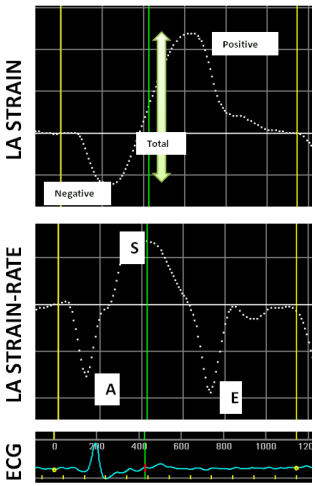

Figure 11:LA strain and strain-rate curves

The atrial function can be characterized using longitudinal strain and strain-rate analysis[122] [Figure 11]. When LA strain is evaluated, two waves (A and S) are obtained: a first negative wave as surrogate of atrial booster pump function and a second positive wave as surrogate of atrial conduit function. The total magnitude of the strain (positive + negative waves) is a surrogate of the atrial reservoir function. Applying the strain rate obtains 3 waves:

- A wave (negative, during atrial contraction) as surrogate of atrial booster pump function.

- S wave (positive, during ventricular contraction) as surrogate of atrial reservoir function.
- E wave (negative, during early ventricular diastole) as surrogate of conduit atrial function.

Table3 summarizes cardiac activity during each atrial phase and its relation to the strain curves and atrial volume.

.

Atrial phase	BOOSTER PUMP	RESERVOIR	CONDUIT
Ventricular activity	End diastole	Ventricular systole	Early diastole
Atrial activity	Volume reduction up to the minimum LA volume	Volume increase up to maximum LA volume	Volume reduction up to the volume before atrial contraction
Blood flow	Atrial contraction forces blood to move to LV	Blood flows from pulmonary veins to the LA	Blood flows from de LA to LV, part of the blood go directly from pulmonary veins to LV
Involved factors	Internal LA contractility	LA relaxation (compliance)	Relaxation of LV (compliance).
	Preload Afterload	Ventricular contraction (extrusion of the mitral annulus to the apex) Systolic pressure of right ventricle	It is inversely related to reservoir function
Strain wave	Positive strain	Total strain	Negative strain
Strain-rate wave	LA SR a wave	LA SR s wave	LA SR e wave

Table 3:Atrial cycle
LA: left atrium; LV: left ventricle; SR: strain rate

Regarding the study of LA strain with speckle-tracking echocardiography, there is a peculiarity as compared to LV strain analysis. The onset for the analysis can be placed at the beginning of the QRS complex (as in the study of LV strain) or at the beginning of the P wave.

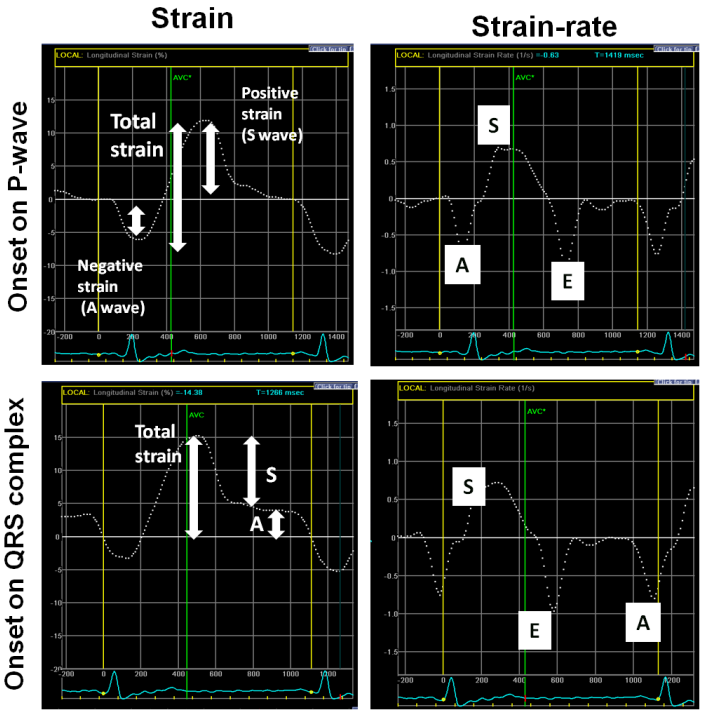

Figure 12: LA Strain and strain-rate curves depending of the selected onset (P-wave or QRS complex)

Using the P wave as onset, it is possible to isolate LA, given the complete relaxation of LV at that moment; all the LA deformation occurring at that point is caused by its

intrinsic contraction. In a recent study, LA strain values were obtained using the P wave as onset and then the R wave of the QRS; the results were compared to LA indices obtained by 3D echocardiography. The correlation between the strain measurements with onset on the P wave and the LA 3D indices were higher than those with the R wave onset[123]. Figure 12 shows the changes in LA strain and strain-rate curves depending on the onset position (P-wave or QRS complex).

4.5 ATRIAL MECHANICS

Interatrial dyssynchrony was initially studied using the ECG to determine the presence of interatrial block (interatrial conduction delay). An interatrial block is defined using the Spodick criteria as a P wave > 120 ms in at least 1 of the 12 ECG leads[124]. The interatrial block, as a marker of electromechanical dysfunction of the LA, has been related to a higher risk of atrial arrhythmias[125, 126] and to a marked reduction of LV filing[127]. For the study of the interatrial block, a low-velocity ECG record and the use of magnifying lens are needed, which are a limitation for correct measurement in clinical practice.

More recently, the presence of interatrial dyssynchrony was determined with pulsed tissue Doppler measuring the

delay between the peak a' wave of the lateral mitral and tricuspid annulus. In patients with HFPEF, a higher proportion of interatrial dyssynchrony was observed with this method as compared to a control group. A cut-off value of 60 ms was established to identify the presence of severe interatrial dyssynchrony[57].

Finally, speckle-tracking echocardiography also has been applied to study the LA asynchrony determining the time delay between the peak strain of the lateral and septal auricular walls[121, 128].

To summarize, HFPEF is a bad condition with an apparently similar poor prognosis to that of HFREF. The role of plasma and imaging biomarkers is still limited in this clinical setting. Moreover, several underlying pathophysiologic abnormalities might be present in these patients. Cardiac imaging, and particularly echocardiography due to its high frame rate and wide availability, can help in characterizing which of these mechanisms are present in order to earlier diagnose HFPEF and to try to find a specific treatment in each patient presenting with this common clinical syndrome.

HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

- The development of new non-invasive tools may improve the understanding of the HFPEF syndrome and contribute to clinical practice in three ways:
  - Simplify the diagnosis of HFPEF
  - Identify HFPEF phenotypes that may allow for more targeted management of patients by improving the characterization of the underlying pathophysiology of a common clinical presentation (i.e., HF)
  - Better stratify the prognosis of HF patients, making possible a closer follow-up of the higher risk patients

GLOBAL OBJECTIVES

1. To characterize the initial mechanisms involved in HFPEF development using echocardiographic techniques (2D echocardiography, Doppler and speckle-tracking strain)

2. To determine the outcomes of outpatients with new-onset HF (either HFPEF or HFREF)

3. To relate the clinical, functional, structural and analytic parameters to cardiovascular prognosis in patients with HFPEF.

ORIGINAL PAPERS

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Left atrial dysfunction relates to symptom onset in patients with heart failure and preserved left ventricular ejection fraction

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Aims Pathophysiology of heart failure (HF) with preserved ejection fraction (HFPEF) remains unclear. Left atrial (LA) function has been related to HF symptoms. Our purpose is to analyse LA function in outpatients with new onset symptoms of HF.

Methods and results An observational study was performed including 138 consecutive outpatients with suspected HF referred to a one-stop clinic. Final diagnosis [HF with reduced EF (HFREF), HFPEF, or non-HF] was established according to current recommendations. Echocardiography was performed in all patients. LA function was analysed using strain derived from speckle tracking in sinus rhythm patients ($n = 83$). Results were analysed with ANOVA and Bonferroni statistical tests. Receiver operating characteristic (ROC) curves were constructed to investigate the predictive ability of LA parameters for the final diagnosis of HF. Patients were 75 $\pm$ 9 years and 63% women. Final diagnosis was 23.2% HFREF, 45.7% HFPEF, and 31.2% non-HF. Left ventricular strain rate showed no differences between non-HF and HFPEF groups, but both groups showed differences with the HFREF group. LA strain rate (A- and S-waves) was significantly reduced in both HF groups (without differences among them) when compared with the non-HF group. LA strain rate and indexed volume showed significant accuracy for HF diagnosis in ROC curves.

Conclusions In outpatients with new-onset symptoms of HF, LA dysfunction was observed. It might be the initial mechanism in the development of symptoms in HFPEF patients. These findings support the relationship of LA dysfunction with HFPEF, suggesting that the analysis of LA function may be useful in sinus rhythm patients with new-onset dyspnoea.

Keywords Outpatient • HFPEF • Speckle-tracking echocardiography • Atrial strain • Heart failure onset

Introduction

Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most prevalent type of HF in the ambulatory setting.[1,2] Despite its high prevalence, it remains underdiagnosed and the corresponding mortality and morbidity are similar to HF with reduced EF (HFREF).[1,3]

In recent years, several mechanisms that could be related to the development of HFPEF have been proposed. Initial studies[4,5] reported left ventricular (LV) diastolic dysfunction and LV systolic longitudinal dysfunction, as shown by reduced longitudinal myocardial velocities and deformation, suggesting that HFPEF could be an HF stage preceding HFREF. However, the heterogeneity of the patient groups studied (ambulatory, in-hospital, recurrent HF, etc.) has produced somewhat contradictory results.[6–8] Left atrial (LA) dysfunction has also been associated with the development of HFPEF; initially, LA indexed volume was related to diastolic dysfunction,[9] exercise capacity,[10] and HFPEF syndrome.[11] In HFPEF patients, atrial fibrillation and loss of atrial function have been related to worse clinical outcomes,[12] and atrial strain analysis has been used to study LA function. Two studies have suggested that abnormal LA strain could be related to clinically overt HF and predictive symptoms. In a study of patient groups that did not differ by LA volume, LA strain was significantly decreased in HF patients (HFPEF and

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***Aims**: Pathophysiology of heart failure (HF) with preserved ejection fraction (HFPEF) remains unclear. Left atrial (LA) function has been related to HF symptoms. Our purpose is to analyze LA function in outpatients with new onset symptoms of HF.*

***Methods and results**: An observational study was performed including 138 consecutive outpatients with suspected HF referred to a one-stop clinic**.** Final diagnosis (HF with reduced ejection fraction (HFREF), HFPEF o non-HF) was established according to current recommendations. Echocardiography was performed in all patients. LA function was analyzed using strain derived from speckle-tracking in sinus rhythm patients (n=83). Results were analyzed with Anova and Bonferroni statistical tests. ROC curves were constructed to investigate predictive ability of LA parameters for the final diagnosis of HF. Patients were 75±9 years and 63% women. Final diagnosis was 23.2% HFREF, 45.7% HFPEF and 31.2% non-HF. Left ventricular strain-rate showed no differences between non-HF and HFPEF groups but both groups showed differences with HFREF group. LA strain-rate (A and S waves) was significantly reduced in both HF groups (without differences among them) as compared to non-HF group. LA strain-rate and indexed volume showed significant accuracy for HF diagnosis in ROC curves.*

***Conclusions**: In outpatients with new onset symptoms of HF, LA dysfunction was observed. It might be the initial mechanism in the development of symptoms in HFPEF patients. These findings support the relationship of LA dysfunction with HFPEF, suggesting that the analysis of LA function may be useful in sinus rhythm patients with new onset dyspnea.*

INTRODUCTION

Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most prevalent type of HF in the ambulatory setting (1,2). Despite its high prevalence, it remains underdiagnosed and the corresponding mortality and morbidity are similar to HF with reduced ejection fraction (HFREF)(1,3).

In recent years, several mechanisms that could be related to the development of HFPEF have been proposed. Initial studies (4,5) reported LV diastolic dysfunction and left ventricular (LV) systolic longitudinal dysfunction, as shown by reduced longitudinal myocardial velocities and deformation, suggesting that HFPEF could be a HF stage preceding HFREF. However, the heterogeneity of the patient groups studied (ambulatory, in-hospital, recurrent HF, etc.) has produced somewhat contradictory results (6-8). Left atrial (LA) dysfunction has also been associated with the development of HFPEF; initially, LA indexed volume was related to diastolic dysfunction (9), exercise capacity (10), and HFPEF syndrome (11). In HFPEF patients, atrial fibrillation and loss of atrial function have been related to worse clinical outcome (12), and atrial strain analysis has been used to study LA function. Two studies have suggested that abnormal LA strain could be related to clinically overt HF and predictive symptoms. In a study of patient groups that did not differ by LA volume, LA strain was significantly decreased in HF patients (HFPEF and particularly HFREF) as

compared to patients with diastolic dysfunction but without HF (13). More recently, impaired LV and LA strain have been described in HFPEF patients, compared to non-HF patients with diastolic dysfunction (14). In addition, atrial dysfunction as evaluated by LA strain has been related to exercise capacity (15-17) and cardiovascular outcome (18).

We hypothesized that LA function could be already impaired in early stages of HFPEF and that this impairment could be at least in part, responsible for the development of clinical symptoms in these patients. Additionally, evaluation of LA function could be useful to improve the differential diagnosis of patients presenting with HF, namely differentiating HFPEF from non-HF. Accordingly, we sought to analyze if there were any differences in LA function among patients with dyspnea and non-HF, HFPEF and HFREF.

METHODS

Study Design and Ethics

The study was observational and descriptive. Patients with new-onset HF symptoms were prospectively included. The study was approved by the Ethics Committee of our institution and complied with the Helsinki declaration. All participants provided written informed consent and all data were treated according to Spain's Organic Law 15/1999 of Personal Data Protection and Royal Decree 1720/2007.

Patients

Consecutive outpatients with new-onset HF symptoms referred by primary health care centers to our one-stop HF clinic for examination between March 2009 and July 2012 were included. Clinical evaluation, determination of BNP plasma levels, and echocardiography were performed as reported elsewhere (2). In accordance with current recommendations (19), patients were diagnosed as HFREF, HFPEF, or non-HF. Exclusion criteria were age <18 years, life expectancy <1 year, and/or inability to complete the diagnostic circuit.

Echocardiography acquisition and analysis

A comprehensive two-dimensional echocardiography study with conventional Doppler and tissue Doppler was performed using a commercially available system (Vivid 7, GE Healthcare, Milwaukee, WI). LV and LA dimensions were determined according to current recommendations (20) and indexed by body surface area (Du Bois method). Evaluation of LV diastolic function was based on 3 factors: (i) LV filling, determining maximum early (E wave) and late (A wave) diastolic velocities and the relationship between both (E/A) and the deceleration time of the E wave; (ii) the peak velocity of systolic and diastolic flow in the pulmonary veins; and (iii) tissue Doppler peak diastolic velocities of the lateral mitral annulus (E' and A') (21).

Two-dimensional echocardiography using dedicated software (2D strain, EchoPAC™, GE Healthcare, Milwaukee, WI) was used to assess LA and LV myocardial deformation. The analysis was performed by a reader blinded to clinical status. The frame rate was set between 60 and 80 frames per second and 3 beats in sinus rhythm and 5 beats in atrial fibrillation patients were averaged to measure the strain and strain-rate. Global longitudinal LV strain was quantified and the values for 6 myocardial LV segments in the apical 4-chamber view were averaged. The LA longitudinal deformation was quantified and averaged for 6 LA segments from the apical 4-chamber view with initial onset in the ECG P wave. Most previous authors have used the QRS as the time reference for the onset of LA strain analysis (14,16-18). We selected P wave of the ECG signal as our starting point in order to isolate LA contractile function, assuming that the LV is completely relaxed at that time; this should guarantee that all the LA shortening was produced by atrial contraction. We are confident that this assumption is valid because none of our patients showed EA waves fusion in the LV inflow, which would indicate incomplete LV relaxation at the time of the P-wave onset. Using the P wave as the onset for deformation analysis, we determined LA peak systolic strain-rate (S-wave) (LASRs) as a surrogate of LA reservoir function and LA peak strain-rate after contraction (A-wave) (LASRa) as a surrogate of LA contractile function (Figure 1). Extreme value (minimum of longitudinal strain) was taken into account for

the analysis. Adequate reproducibility for LA deformation analysis in our Laboratory has been previously reported (22).

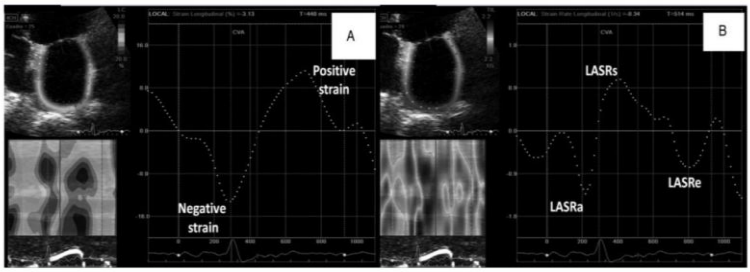

Figure 1 Left atrial strain waves (speckle-tracking echocardiography). (A) Left atrial longitudinal strain waves. (B) Left atrial longitudinal strain-rate waves. LASRa, left atrial strain-rate A-wave; LASRs, left atrial strain-rate S-wave; LASRe, left atrial strain-rate E-wave.

Statistical Analysis

Quantitative variables are shown as mean ± standard deviation. Qualitative variables are shown as total number and percentage. Descriptive and comparative analyses of the different diagnostic groups were performed. Normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Inter-group differences (unpaired data) were assessed by the $\chi 2$-test or Fisher test for categorical variables and Student *t*-test for quantitative variables.

Anova and Bonferroni statistical tests were used to compare quantitative variables between more than two groups. The Receiver Operating Characteristic (ROC) curve was assessed to identify correlation of echocardiographic parameters with diagnosis and to determine cut-off values.

Pearson test was used to correlate quantitative variables. A p-value <0.05 (two sided) was considered statistically significant. Data were processed with SPSS version 18 (IBM, Armonk, NY).

RESULTS

Demographics and clinical data

A total of 138 elderly patients (mean age 75±9 years) with complete echocardiography studies were included. Participants were mainly hypertensive (77.5%) and women (65.2%). The mean time from onset of symptoms to the outpatient visit was 131 ± 124 days. The final diagnosis, determined according to current guidelines (19), was HFPEF in 45.7% (n=63), HFREF in 23.2% (n=32), and non-HF in 31.2% (n=43) of the studied patients.

The baseline patient characteristics are shown in Table 1. The 3 diagnostic groups were similar in age, diabetes status, and previous occurrence of atrial fibrillation. Women were more prevalent in the HFPEF and non-HF groups; there were fewer patients with hypertension in the non-HF group. Patients in the HFREF group had higher prevalence of tobacco use and lower body mass index. The group of sinus rhythm patients (n=93) had similar baseline characteristics (74.2±9.4 years, 69% women, 79.3% hypertension, 29.3% diabetics, 31.7% smokers, body mass index 30.6±5 kg/m^2).

Table 1 Baseline characteristics

	HFPEF (n = 63)	HFREF (n = 32)	Non-heart failure (n = 43)	Total (n = 138)	P-value
Age (years)	76 ± 8	74 ± 12	73 ± 8	75 ± 9	0.155
Female	45 (71.4%)	**12 (37.5%)**	33 (76.7%)	90 (65.2%)	**<0.001**
Hypertension	54 (85.7%)	25 (78.1%)	**28 (65.1%)**	107 (77.5%)	**0.024**
Diabetes	15 (23.8%)	14 (43.8%)	8 (18.6%)	37 (26.8%)	0.082
Smoker	19 (30.2%)	**18 (56.3%)**	14 (32.6%)	51 (37%)	**0.002**
Previous known AF	25 (39.7%)	16 (50%)	4 (9.3%)	49 (35.5%)	**<0.001**
Degree of LV diastolic dysfunction	1.61 ± 0.07	2.02 ± 0.12	0.89 ± 04	1.47 ± 0.06	**<0.001**
Body mass index (kg/m^2)	29.62 ± 4.94	28.08 ± 5.6	**31.66 ± 4.36**	29.93 ± 5.09	**0.002**
Class of dyspnoea (NYHA) >2	27 (42.9%)	16 (50%)	**7 (16.3%)**	50 (36.2%)	**0.005**
BNP (ng/mL)	160.20 ± 124.30	300.40 ± 252.89	40.19 ± 26.41	153.00 ± 175.89	**<0.001**

AF, atrial fibrillation; BNP, natriuretic peptide B-type; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; LV, left ventricle; NYHA, New York Heart Association.
Bold values refers to statistically significant values.

Table 2 Echocardiographic parameters of all included patients (n = 138)

	Mean (n)			Statistical significance (P-value)		
	HFPEF (n = 63)	HFREF (n = 32)	Non-HF (n = 43)	Non-HF vs. HFPEF	Non-HF vs. HFREF	HFPEF vs. HFREF
LV end-diastolic volume (mL/m^2)	60 ± 15 (63)	102 ± 38 (32)	57 ± 15 (43)	1	**<0.001**	**<0.001**
LV end-diastolic diameter (mm)	50 ± 5 (63)	58 ± 9 (32)	48 ± 5 (43)	0.887	**<0.001**	**<0.001**
LV mass (g/m^2)	128.2 ± 27.6 (63)	148.8 ± 36.6 (32)	108.8 ± 21 (43)	**0.001**	**<0.001**	**0.010**
LVEF (%)	60 ± 5 (63)	34 ± 10 (32)	60 ± 4 (43)	1	**<0.001**	**<0.001**
LV longitudinal strain (%)	−16 ± 3.7 (54)	−9.5 ± 4.5 (30)	−17 ± 3.5 (37)	1	**<0.001**	**<0.001**
LV longitudinal strain rate (s^{-1})	−0.98 ± 0.26 (54)	−0.63 ± 0.23 (30)	−1.04 ± 0.26 (37)	0.951	**<0.001**	**<0.001**
LA volume (mL/m^2)	58.9 ± 23.3 (63)	57.8 ± 20.8 (32)	33.7 ± 13 (43)	**<0.001**	**<0.001**	0.129
LA anteroposterior diameter (mm)	42.7 ± 7.7 (63)	45.69 ± 6.7 (32)	36.2 ± 4.4 (43)	**<0.001**	**<0.001**	0.129
E/A	1.0 ± 0.6 (38)	1.7 ± 1.4 (16)	0.76 ± 0.2 (39)	**0.003**	**<0.001**	0.256
E-wave DT	218.7 ± 62.4 (63)	171.9 ± 45.7 (32)	239.1 ± 45.9 (43)	0.177	**<0.001**	**<0.001**
E/e′	11.3 ± 5.5 (63)	11.6 ± 7.6 (32)	7.4 ± 2.2 (43)	**0.001**	**0.003**	1.000
Pulmonary artery systolic pressure (Doppler derived)	40 ± 11 (46)	41 ± 11 (28)	33 ± 8 (14)	0.267	0.399	1.000

DT, deceleration time; LA, left atrial; LV, left ventricular; HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; Non-HF, non-heart failure; NYHA, New York Heart Association.
Bold values refers to statistically significant values.

Echocardiographic findings

Table 2 shows LV dimensions, diastolic and systolic function, and LA dimensions in the 3 groups of patients. The LV was enlarged in the HFREF group, compared to the HFPEF and non-HF groups. According to the diagnostic criteria, the LV ejection fraction was normal in non-HF and

HFPEF patients (no differences between groups) and significantly lower in the HFREF group. LV strain could be measured in 121 patients (87.7%). Impairment of LV longitudinal deformation (strain and strain-rate) was observed in the HFREF group as compared to the HFPEF and non-HF groups, with no differences between the latter two. Compared to the non-HF group, LA was significantly enlarged in both HF groups (with no statistically significant differences between them). Regarding diastolic function, E/e' and E/A index showed no differences between HF groups but significant differences with the non-HF group. E wave deceleration time was also significantly shorter in the HFREF group as compared to the HFPEF patients.

Table 3 shows LV and LA dimensions and function only for patients with sinus rhythm (n=93); LA strain could be measured in 82 of these patients (88.2%). LASRa and LASRs were significantly impaired and the LA significantly dilated in both HF groups as compared to non-HF patients, with no differences between HF groups. Again, there were no differences in the parameters of LV dimensions and systolic function between the non-HF and HFPEF groups.

The comparison of indexed LV and LA volumes, LV mass and LVEF between patients with (n=45) or without AF (n=93) at the moment of inclusion was not significantly different (p values = 0.746, 0.111, 0.520 and 0.744)

Table 3 Echocardiographic parameters of patients in sinus rhythm (ventricular and atrial measures) (n = 93)

	Mean (N)			Statistical significance (P-value)		
	HFPEF (n = 38)	HFREF (n = 16)	Non-HF (n = 39)	Non-HF vs. HFPEF	Non-HF vs. HFREF	HFPEF vs. HFREF
LV end-diastolic volume (mL/m^2)	63.7 ± 14.6 (38)	117.5 ± 44.7 (16)	57.6 ± 15.8 (39)	0.730	**<0.001**	**<0.001**
LV end-diastolic diameter (mm)	50.4 ± 5.9 (38)	61.1 ± 10.8 (16)	48.5 ± 5.2 (39)	0.672	**<0.001**	**<0.001**
LV mass (g/m^2)	136.5 ± 26.9 (38)	155.5 ± 48.3 (16)	108.3 ± 21.3 (39)	**<0.001**	**<0.001**	0.103
LVEF (%)	59.8 ± 5.3 (38)	30.1 ± 10.6 (16)	60.8 ± 3.9 (39)	1	**<0.001**	**<0.001**
LV longitudinal strain (%)	−16.7 ± 3.9 (32)	−9.8 ± 4.6 (14)	−17.1 ± 3.5 (34)	1	**<0.001**	**<0.001**
LV longitudinal strain rate (s^{-1})	−0.95 ± 0.25 (32)	−0.60 ± 0.24 (14)	−1.06 ± 0.26 (34)	0.311	**<0.001**	**<0.001**
LA volume (mL/m^2)	54.6 ± 16 (38)	54.5 ± 22.1 (16)	33.4 ± 13.1 (39)	**<0.001**	**<0.001**	1
LA positive strain (%)	8.9 ± 4.9 (36)	6.5 ± 5.4 (14)	9.9 ± 5.6 (32)	1.000	0.155	0.478
LA negative strain (%)	−10.8 ± 10.6 (36)	−11 ± 5.3 (14)	−15.2 ± 5 (32)	**0.016**	0.132	1.000
LASRa (s^{-1})	−1.22 ± 0.71 (36)	−1.10 ± 0.63 (14)	−1.97 ± 0.53 (32)	**<0.001**	**<0.001**	1
LASRs (s^{-1})	0.98 ± 0.35 (36)	0.73 ± 0.46 (14)	1.38 ± 0.40 (32)	**<0.001**	**<0.001**	0.157
LASRe (s^{-1})	−2.06 ± 8.58 (36)	−0.52 ± 0.55 (14)	−0.76 ± 0.58 (32)	1.000	1.000	1.000

HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; Non-HF, non-heart failure; LA, left atrial; LASRa, LA strain rate post A-wave; LASRs LA systolic strain rate; LV, left ventricular; LASRe, left atrial strain-rate E-wave.
Bold values refers to statistically significant values.

LA parameters for HF diagnosis

LA volume, LASRa, and LASRs were significantly correlated with BNP levels (Pearson correlation 0.326, -0.421, and -0.462, respectively; all p <0.001). Higher LA volumes and lower levels of LA strain-rate were related to higher BNP levels. These parameters were also related to the degree of LV diastolic dysfunction (Pearson correlation with LA volume: 0.417; LASRa: 0.498; LASRs: -0.462; p<0.001 in all cases).

Figure 2 shows the ROC curve for the final HF diagnosis, comparing the diagnostic values of LA dimension and function in patients with sinus rhythm. LASRa, LASRs, and LA volume predicted HF diagnosis with an area under the curve (AUC) of 0.801, 0.847, and 0.852, respectively (all

with p-value <0.001). The ratio of LASRs / LA volume index (normalization of LA deformation with LA volume, as both being determinants of LA stroke volume) had an AUC of 0.902 for HF diagnosis.

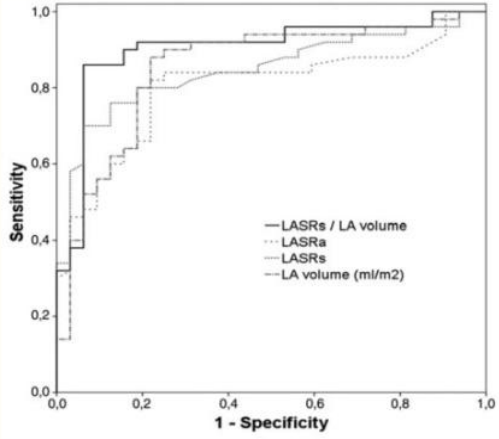

Figure 2 ROC curve for heart failure (preserved or reduced EF) diagnosis in patients in sinus rhythm. LA, left atrium; LASRa, LA strain-rate post-A-wave; LASRs, LA systolic strain rate.

Table 4 shows the cut-off values for each parameter; the LASRs / LA volume index ratio with a cut-off value of 0.025 had the best specificity, sensitivity, and positive-negative predictive values.

Table 4 Cut-off values for HF diagnosis of left atrium derived parameters

	Area under the curve	Cut-off value	Sensitivity (%)	Specificity (%)	Positive-predictive value (%)	Negative-predictive value (%)
LASRa (s^{-1})	0.801	**−1.690**	80	78	78	79
LASRs (s^{-1})	0.847	**1.065**	81	80	85	81
LA volume (mL/m^2)	0.852	**43**	80	81	81	80
LASRs/LA volume	**0.902**	**0.025**	**87**	**86**	**86**	**87**

LA, left atrial; LASRa, LA strain rate post A-wave; LASRs, LA systolic strain rate.
Bold values refers to statistically significant values.

DISCUSSION

In this study, LA function (LASRa and LASRs) was significantly impaired and LA volumes were significantly larger in both groups with HF (HFPEF and HFREF) and sinus rhythm, as compared to the non-HF group; there were no differences in LV systolic function between non-HF and HFPEF groups. In patients with sinus rhythm, LA function (strain-rate) and dimensions (LA volume) were highly predictive for the final diagnosis of HF; particularly, the greatest predictive value was achieved by combining atrial deformation and size (LASRs/LA volume index).

Previous studies have reported that LA volume helps to identify HFPEF (11) with a sensitivity and specificity similar to our results (close to 80%). In HFPEF patients, LA volume (10) and function (15,17) have been related with exercise capacity. In our study, LA function (LASRa and LASRs) was related to HF diagnosis early after symptoms onset. Additionally, effort dyspnea was the main symptom for referral to our clinic, supporting the relationship between atrial function and exercise capacity. The association of LA dysfunction or atrial fibrillation with worse clinical outcomes has been reported in previous studies (12,18); however, our data also show that these abnormalities are already present in the early stages of the disease. Similar to the findings of previous studies (13,14), we observed a significant impairment of LA deformation in both HF groups as

compared to the non-HF group, with no differences between HF groups.

In our study, LA indexed volume, LASRa, and LASRs had similar AUC for HF diagnosis. Another study compared total LA strain with LA volume (18) to assess cardiovascular prognosis in a non-HF population at time of inclusion, reporting that LA strain was the more powerful predictor of cardiovascular events Accordingly, in our study, LA deformation (LASRs, LASRa and LASRs/LAvolume) were better correlated with BNP.

We found no differences in LV deformation between the non-HF and HFPEF groups. In previous studies, the isolated analysis of LV strain in patients with HFPEF has produced controversial results (6-8). If patients were recruited mostly after a hospital admission (6,8,14), LV strain was impaired in both HFPEF and HFREF patients, with worse values in HFREF patients. However, more advanced HF patients could have been included because some of these studies applied a cut-off point of 45% to define preserved LV ejection fraction (7). Results might have also varied according to the age of the participants. *In our cohort, main LV global strain in patients with non-HF is -17.1%.* This relative low value could be explained by considering the advanced age of our patients (73±8 years) as an age-related decline in longitudinal left ventricular strain has been also previously observed (23). The lack of differences in LV strain between the HFPEF and non-HF groups in our study could be related to the fact that our

population consisted of outpatient subjects with new-onset HF symptoms. Therefore, we could hypothesize that the LA is the first to fail in the early stages of HFPEF, as LA dysfunction seems to be related to symptoms development. We observed a significant correlation between LA function (LASRa and LASRs) and LV diastolic function. If the disease progresses, LV systolic function could be more impaired, as shown in other studies with in-hospital HF diagnosis (6,8).

If atrial dysfunction is the initial mechanism in HF development, assessing LA function and dimensions could be useful for improving HF diagnosis. Our results show that LASR and LA volume have similarly good predictive values for HF diagnosis, with LASRs providing the best correlation with BNP and HF diagnosis. The combination of LA function and size, using the LASRs/LA volume index, seems to be the best predictor for HF diagnosis.

Clinical implications

Our study demonstrates structural and functional changes in the LA, even in the early stages of HFPEF. If LA function could be preserved or even improved, symptoms might improve in patients with HFPEF. More studies are needed to determine whether structural LA changes are reversible, but pharmacological (antiarrhythmic drugs) or nonpharmacological (catheter or surgical ablation) therapies aimed at maintaining sinus rhythm could potentially help to preserve LA function (24-25). Subclinical LA dysfunction can currently be identified with noninvasive imaging such as

echocardiography; therefore, LA assessment should be mandatory in this type of patients with new-onset HF symptoms.

Given difficulties in the differential diagnosis of HFPEF, the analysis of LA could be useful in daily clinical practice. The presence of an enlarged LA with normal LV ejection fraction should make clinicians consider the possibility of a HFPEF diagnosis. LA indexed volume could be a rapid and simple method to diagnose HF in ambulatory patients with new-onset HF symptoms. Additionally, LA strain analysis could add more evidence of atrial dysfunction and potentially identify those patients at higher risk of presenting overt HF symptoms.

Potential limitations

This is a descriptive study with cases and controls obtained from the same cohort. The index-symptom is dyspnea; therefore, other unknown diagnoses may exist in the non-HF group, and these could be confounding. The number of patients was limited, so these results must be confirmed by larger studies. The LA strain analysis was obtained with ECG P wave onset; other studies were performed with initial onset on QRS.

DISCLOSURES: None.

CONCLUSIONS

In an outpatient population with new-onset HF symptoms and sinus rhythm, LA volume and function measured with deformation imaging are impaired in HFPEF patients as compared to a non-HF group (while LV deformation remains normal), with no differences between HFREF and HFPEF groups.

Atrial dysfunction could be one, among others, of the initial mechanisms in the development of symptoms in HFPEF patients

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ORIGINAL INVESTIGATION

Interatrial Dyssynchrony May Contribute to Heart Failure Symptoms in Patients with Preserved Ejection Fraction

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Purpose: Heart failure (HF) with preserved ejection fraction (HFPEF) is the most prevalent type of HF in nonhospitalized patients, but its pathophysiology remains poorly understood. The aim of our study was to assess the existence of interatrial dyssynchrony (IAD), a potentially treatable condition, in the development of HF symptoms. Methods: Consecutive patients with new onset of shortening of breath, referred for suspected HF, were screened. In all cases, a transthoracic echocardiography, ECG, and determination of plasma BNP level were performed at initial consultation. Patients were diagnosed according to current guidelines. Patients with HF and reduced ejection fraction were excluded. Later, the time from P-wave onset on the ECG to peak negative strain (atrial contraction) was determined using speckle tracking echocardiography; the time difference between both atria (ms) was used as an index of IAD. Results: Sixty-six patients were included. Mean age was 74 ± 8 years (74% female, 77% hypertensive). HFPEF patients (n = 32) showed an increased IAD as compared to subjects with non-HF (n = 34; interatrial time difference 72.7 ± 27 vs. 28 ± 7 ms, P < 0.001). IAD showed a significant correlation with BNP levels, diastolic pattern, and echocardiographic parameters indicative of elevated LV filling pressures. LA function assessed by LA strain rate was not significantly different between HPPEF patients with and without IAD > 60 ms. Conclusions: We showed that IAD was present at initial stages of symptomatic HFPEF. It might be an important mechanism involved in the development of symptoms in HFPEF and a potential target amenable to be treated with device therapy.
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Key words: heart failure with preserved ejection fraction, interatrial dyssynchrony, speckle tracking echocardiography, outpatients

Heart failure (HF) with preserved ejection fraction (HFPEF) represents more than 50% of all HF outpatients.[1] Despite its high prevalence, its pathophysiology continues being poorly understood,[1] and potential therapies to address this clinical syndrome are therefore scarce. Diastolic impairment was suggested as the major contributor to the pathophysiology of HFPEF, but it is not the unique one, indeed, it is also observed in HF patients with reduced ejection fraction (HFREF).[2]

Many mechanisms have been investigated on top of diastolic abnormalities as a potential underlying etiology of HFPEF, including exercise-induced ventricular dysfunction,[3,4] impaired ventricular-arterial coupling,[5] chronotropic incompetence,[6] pulmonary hypertension,[7] and even a systemic pro-inflammatory state.[8] Additionally, several authors have described mechanical ventricular abnormalities in HFPEF patients reporting changes in longitudinal [9,10] radial and torsional motion.[11] They support the hypothesis of the existence of a potential latent ventricular systolic dysfunction not diagnosed by conventional methods. More recently, though, an "atrial hypothesis" suggesting atrial dysfunction as a contributor to symptoms among HFPEF patients is gaining ground.[12] Interatrial conduction delay (interatrial block) is associated with abnormal atrial excitability, leading to electromechanical dysfunction of the left atrium (LA) and a markedly reduction of left ventricular filing.[13]

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Purpose: *Heart failure (HF) with preserved ejection fraction (HFPEF) is the most prevalent type of HF in non-hospitalized patients, but its pathophysiology remains poorly understood. The aim of our study was to assess the existence of inter-atrial dyssynchrony (IAD), a potentially treatable condition, in the development of HF symptoms.*

Methods: *Consecutive patients with new onset of shortening of breath, referred for suspected HF were screened. In all cases, a transthoracic echocardiography, ECG and determination of plasma BNP level were performed at initial consultation. Patients were diagnosed according to current guidelines. Patients with HF and reduced ejection fraction were excluded. Later, the time from P wave onset on the ECG to peak negative strain (atrial contraction) was determined using speckle tracking echocardiography; the time difference between both atria (ms) was used as an index of IAD.*

Results: *Sixty-six patients were included. Mean age was 74±8 years (74% female, 77% hypertensive). HFPEF patients (n=32) showed an increased IAD as compared to subjects with non-HF (n=34) (inter-atrial time difference 72.7±27 vs. 28±7ms, p<0.001). IAD showed a significant correlation with BNP levels, diastolic pattern, and echocardiographic parameters indicative of elevated LV filling pressures. LA function assessed by LA strain-rate was not significantly different between HPPEF patients with and without IAD > 60 ms.*

Conclusions: *We showed that IAD was present at initial stages of symptomatic HFPEF. It might be an important mechanism involved in the development of symptoms in HFPEF and a potential target amenable to be treated with device therapy.*

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFPEF) represents more than 50% of all HF outpatients[1]. Despite its high prevalence, its pathophysiology continues being poorly understood[1], and potential therapies to address this clinical syndrome are therefore scarce. Diastolic impairment was suggested as the major contributor to the pathophysiology of HFPEF but it is not the unique one, indeed it is also observed in HF patients with reduced ejection fraction (HFREF) [2].

Many mechanisms have been investigated on top of diastolic abnormalities as a potential underlying etiology of HFPEF, including exercise-induced ventricular dysfunction[3,4], impaired ventricular-arterial coupling[5], chronotropic incompetence[6], pulmonary hypertension[6] and even a systemic pro-inflammatory state[8]. Additionally, several authors have described mechanical ventricular abnormalities in HFPEF patients reporting changes in longitudinal[9,10] radial and torsional motion[11]. They support the hypothesis of the existence of a potential latent ventricular systolic dysfunction not diagnosed by conventional methods. More recently, though, an “atrial hypothesis” suggesting atrial dysfunction as a contributor to symptoms among HFPEF patients is gaining ground[12]. Inter-atrial conduction delay (inter-atrial block) is associated with abnormal atrial excitability, leading to electromechanical dysfunction of the left atrium (LA) and a markedly reduction

of left ventricular filling[13]. Recently, *Eicher et al.* proposed inter-atrial dyssynchrony (IAD), assessed by pulse wave Doppler study of the mitral and tricuspid inflows, as a potential mechanism in a small group of HFPEF patients[14] that could be improved with pacing[15]. Speckle- tracking strain has been also applied to evaluate LA asynchrony in previous studies [16]; accordingly we used speckle- tracking echocardiography to determine IAD.

Our objective was to study the prevalence and distribution of IAD in a group of patients with new-onset HF symptoms and preserved left ventricular (LV) ejection fraction using speckle-tracking echocardiography.

MATERIALS AND METHODS

All patients with new-onset symptoms suggestive of HF, who were referred to a one-stop clinic for diagnosis between 2009 and 2012, were screened (n=172). All of them provided a written informed consent at the moment of the inclusion in the study. The study complies with the Declaration of Helsinki and was approved by the Local Ethics Committee at the Hospital. Inclusion criteria were patients with recent onset of symptoms suggestive of HF and with no previous cardiologic study. Exclusion criteria were age under 18 years, comorbidity with life expectancy lower than one year, atrial fibrillation or flutter at the moment of the visit, reduced left ventricular ejection fraction and significant heart valve disease (severity of dysfunction more than mild).

At the initial consultation, a clinical evaluation by a cardiologist was performed together with an ECG, chest X-ray, blood tests with determination of plasma BNP, and a comprehensive transthoracic echocardiography. The final diagnosis (HFPEF, HFREF or non-HF) was established in each patient according to the current guidelines using the modified algorithm proposed by *Paulus et al*[17]. As previously stated, patients with HFREF were excluded from the present study. BNP plasma levels were determined using the immunoassay Chemiluminescence and autoanalyzer ADVIA Centaur BNP kit (Siemens Healthcare Diagnostics).

Echocardiography was performed using a commercial ultrasound machine (Vivid 7, General Electric, Milwaukee, WI, USA). Left ventricular (LV) ejection fraction and mass were determined using the biplane Simpson method and the Devereux formula, respectively. LV diastolic function was evaluated using pulsed Doppler interrogation of the mitral valve inflow (early and late mitral peak velocities (E, A), deceleration time of E and A, E/A ratio), pulmonary vein flow (systolic and diastolic waves) and tissue Doppler to determine early and late diastolic myocardial velocities at the lateral mitral annulus (E', A' and E/E' ratio). LV diastolic function was graded as normal, mild dysfunction (grade I), moderate dysfunction (grade II) and severe dysfunction (grade III) using current recommendations[18]. Systolic pulmonary arterial pressure (PAP) was estimated from the tricuspid regurgitation peak velocity. LA volumes were calculated by

modified Simpson's Method from images in the 4-chamber apical view. LA active volume was calculated as the difference between LA volume at the onset of the P wave on the ECG (pre-atrial contraction volume) and LA minimum volume. LA passive volume was calculated as the difference between LA maximum volume and LA volume at the onset of the P wave on the ECG (pre-atrial contraction volume). LA deformation was measured with a commercially available dedicated software from 2D echocardiographic images (2D strain, EchoPACTM, GE Healthcare, Milwaukee, WI). In order to measure LA function, location of the trigger was set at the P wave on the ECG instead of the QRS and adequate tracking of the LA walls was ensured before processing the images. The frame rate was set between 60 and 80 frames. Global longitudinal LV strain-rate (6 segments from the 4-chamber view) and LA strain-rate waves (LA peak systolic strain-rate (s-wave) and LA peak strain-rate after atrial contraction (a-wave)) (6 segments from the 4-chamber view) were quantified.

Interatrial electrical and mechanical dyssynchrony

The presence of mechanical IAD was evaluated using speckle tracking echocardiography in an off-line analysis using commercially available software (2Dstrain, EchoPac, General Electric, Milwaukee, WI, USA). Global longitudinal myocardial strain of both atria was obtained from the apical 4-chamber view. The electromechanical delay from the P wave onset to the peak of left and right atrium systole was

estimated as the difference between the time from onset of the P wave on the surface ECG and the time to peak negative longitudinal strain (atrial contraction) of the left (LAps) and right atria (RAps). The time difference between both atria (LAps-RAps) (ms) was used as an index of mechanical IAD (Figure 1). Intra-LA delay was measured as the delay between the peak negative longitudinal strain of the septal and lateral LA wall.

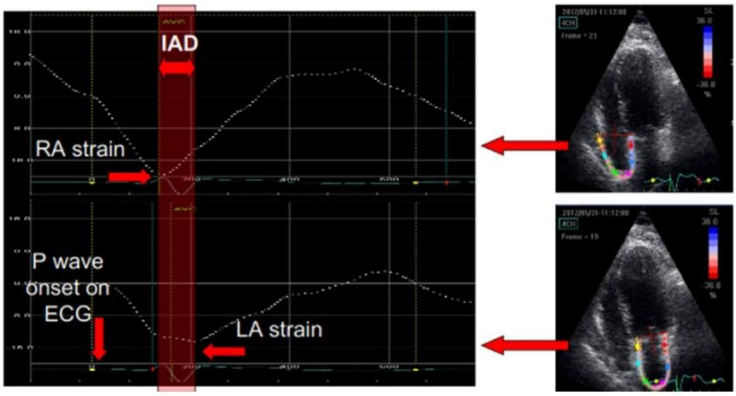

Figure 1. Interatrial dyssynchrony determination using speckle tracking echocardiography. In all subjects, the time from onset of the P-wave on the ECG to peak negative strain (atrial contraction) was determined using speckle tracking from apical four-chamber views; the time difference between both atria (ms) was used as an index of IAD. IAD = interatrial dyssynchrony; RA = right atria; LA = left atria.

Inter-atrial electrical dyssynchrony was evaluated assessing the inter-atrial conduction delay on the surface ECG, which was performed at 25 mm/s speed. P wave duration, QRS width, PR interval and the interval between the onset of the P to the end of the R waves (PeR) were measured. Additionally, and according to the Spodick Criteria, inter-atrial conduction delay was defined as the

prolongation of P by more than 120ms in at least one of the 12 leads[19].

Statistical analysis

Data are reported as percentages or mean values ± standard deviation. Comparison between categorical or quantitative groups was done with Chi-squared or T-Student, when appropriate. Pearson correlation test was used to explore correlations between quantitative variables. A p-value lower than 0.05 (two sided) was considered statistically significant. All the statistical analysis was performed with SPSS© v.19 (IBM Corporation, Armonk, NY, USA).

RESULTS

Clinical characteristics

One hundred and thirty-eight patients were screened with suitable echocardiograhic images acquisition; final diagnoses were as follows: 23.2% (n=32) patients with HFREF, 45.7% (n=63) with HFPEF and 31.2% (n=43) with non-HF. Then, HFREF patients (n=32) and those with atrial fibrillation at the moment of the echocardiography (n=29) were excluded according to the pre-established exclusion criteria of the study. Eleven additional patients were also excluded for significant heart valve disease. Finally, a group of 66 patients constituted the present study population.

Mean age was 74±8 years and 74% were females. Final diagnosis was HFPEF in 34 patients (51.5%) and non-HF in

32 (48.5 %). There were no significant differences between the two groups regarding age, gender, NYHA functional class and cardiovascular risk factor profiles, except for systemic hypertension that was more pre-valent in the HFPEF group. In HFPEF patients, higher BNP levels were also obser-ved. Table 1 summarizes the clinical features of the study population.

TABLE I

Clinical Characteristics of Diagnostic Groups

	HFPEF (n = 34)	Non-HF (n = 32)	P-Value
Age (years)	75.2 ± 8.9	72.9 ± 7.5	0.254
Male	28% (9)	23% (8)	0.525
BMI	30.1 ± 5.1	31.2 ± 3.6	0.329
Hypertension	93.6% (30)	61.8% (21)	**<0.001**
Smokers	25% (8)	35.3% (12)	0.363
GFR < 60 mL/min	40.6% (13)	23.5% (8)	0.136
Diabetes	21.9% (7)	17.6% (6)	0.666
Dyslipemia	44.1% (15)	53.1% (17)	0.806
BNP	119.9 ± 112.0	37.4 ± 21.0	**<0.001**
FC NYHA > II	25% (8)	8.8% (3)	0.078

Bold values indicate statistically significant differences. BMI = body mass index; BNP = brain natriuretic peptide; FC NYHA = functional class New York Heart Association.

TABLE II

ECG Intervals

	HFPEF	Non-HF	P-Value
P-wave (ms)	81 ± 35	74 ± 33	0.430
PR (ms)	173 ± 26	158 ± 36	0.089
PeR (ms)	86.3 ± 31	84.5 ± 30	0.828
QRS (ms)	95 ± 24	97 ± 27	0.783
IAB (n)	18.8% (6)	11.8% (4)	0.429

IAB = presence of interatrial block; PeR = end of P to R interval; PR = PR interval; QRS = QRS interval.

TABLE III

Echocardiographic Measures

	HFPEF (n = 34)	Non-HF (n = 32)	P-Value
LVEF (%)	59.6 ± 5	60.6 ± 4	0.379
LVMi (g/m^2)	133.2 ± 28	110.9 ± 26	**<0.001**
LVTDD (mm)	51 ± 5.9	49 ± 5.2	0.153
LVTDVi (mL/m^2)	116.9 ± 39.6	106.5 ± 29.4	0.229
LAVi (mL/m^2)	58.2 ± 16	32 ± 11	**<0.001**
LA active volume (mL)	16.9 ± 10.7	15.5 ± 9.8	0.628
LA passive volume (mL)	20.5 ± 12.2	17.4 ± 11.7	0.349
E/e′	12.3 ± 6	7.4 ± 2	**<0.001**
E/A	1.08 ± 0.6	0.79 ± 0.25	**0.022**
Mitral E DT (ms)	233 ± 32	237 ± 45	0.810
PAPs (mmHg)	37.5 ± 6	33.7 ± 9	0.171
Degree diastolic dysfunction ≥ 2	40.6%	0	**<0.001**
IAD (ms)	72.7 ± 27.2	27.8 ± 7.5	**<0.001**
LV longitudinal SR (/sec)	−0.98 ± 0.27	−1.02 ± 0.3	0.582
LA global strain (%)	19.27 ± 5.17	25.26 ± 6.21	**0.001**
LA SR a-wave (/sec)	−1.14 ± 0.72	−1.92 ± 0.53	**<0.001**
LA SR s-wave (/sec)	0.94 ± 0.32	1.42 ± 0.37	**<0.001**
RA global strain (%)	22.50 ± 7.36	24.08 ± 9.23	0.532
RA SRa (/sec)	−1.47 ± 0.57	−1.80 ± 0.62	0.079
RA SRs (/sec)	1.18 ± 0.49	1.31 ± 0.59	0.413

Interatrial dyssynchrony

Electrical IAD parameters are shown in Table 2. The prevalence of an inter-atrial block as defined on the surface ECG and the length of the PR interval were not statistically different in both groups, despite a trend to higher prevalence of electrical inter-atrial dyssynchrony and longer PR intervals in the HFPEF group. Additionally, no differences existed regarding P wave or QRS duration, either. Table 3 depicts the echocardiographic characteristics of both groups of patients including the assessment of mechanical IAD. LV ejection fraction, dimensions and longitudinal strain-rate were not significantly different in the HFPEF and non-HF groups. LV mass was significantly larger in the HFPEF group. PAP was mildly elevated in the two groups without significant differences between them (37.5±6 vs. 33.7±9mmHg). As anticipated, we found a higher LA volume and parameters indicative of elevated LV filling pressure in the HFPEF group (higher E/e' and E/A ratios). LA strain and strain-rate ("a" - depicting atrial contraction- and "s" –depicting ventricular systolic- peak strain-rate) were significantly decreased in HFPEF group, while RA strain and strain-rate showed no statistically significant differences between groups. HFPEF patients also showed an increased inter-atrial time difference to peak atrial contraction as a marker of IAD as compared to the non-HF group (72 ±27 vs. 28 ±7 ms, $p<0.001$).

Significant LV diastolic dysfunction (grade ≥ II) was present in 40.6% of the HFPEF patients and in none of the non-HF patients. Patients with HFPEF and grade II LV diastolic dysfunction had significantly higher systolic pulmonary artery pressure estimates (40.8 ±6 vs. 34.8 ± 7 mmHg; p=0.040) and more IAD as shown by longer inter-atrial time difference to atrial contraction (83.3±26 vs. 41.4±25 ms; p<0.001).

Relation between elevated filling pressures and interatrial dyssynchrony

IAD had a significant correlation with echocardiographic parameters of elevated LV filling pressures (E/E' r=0.46, p<0.001; E/A r=0.41, p<0.001), LA indexed volume (r=0.43, p<0.001), diastolic pattern (r=0.53, p<0.001) and BNP levels (r=0.37, p=0.002).

Figure 2 shows the relationship between BNP plasma levels and IAD, representing each individual by his/her final diagnosis and LV diastolic function pattern. Patients with higher IAD showed higher BNP levels. All patients with non-HF (all with normal LV diastolic pattern or grade I diastolic dysfunction) are depicted in a small area of the graph with BNP levels below 100 ng/ml and IAD less than 60 ms. Conversely, HFPEF patients are mainly depicted outside this area.

The prevalence of severe IAD, as defined by a cut-off point of 60 ms as previously described[14], was 66% in HFPEF patients and 0% in the non-HF group.

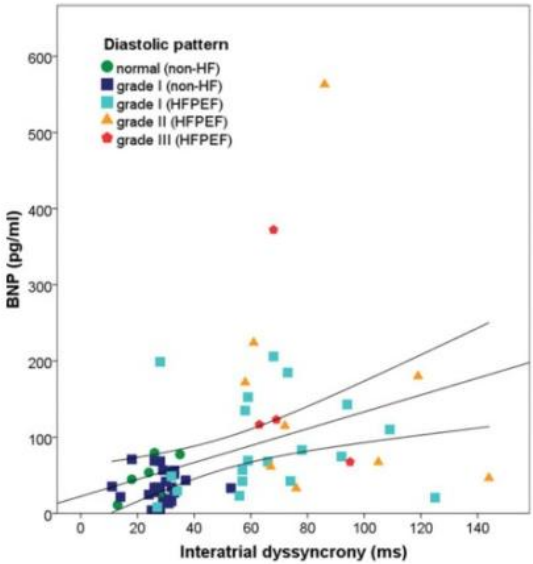

Figure 2. Correlation of interatrial dyssynchrony with BNP (r = 0.372; P = 0.002). Individual diastolic pattern is showed. HFPEF = heart failure preserved ejection fraction; non-HF = no heart failure.

Table 4 shows the clinical and echocardiographic characteristics of HFPEF patients depending of the severity of the IAD. There were no significant differences between groups in age, LA size or arterial systolic pressure. The measurement of LA and RA strain and strain-rate showed no statistically significant differences between groups despite a trend to lower LA SRs in patients with IAD >60 ms was observed. Patients with IAD > 60 ms also showed higher

prevalence of significant LV diastolic dysfunction with a trend towards higher levels of plasma BNP levels. Intra-LA delay showed no significant differences between groups.

TABLE IV

Comparison between Patients According to the IAD (HFPEF Patients)

	IAD < 60 ms (n = 11)	IAD ≥ 60 ms (n = 21)	P-Value
IAD	47.73 ± 14	85.90 ± 22.99	**<0.001**
Age (years)	75.91 ± 10.29	74.86 ± 8.34	0.773
BNP	85.03 ± 66.82	138.11 ± 127.23	0.208
LAVi (mL/m^2)	60.48 ± 13.93	57.02 ± 16.62	0.561
E/e'	11.16 ± 2.11	12.93 ± 6.95	0.417
E/A	0.78 ± 0.31	1.25 ± 0.70	0.048
Mitral E DT (ms)	246.64 ± 52.04	226.19 ± 71.73	0.411
PAPs (mmHg)	36.63 ± 7.73	38.18 ± 4.73	0.593
Grade diastolic dysfunction ≥ 2	9.1%	57.1%	**0.007**
NYHA > II	18.2%	28.6%	0.535
Previous use of diuretics	45.4%	47.62%	0.519
LA global strain (%)	20.00 ± 4.05	18.90 ± 5.72	0.608
LA SR a-wave (/sec)	−1.33 ± 0.69	−1.04 ± 0.73	0.348
LA SR s-wave (/sec)	1.09 ± 0.38	0.86 ± 0.26	0.079
RA global strain (%)	25.35 ± 6.70	20.67 ± 7.23	0.140
RA SRa (/sec)	−1.68 ± 0.40	−1.34 ± 0.63	0.170
RA SRs (/sec)	1.21 ± 0.36	1.16 ± 0.57	0.833
Intra-LA delay (ms)	41.25 ± 36.71	57.19 ± 35.12	0.268

Bold values indicate statistically significant differences. IAD = interatrial dysssynchrony; LA = left atrial; LAVi = left atrial indexed volume; LV = left ventricular; PAPs = systolic pulmonary artery pressure; RA = right atria; SRa = peak atrial strain rate; SRs = peak systolic strain rate.

DISCUSSION

Patients with new-onset symptoms of HF and a final diagnosis of HFPEF according to the Paulus criteria[17] presented more IAD than non-HF patients. A significant correlation was also found between BNP levels and the presence of IAD in the studied population.

It is well known that electromechanical abnormalities of the LA correlate with its contractile dysfunction and represent a risk factor for the development of congestive HF and atrial arrhythmias[13,21]. In our study, the surface ECG was

registered at a 25 mm/s speed, which might explain its low sensibility and specificity to assess the atrial electromechanical delay as compared to the report of Spoddick. Indeed, we found a low prevalence of inter-atrial block (non-HF 11.8% versus HFPEF 18.8%; p=0.429) with no significant increase of P wave duration in the two study groups. However, when we analysed mechanical IAD with the use of speckle tracking echocardiography, we found a significantly high prevalence of IAD in patients with HFPEF, which is in accordance to what has been previously reported[14]. We found that patients with HFPEF presented a mean time difference to peak atrial contraction between both atria 72 ± 27 ms, which is similar to that described by *Eicher et al*. [14]; also, values observed in our control group and those reported by *Eicher et al* in their control group were similar (27.8 ± 7 versus 24.1 ± 12 ms). However, our population included only patients with new onset symptoms, indicating the presence of this mechanical abnormality even in early stages of HF and suggesting a potential role in the pathogenesis and development of symptoms in patients with HFPEF.

The linear relationship between IAD and plasma BNP also suggests a correlation between higher IAD value and worse clinical status[20]. According with the cut-off point of severe IAD (≥ 60 ms) previously established by *Eicher et al*[14] we found a significantly worse diastolic pattern and a trend to higher BNP levels in the group of patients with more severe IAD (i.e. longer time differences between onset of

contraction of both atria). Despite there was a significant correlation of IAD with LA volume, the latter was not significantly different in the HFPEF patients with or without severe IAD. If we focused on LA function, it was significantly decreased in HFPEF respect non-HF group (lower atrial strain-rate), but when we compared HFPEF patients with an IAD lower and higher than 60 ms, no differences were noted in LA function (LA strain rate). These findings are important because the group of patients with severe IAD had worse classical clinical indicators of HF (BNP and LV diastolic dysfunction pattern) with similar LA size and strain-rate, suggesting that IAD is an independent mechanism implicated in HFPEF beyond LV diastolic dysfunction or LA strain. On the other hand, we found patients with LV diastolic dysfunction grade I (impaired relaxation) in non-HF and HFPEF groups, but HFPEF patients had higher BNP levels and longer inter-atrial time differences for reaching atrial contraction (i.e. more IAD), as compared to non-HF patients. This finding also indicates that diastolic function impairment is not the same as HFPEF. It is a complex clinical syndrome with several involved mechanisms with LV diastolic dysfunction being only one of them.

According to our findings, our hypothesis is that IAD is not only a consequence of an elevated LA filling pressure but might be also a contributor to the development of overt clinical HFPEF. A delayed atrial contraction induces loss of

atrio-ventricular coupling and consequently the loss of “atrial kick”, reducing atrial emptying volume and increasing atrial afterload and filling pressure. Moreover, this mechanism could be exacerbated during exercise with higher heart rates. The LA responds to higher volume and pressure overload with progressive dilatation and fibrosis[22,23], its performance finally getting impaired when dilatation is excessive[24].

A dual chamber pacemaker (one lead in coronary sinus and one lead at inter-ventricular septum) has been attempted in six patients with high degree of IAD and severe LV diastolic dysfunction with an improvement in exercise capacity, ventricular filling, and symptoms as well as a reduction in hospital admissions at 1 year of follow-up[15]. Therefore, pacing may be effective by interrupting a vicious circle where the alteration in the conduction of the electrical signal secondary to LA enlargement and fibrosis irreversibly deteriorate already sick atria.

LIMITATIONS

Our study had several limitations. This is an observational study with a reduced number of patients; the control group (non-HF patients) was also derived to the one-stop clinic for suspected HF but this diagnosis was ruled out after the consultation; therefore, they were not a pure healthy

control group and they could indeed, have other conditions that could act as confounders.

We did not perform electrophysiological studies to the studied population. Consequently, there was no direct comparison of the IAD data obtained with speckle tracking echocardiography and the electrophysiological study. However, the reproducibility with the data of *Eicher at al.* [14] suggests a good concordance with the electrophysiological data and validates our measurements. Even though mechanical dyssynchrony is complex to assess by single measurements such as time-to-peak, we believe that its relevance is enough for the perspective of our application. The low prevalence of inter-atrial block and the low mean values of P wave duration as compared to previous studies may be explained by the fact that we did not use a magnifying lens and that ECGs were registered at a 25 mm/s, which limited the accuracy in the measurement of ECG segments. However, we believe that our observations are at least enough to generate this pathophysiologic hypothesis that should certainly be confirmed with larger prospective studies.

CONCLUSIONS

In outpatients with HF symptoms onset and HFPEF, there is an increased prevalence of IAD. Our findings suggest that IAD could be an early abnormality in HFPEF, and that it could contribute to overt clinical symptoms in these patients. IAD would worsen LA filling pressure, thus worsening

exercise performance in the early stage of HFPEF; later on, it would contribute to resting symptoms.

Speckle tracking echocardiography to assess IAD is a reliable and non-invasive technique that could be added to the conventional echocardiographic study of symptomatic patients with suspected HFPEF in order to identify a potential target for device therapy.

CONFLICT OF INTEREST: None declared

AUTHORS CONTRIBUTION:
Laura Sanchis: Concept /design, Data analysis /interpretation, Statistics, Drafting article, Data collection, Approval of article.
Luca Vannini: Concept /design, Data analysis /interpretation, Statistics, Drafting article, Data collection, Approval of article.
Luigi Gabrielli: Concept /design, Data analysis/interpretation, Critical revision of article, Approval of article.
Nicolas Duchateau: Critical revision of article, Approval of article.
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Rut Andrea: Critical revision of article, Approval of article.
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Marta Sitges: Concept /design, Critical revision of article, Approval of article.

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ORIGINAL ARTICLE

Prognosis of new-onset heart failure outpatients and collagen biomarkers

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ABSTRACT

Background Prognosis of heart failure patients has been defined in hospital-based or retrospective studies. This study aimed to characterize prognosis of outpatients with new-onset preserved or reduced ejection fraction heart failure; to explore the role of collagen turnover biomarkers (MMP2, MMP9, TIMP1) in predicting prognosis; and to analyse their relationship with echocardiographic parameters and final diagnosis.

Methods This is an observational, prospective, longitudinal study. Outpatients with new-onset heart failure symptoms referred to a one-stop clinic were included. Echocardiography and biomarkers plasma levels determination were performed at the inclusion. A prospective follow-up was conducted to report cardiovascular events. The discriminant analysis was applied to identify the parameters related to cardiovascular outcomes.

Results A total of 172 patients (75 ± 9 years) were included, 67% with heart failure (64% preserved and 36% with reduced ejection fraction). During follow-up (median 34·5 months), 32·6% had at least one cardiovascular event and 9·9% died. Heart failure groups showed no differences in cardiovascular outcomes with a higher rate of events than nonheart failure patients. MMP2 and TIMP1 were correlated with diastolic dysfunction (Rho 0·349 and 0·294, $P < 0·001$). In the discriminant analysis, the combination of biomarkers with clinical, biochemical and echocardiographic parameters was useful to predict cardiovascular outcomes (AUC ROC 0·806, Wilks lambda 0·7688, $P < 0·001$).

Conclusions Prognosis of outpatients with new-onset heart failure symptoms is comparable between heart failure with preserved or reduced subgroups. The addition of biomarkers specially MMP2 and high sensitive troponin I to other clinical, biochemical and echocardiographic variables can predict cardiovascular prognosis at the time of diagnosis.

Keywords collagent turnover biomarkers, discriminant analysis, heart failure, heart failure with preserved left ventricular ejection fraction, outpantients, prognosis.

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Introduction

Heart failure (HF) is prevalent in the outpatient population and associated with elevated morbidity and mortality [1]. The disease occurs in 1% of the population older than 40 years, and its prevalence doubles with each 10 years of age, reaching 10% in the population older than 70 years [2]. In ambulatory patients, the most prevalent form is HF with preserved left ventricle ejection fraction (HFPEF) [3], with an increasing trend in its proportion of these diagnoses [4]. In the reference area of our hospital, two-third of patients with HF have HFPEF [5]. Left ventricular ejection fraction (as a surrogate of systolic function measured by standard echocardiography) is normal in HFPEF, making its diagnosis more difficult than in HF with reduced ejection fraction (HFREF). Therefore, a significant proportion of HFPEF patients may remain underdiagnosed despite its elevated prevalence. Diagnosis of HFPEF using specific algorithms can be readily performed in a one-stop outpatient clinic, as it has been previously reported [5].

Previous studies showed similar morbidity and mortality between HFPEF and HFREF [3,6–9], although in a few instances, HFPEF had a better prognosis [10]. Almost all of the studies evaluated HF prognosis in populations diagnosed after hospital admission [3,6,9] or in retrospective studies [4,7]. The outcomes of patients with HF diagnosed in ambulatory setting have not been well reported. Early diagnosis of HF would improve the prognosis of these patients by early treatment and close follow-up. Some scores have been developed to predict

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INTRODUCTION

Heart failure (HF) is prevalent in the outpatient population and associated with elevated morbidity and mortality[1]. The disease occurs in 1% of the population older than 40 years, and its prevalence doubles with each 10 years of age, reaching 10% in the population older than 70 years[2]. In ambulatory patients, the most prevalent form is HF with preserved left ventricle ejection fraction (HFPEF)[3], with an increasing trend in its proportion of these diagnoses[4]. In the reference area of our hospital, two thirds of patients with HF have HFPEF[5]. Left ventricular ejection fraction (as a surrogate of systolic function measured by standard echocardiography) is normal in HFPEF, making its diagnosis more difficult than in HF with reduced ejection fraction (HFREF). Therefore, a significant proportion of HFPEF patients may remain underdiagnosed despite its elevated prevalence. Diagnosis of HFPEF using specific algorithms can be readily performed in a one-stop outpatient clinic, as it has been previously reported[5].

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close follow-up. Some scores have been developed to predict incident HF in general population. The health ABC Heart Failure Score was created to predict new-onset HF requiring hospitalization in the elderly general population including clinical, biochemical and echocardiographic variables (age, history of coronary disease, smoking, baseline systolic blood pressure, heart rate, serum glucose, creatinine, albumin levels and left ventricular hypertrophy) [11].

The B-type natriuretic peptide (BNP) is useful in diagnosing HF and predicting prognosis [3,12,13]. Patients with HF have an increased myocardial stiffness secondary to a higher proportion of collagen and an increase in cardiomyocyte stiffness [14]. Metalloproteases are involved in the collagen turnover and they are related to ventricular fibrosis [15]. Metalloproteases have been also related to the presence of left ventricular hypertrophy and diastolic dysfunction [16,17]. These biomarkers were initially studied for HF diagnosis[18,19], and their utility in predicting prognosis has been explored only partially in HFREF diagnosed after hospital admission[20]. Little is known about their usefulness in HFPEF prognosis.

The main objectives of this study were to characterize prognosis of outpatients diagnosed in a one-stop HF clinic with new-onset HF symptoms (including both HFPEF and HFREF), and to explore the predictive value of matrix metalloproteases 2 and 9 (MMP2 and MMP9) and the tissue inhibitor of metalloproteases-1 (TIMP1), combined with other

clinical and classical predictors of prognosis. We also aimed to assess the relationship of these metalloproteases with diastolic function and diagnosis of HF (HFPEF and HFREF).

METHODS

Study Design and Ethics

This is an observational, prospective, longitudinal study performed in a cohort of outpatients who presented with new-onset HF symptoms. The study protocol complied with the declaration of Helsinki, was approved by the Ethics Committee of our institution, and all participants provided written informed consent. Reporting of the study conforms to STROBE statement.[21]

Patients

We included consecutive patients with new-onset HF symptoms referred to our one-stop cardiology clinic for HF diagnosis[5]. They were diagnosed as HFPEF, HFREF or non-HF following a systematic algorithm, based on the consensus statement of the European Society of Cardiology [22,23]. The algorithm included clinical evaluation, BNP and an echocardiography study. It was previously reported elsewhere[5]. The cut-off value to define reduced or preserved left ventricular ejection fraction was 50%[23]. Patients were referred from primary health centers in our reference area (population 350 000). The methodology of this one-stop clinic has been previously reported[5]. Briefly, all

patients underwent clinical evaluation, electrocardiogram, and comprehensive conventional 2-dimensional Doppler echocardiography that included assessment of cardiac dimensions, ventricular systolic and diastolic function, and valve function. At the time of inclusion, BNP and high sensitive Troponin I (HsTnI) were analyzed (ADVIA Centaur; Siemens Healthcare Diagnostics, Tarrytown, NY) and MMP2, MMP9, and TIMP1 plasma concentrations were measured by ELISA (R&D Systems; Minneapolis, MN) in peripheral blood samples. The intra-assay coefficient of variability and cut-offs values of tested biomarkers were: BNP <5%, 37 pg/ml; HsTnI <5%, 0.05 ng/ml; MMP2 <5.9%, 267 ng/ml; MMP9 <5%, 105 ng/ml and TIMP1 <5%, 279 ng/ml. The echocardiographer was blinded to the biomarkers results.

Exclusion criteria were age <18 years, life expectancy <1 year, inability to perform diagnostic circuit and/or prior hospitalization due to HF.

Follow-up

Clinical follow-up was provided by the primary care physicians and cardiologists responsible for prospectively reporting events, and a telephone interview was also conducted every 12 months by the research team. All of them were blinded to the results of biomarkers. All emergency room visits, hospital admissions, and deaths were reported. Follow-up duration was defined as the interval between the

date of the first visit to the outpatient clinic for diagnosis and the date of the last contact or death.

Primary endpoint was a composite endpoint of all-cause death, any cardiovascular hospitalization, or any visit to the emergency room due to cardiovascular cause. Cardiovascular events included HF, acute coronary syndrome, arrhythmic event, cardiogenic syncope, hypertensive emergency, stroke, sudden death, and death.

Statistical Analysis

The variables are shown as mean ± standard deviation, frequency distribution, or proportions, as appropriate. A descriptive and comparative analysis was performed for the HFPEF and HFREF subgroups. The $\chi 2$-test or Fisher test was used to compare categorical variables and the t-student for independent samples for quantitative variables. Discriminant analysis was applied to test a combination of variables related to cardiovascular prognosis. This type of statistical analysis was previously used to stratify risk in cardiac patients[24]. The value obtained in the discriminant analysis was explored as a predictor of cardiovascular events by a receiver operating characteristic (ROC) analysis. Reclassification index was assessed to evaluate the additional value of biomarkers in risk stratification. Survival curves for patient groups were estimated using the Kaplan-Meier product-limit estimator and these were compared using the log-rank test. A p-value <0.05 (two sided) was considered statistically significant. SPSS® version 18.0 software was used for statistical analysis.

RESULTS

Demographics and clinical data

172 consecutive patients attended in the HF clinic were included. Metalloproteinase assessments were not available for the first 21 consecutive patients. Most patients were referred from primary health care centers, by cardiologists (n=88; 51.2%) and general practitioners (n=56;32.6%). The remaining 16.3% (n=28) were referred from the hospital emergency room. Overall, patients were elderly (mean age 75±9years) and a majority were women (63.9%). Only 12 patients had significantly impaired renal function (glomerular filtration <30 ml/min), 4 (7%) in the non-HF group and 8 (7%) in the HF group. Following current guidelines[22], the final diagnosis of HF was reached in 115 patients (66.8%), 74 (64.3%) HFPEF and 41 (35.7%) HFREF. Baseline characteristics of all patient groups are presented in Table 1.

Table 1 Baseline characteristics of patients according to diagnosis

	Non-HF *n* = 57	HF *n* = 115	*P* value	HFREF *n* = 41	HFPEF *n* = 74	*P* value
Age	73·2 ± 8·6	75·4 ± 9·9	0·149	73·9 ± 12·2	76·3 ± 8·3	0·270
Female	41 (71·9%)	69 (60%)	0·125	14 (34·1%)	55 (74·3%)	**<0·001**
Hypertension	39 (68·4%)	96 (83·5%)	**0·024**	31 (75·6%)	65 (87·8%)	0·091
Dyslipidaemia	26 (45·6%)	57 (49·6%)	0·625	21 (51·2%)	36 (48·6%)	0·792
Diabetes	12 (21·1%)	37 (32·2%)	0·128	17 (51·5%)	20 (27%)	0·112
Tobacco	21 (36·8%)	46 (40%)	0·689	25 (61%)	21 (28·4%)	**<0·001**
AF	5 (8·8%)	54 (47%)	**<0·001**	21 (51·2%)	33 (44·6%)	0·495
BMI (Kg/m^2)	31·7 ± 4·4	29·1 ± 5·2	**<0·001**	28·1 ± 5·6	29·6 ± 4·9	0·130
FC (NYHA) ≥ 3	7 (12·3%)	43 (37·4%)	**<0·001**	16 (39%)	27 (36·5%)	0·788

AF, atrial fibrillation; BMI, body mass index; GF, glomerular filtration; FC (NYHA), functional class (New York Heart Association)); HF, heart failure; HFREF: HF with reduced ejection fraction; HFPEF, HF with preserved ejection fraction.
Bold values refer to statistically significant variables.

Hypertension and atrial fibrillation were more prevalent in both HF subgroups than in non-HF patients. Conversely, the latter had higher body mass index than HF patients. HFREF patients were more exposed to tobacco and HFPEF patients were mostly females.

Follow-up

Median follow-up was 34.5 months (P_{25-75} 23.2-43.8 months). During follow-up, 1 patient was lost, 17 died, and 56 had at least 1 cardiovascular event.

In the HFREF subgroup, 6 patients (14.6%) died: 3 due to sudden death, 1 due to terminal HF, and 2 from unknown causes. In the HFPEF subgroup, 8 patients (10.8%) died: 1 due to sudden death, 2 due to terminal HF, 2 due to a stroke, and 3 from noncardiovascular causes (2 colon cancer, 1 hemoptysis). In the group of patients without HF, there were 3 deaths (5.4%), all from noncardiovascular causes (lymphoma, advanced chronic renal dysfunction, and sepsis).

One third of the patients (n=67) had at least one hospital admission during follow-up, 31 (46.3%) of them due to a cardiovascular reason. More than half of patients (n=104) were visited on the emergency room at least once, 39 of them (37.5%) due to cardiovascular reasons (Table 2).

During follow-up, the result of the etiologic study of HFREF was: Ischemic heart disease 34.1% (n=14), valvular heart disease 12.2% (n=5), non-compaction cardiomyopathy 4.9% (n=2), alcoholic cardiomyopathy 2.4% (n=1), idiopathic

cardiomyopathy 21.9% (n=9), tachycardiomyopathy 14.6% (n=6), hypertrophic cardiomyopathy 2.4% (n=1) and unknown etiology 7.3% (n=3).

Table 2 Clinical events during follow-up

	HFPEF (*n* = 74)	HFREF (*n* = 41)	Non-HF (*n* = 56)	Total (*n* = 171)
Deaths	**8 (10·8%)**	**6 (14·6%)**	**3 (5·4%)**	**17 (9·9%)**
CV hospital admission*	**20 (27%)**	**9 (21·9%)**	**2 (3·6%)**	**31 (18·1%)**
All causes hospital admission*	36 (48·6%)	14 (34·1%)	17 (30·5%)	67 (39·2%)
Emergency room CV visit*	**21 (28·4%)**	**11 (26·8%)**	**7 (12·5%)**	**39 (22·8%)**
Emergency room all causes visit*	48 (64·9%)	22 (53·7%)	34 (60·7%)	104 (60·8%)

*At least one episode.
CV, cardiovascular; HF, heart failure; HFREF, HF with reduced ejection fraction; HFPEF, HF with preserved ejection fraction.
Bold values refer to variables included in the composite endpoint to define cardiovascular prognosis.

Biomarkers and heart failure

The mean BNP value was 170.6±290.2ng/ml; the median was 84 ng/ml. The mean HsTnI value was 0.030±0.004ng/ml, median 0.017ng/ml. Metalloprotease results were as follows: MMP2, mean 343.9±101.2ng/ml, median 337.8ng/ml; MMP9, mean 101.8±71.1 ng/ml, median 81.25ng/ml; TIMP1, mean 153.3±58.7ng/ml, median 141.1ng/ml.

When we compared biomarkers between HF and non-HF patients (Figure 1A), BNP, HsTnI, MMP2, and TIMP1 levels were significantly increased in the HF group; MMP9 levels were comparable between groups (BNP 191 ± 160 vs. 42 ± 26ng/ml, p<0.001; HsTnI 0.036 ± 0.066 vs. 0.017 ± 0.001ng/ml , p=0.003; MMP2 407 ± 109 vs. 312 ± 66ng/ml, p<0.001; TIMP1 172 ± 56 vs. 128 ± 32ng/ml, p<0.001; MMP9 97 ± 54 vs. 78 ± 52ng/ml, p=0.156).

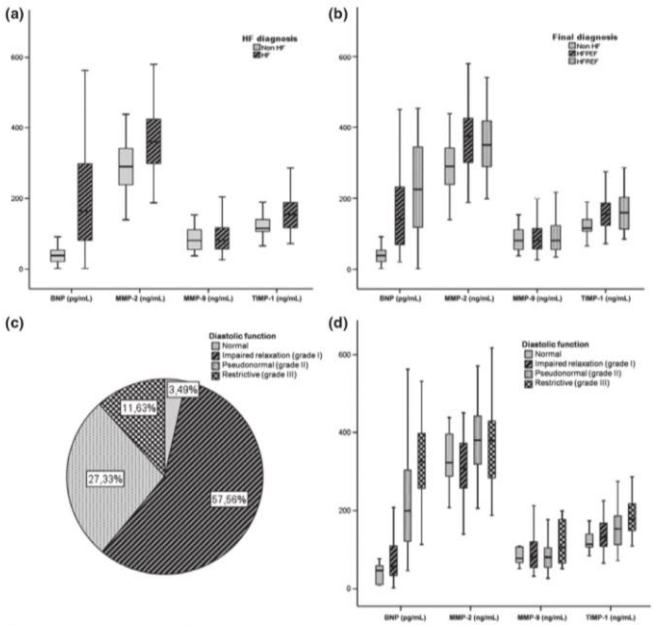

Figure 1 Levels of metalloproteinases and BNP according to final diagnosis or diastolic pattern. (a) Biomarkers according to diagnosis of HF or non-HF. (b): Biomarkers according to diagnosis of non-HF, HFPEF or HFREF. (c): Distribution of patients according to each type of diastolic pattern in the total population. (d): Levels of metalloproteases and BNP according to the left ventricular diastolic pattern. BNP: brain natriuretic peptide B-type; HF: heart failure; HFPEF: HF with preserved ejection fraction; HFREF: HF with reduced ejection fraction; MMP: matrix metalloprotease; TIMP: metallopeptidase inhibitor.

However, in a comparison between the HFPEF and HFREF subgroups (Figure 1B) only BNP and HsTnI levels have significant difference between the subgroups (BNP 175.62 vs. 366.37ng/ml, p=0.028; HsTnI 0.023 vs. 0.060ng/ml, p=0.001; MMP2 376.20 vs. 364.30ng/ml, p=0.570; MMP9 106.57 vs. 109.56ng/ml, p=0.857; TIMP1

164.64 vs. 169.46ng/ml, p=0.717). (Figure 1 shows levels of metalloproteases according final diagnosis and diastolic pattern)

MMP2, TIMP1, BNP and HsTnI (but not MMP9) showed a good correlation with left ventricular diastolic dysfunction (Figures 1C and 1D) and echocardiographic parameters (left atrial volume, E/e' index and pulmonary arterial pressure). Left ventricular ejection fraction was related only to BNP and HsTnI (Table 3).

Table 3 Correlation of collagen turnover biomarkers with echocardiographic parameters of heart failure and B-type natriuretic peptide with the Rho Spearman test

	LVEF (%)	BNP (pg/mL)	LAV (mL/m^2)	LAV (mL/m^2)	E/e' index	PAP (mmHg)	Diastolic pattern
BNP (pg/mL)	Rho = −0·412 *P* < 0·001		Rho = 0·613 *P* < 0·001	Rho = 0·613 *P* < 0·001	Rho = 0·377 *P* < 0·001	Rho = 0·485 *P* < 0·001	Rho = 0·633 *P* < 0·001
MMP-2 (ng/mL)	Rho = −0·062 *P* = 0·446	Rho = 0·447 *P* < 0·001	Rho = 0·432 *P* < 0·001	Rho = 0·432 *P* < 0·001	Rho = 0·181 *P* = 0·026	Rho = 0·297 *P* = 0·004	Rho = 0·349 *P* < 0·001
MMP-9 (ng/mL)	Rho = −0·038 *P* = 0·648	Rho = 0·138 *P* = 0·920	Rho = 0·014 *P* = 0·868	Rho = 0·014 *P* = 0·868	Rho = 0·110 *P* = 0·179	Rho = 0·146 *P* = 0·164	Rho = 0·054 *P* = 0·512
TIMP-1 (ng/mL)	Rho = −0·109 *P* = 0·183	Rho = 0·413 *P* < 0·001	Rho = 0·290 *P* < 0·001	Rho = 0·290 *P* < 0·001	Rho = 0·229 *P* = 0·005	Rho = 0·340 *P* < 0·001	Rho = 0·294 *P* < 0·001

BNP: B-type natriuretic brain peptide; LAV: left atrial volume; LVEF: left ventricular ejection fraction; MMP: matrix metalloprotease; PAP: pulmonary arterial pressure; TIMP: metallopeptidase inhibitor.

The ROC curve was used to investigate the individual predictive capacity of each biomarker related to the prognosis of cardiovascular events in patients with symptoms of new-onset HF. The area under the curve value was statistically significant in MMP-2 (0.678, CI 0.602-0.772, p<0.001), TIMP-1 (0.660, CI 0.567-0.752, p=0.002), and BNP (0.702, CI 0.602-0.772, p<0.001), HsTnI (0.640, CI 0.548-0.732, p=0.003) but not MMP9 (0.548, CI 0.449-0.646, p=0.345).

Clinical outcomes

No differences were observed between HFREF and HFPEF in the cumulative rates of cardiovascular events (37.5% vs. 44.6%, respectively; p=0.921). However, both HF subgroups showed higher incidence of cardiovascular events than non-HF patients (HFPEF 44.6% vs. non-HF 14.3%, p=0.001; HFREF 37.5% vs. non-HF 14.3%, p=0.003), Figure 2A. No significant differences were observed in the survival analysis of all visits to the emergency room, hospital admissions and deaths, including noncardiovascular causes; however, the incidence of all-cause events was high (nearly 60%) in all patient groups (Figure 2B).

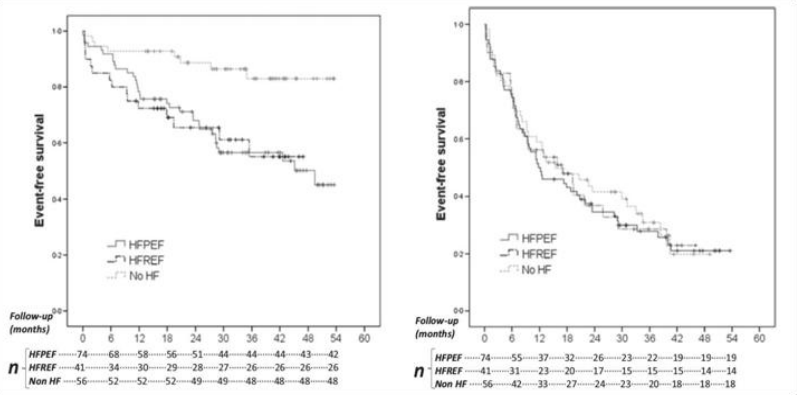

Figure 2 Kaplan–Meier curves for all population according to the final diagnosis. (a) Cumulative survival curves of freedom from death and cardiovascular events (HFREF 37·5% vs. HFPEF 44·6%, *P* = 0·921; HFPEF 44·6% vs. non-HF 14·3%, *P* = 0·001; HFREF 37·5% vs. non-HF 14·3%, *P* = 0·003). (b) Cumulative survival curves of freedom from death, hospital admission and visit to the emergency room from any cause. (HFREF 65·9% vs. HFPEF 74·3%, *P* = 0·868; HFPEF 74·3% vs. non-HF 67·9%, *P* = 0·564; HFREF 65·9% vs. non-HF 67·9%, *P* = 0·804). HF: heart failure; HFPEF: HF preserved ejection fraction; HFREF: HF reduced ejection fraction.

The variables tested in the discriminant analysis included baseline characteristics, laboratory tests, and

echocardiographic measures. The following variables with their standardized coefficients were identified in the discriminant analysis as the best combination to determine cardiovascular outcomes: female sex (-0.109387), hypertension (0.692631), atrial fibrillation (0.280468), hemoglobin (-0.280363), HsTnI (0.378913), BNP (0.0451343), MMP2 (0.309416), TIMP1 (0.111879), left atrial volume (0.133281) and E/e' index (0.233502). The combination of these variables resulted in an area under the curve of 0.806 in the ROC curve analysis to predict cardiovascular events. The discriminant function yielded a Wilks lambda of 0.7688 ($p<0.001$) and the logistic model resulted in a significant likelihood test (Chi-squared=39.64, $p<0.001$).

The biomarkers selected by the discrimant analysis with higher prognostic value were MMP2 and HsTnI. The reclassification evaluation for these two biomarkers showed an improvement in the area under the curve from 0.786 to 0.806 for MMP2 (reclassification index of 2.5%) and from 0.797 to 0.806 for HsTnI (reclassification index of 1.2%). In a traditional clinical risk model, as the health ABC Heart Failure Score [11], the area under the curve in the ROC analysis for our population was 0.768. The addition of MMP2 to this latter model improved the area under the curve from 0.768 to 0.785 (reclassification index of 2.2%) and the addition of HsTnI improved the area under the curve from 0.768 to 0.776 (reclassification index of 1.0%)

DISCUSSION

The main finding of this study is that cardiovascular prognosis is similar for HFPEF and HFREF even if patients are diagnosed in an ambulatory setting after new-onset HF symptoms. Biomarkers (BNP, HsTnI, MMP2, and TIMP1) assessed at the time of diagnosis were positively correlated with severity of diastolic dysfunction, evaluated with echocardiography; however, only BNP and HsTnI were correlated with left ventricle ejection fraction. In combination with other clinical and echocardiographic variables, these biomarkers, specially MMP2 and HsTnI, were useful in predicting cardiovascular events in this initial phase of the disease.

The association of these collagen myocardial turnover biomarkers with diastolic dysfunction and prognosis and their lack of correlation with ejection fraction could be explained by the predominance of HFPEF in this outpatient population. In this setting, the fibrotic process and removal of extracellular matrix seem to have been activated before symptoms onset; this could explain the poor cardiovascular prognosis observed in our cohort.

The cardiovascular events rate was comparable between HFPEF and HFREF subgroups, despite the fact that our patients had new-onset HF symptoms and were diagnosed in an ambulatory setting. Our results are in accordance with the prognostic rates reported in cohorts with in-hospital diagnosis of HF[6,9]. Initial studies[4] showed better prognosis in

patients with HFPEF, which could in part be secondary to suboptimal pharmacological treatment of patients with HFREF (i.e., beta-blockers not fully implemented). A 2012 meta-analysis concluded that HFPEF patients had a lower mortality risk than HFREF patients; however, variable origins and different diagnostic criteria were reported for HFPEF in the HF population[25]. It would of course be desirable to use common diagnostic criteria to establish the prognosis of patients with HFPEF. Notably, overall mortality in our study is lower than previously reported [3,7]; as described elsewhere[26], however, deaths in our HFPEF subgroup were primarily due to cardiovascular causes. One plausible explanation is that our outpatients had a first event of symptomatic HF, and therefore could be at an earlier stage of the disease than a population diagnosed in-hospital.

The value of biomarkers to assess prognosis in HF patients has also been investigated. As proposed in last American guidelines for the Management of HF[27], HsTnI has an additive value in HF risk stratification. In our cohort it had a strong relation with prognosis having the higher standardized coefficient of tested biomarkers in discriminant analysis. The relationship of BNP with prognosis has been previously established[13,28,29]. In our study BNP had a positive correlation with the composite endpoint of cardiovascular events, but in the discriminant analysis its standardized coefficient was lower than HsTnI or MMP2, suggesting that in outpatients with suspected new-onset of HF other biomarkers could be better for risk stratification.

Little is known about the relationship between metalloproteases and prognosis in HF patients. Only MMP9 has been associated with a higher risk of mortality in HFREF patients[20], but without defining its role in predicting cardiovascular events in HFPEF patients. In our study, we observed a null correlation of MMP9 with prognosis or echocardiographic parameters at the time of diagnosis.

Interpretation of findings

Cardiovascular prognosis was comparable for outpatients with HFPEF and HFREF. This finding underscores the need to consider HFPEF as an entity with significant morbidity and mortality that must be taken into account at the time of symptoms onset.

Our population also had a high incidence of all-cause events. This may be related to the advanced age and therefore the likely prevalence of comorbidities in all 3 patient groups. HF groups had a higher prevalence of hypertension and atrial fibrillation that may have also contributed to their higher rate of cardiovascular events. In addition, our non-HF patients were not a completely healthy control group, having presented with dyspnea and other symptoms mimicking HF.

All of the biomarkers studied (MMP2, TIMP1, BNP and HsTnI), except MMP9 had a good correlation with diastolic dysfunction in the echocardiographic parameters. However, a more limited association was observed with prognosis and the occurrence of cardiovascular events. This may be a

consequence of the values being determined at a very early stage of the disease. In addition, in the discriminant analysis, the combination of prognostic factors such male sex, hypertension, laboratory tests (lower values of hemoglobin and higher values of HsTnI, MMP2, TIMP1, and BNP) and echocardiographic parameters (E/e' index and left atrial volume) appeared to be associated with worse prognosis. The combination of these factors had a significant prognostic value to determine cardiovascular event risk (area under the curve 0.8). As previously noted, the most important variable in this function was the presence of hypertension, followed by levels of HsTnI and MMP2, decreased hemoglobin, and the presence of atrial fibrillation.

Clinical implications

In outpatients with new-onset HF symptoms diagnosed by applying a systematic algorithm[5,23], prognosis for patients with ambulatory diagnosis of HFPEF and those with HFREF is comparable. This finding should encourage physicians to consider a diagnosis of HFPEF in symptomatic outpatients, despite potential confounding factors such as the coexistence of comorbidities (particularly lung function abnormalities[30]). Although some of the biomarkers tested were well correlated with diastolic echochardiographic parameters at the time of diagnosis, their individual value to predict prognosis remains unclear at this early stage of the disease. Nevertheless, when considered in combination with other clinical and echocardiographic parameters in

ambulatory HF patients, BNP, MMP2, and TIMP1 contributed to the prediction of cardiovascular events during follow-up. Importantly, the correlations we observed were already present at the time of symptoms onset. Our study highlights the need for further research on HFPEF therapies that will improve prognosis in these patients.

Potential limitations

Our study has two main limitations. First, the number of patients is limited for a study of prognosis; however, patients were rigorously diagnosed, following a step-by-step algorithm[5], and the follow-up was long enough to allow us to clearly determine clinical outcomes. Second, the most prevalent symptom for all the patient groups was dyspnea, which may be a confounding factor and especially in the non-HF group. Nonetheless, cardiovascular outcomes differed significantly between the HF and non-HF groups.

CONCLUSIONS

Despite the widespread underdiagnosis of HFPEF, mortality and cardiovascular morbidity are similar to HFREF, even in outpatients with ambulatory diagnosis of HF. This finding could encourage physicians to test for HFPEF in outpatients when symptoms appear.

The addition of biomarkers, specially MMP-2 and HsTnI, to other clinical, biochemical, and echocardiographic

variables can predict cardiovascular prognosis at the time of diagnosis.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

All authors have significantly contributed to the study, have critically reviewed and approved the final version of the paper.

- L. Sanchis: follow-up of patients, collection, analysis and interpretation of data, drafting manuscript and final approval.
- R. Andrea: conception and design the study, recruitment and follow-up of patients, interpretation of data, critical revision of the manuscript, final approval.
- C. Falces: conception and design the study, recruitment of patients, critical revision of the manuscript, final approval.
- J. Llopis: Interpretation of data, statistical analysis, critical revision of the manuscript, final approval.
- M. Morales-Ruiz: supervising lab blood test, critical revision of the manuscript, final approval.
- Teresa López-Sobrino: follow-up of patients, critical revision of the manuscript, final approval.
- F. Perez-Villa: critical revision of the manuscript, final approval.
- M. Sitges: critical revision of the manuscript, final approval.
- M. Sabate: critical revision of the manuscript, final approval.
- J. Brugada: critical revision of the manuscript, final approval.

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Prognostic Value of Left Atrial Strain in Outpatients with De Novo Heart Failure

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Background: Left atrial (LA) dysfunction has been related to symptom onset in patients with heart failure (HF). However, the potential prognostic role of LA function has been scarcely studied in outpatients with new-onset HF symptoms.

Methods: Consecutive outpatients with suspected HF onset evaluated at a one-stop clinic were screened. HF diagnosis was performed according to current guidelines. LA function was analyzed in patients in sinus rhythm by speckle-tracking echocardiography, determining LA peak strain rate after atrial contraction (LASRa) as a surrogate of atrial contractile function. Yearly prospective follow-up was conducted to report cardiovascular hospital admission or death. Patients without HF in sinus rhythm were followed as a control group. Survival curves were estimated using the Kaplan-Meier method.

Results: One hundred fifty-four outpatients were included (mean age, 74 ± 10 years; 67% women) with a median follow-up duration of 44.4 months (interquartile range, 31–58 months). Final diagnosis was 29.9% non-HF and 70.1% HF. More than two in five patients with HF (44.4%) had AF (n = 48), and 55.6% (n = 60) were in sinus rhythm. The latter were divided according to LASRa tertile: highest, $-1.93 \pm 0.39\ sec^{-1}$; middle, $-1.08 \pm 0.21\ sec^{-1}$; and lowest, $-0.47 \pm 0.18\ sec^{-1}$. At the end of follow-up, patients with atrial fibrillation had a low event-free survival rate (56.3%), similar to those in the lower LASRa tertile (55.0%). The non-HF group had the best prognosis, and the higher and middle LASRa tertiles had intermediate prognoses (event-free survival, 85%, 75%, and 70%, respectively).

Conclusions: The study of contractile LA function in outpatients with new-onset HF provides prognostic stratification. The early identification of patients at higher risk on the basis of their atrial function would allow focusing on them independently of their final diagnoses. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Outpatient, Atrial strain, Heart failure, Prognosis, Preserved left ventricular ejection fraction

Heart failure (HF) with reduced ejection fraction (HFREF) can be easily diagnosed using echocardiography by a reduced left ventricular (LV) ejection fraction. HF with preserved ejection fraction (HFPEF) is more difficult to diagnose, although it is the most prevalent type of HF in outpatients[1] and has high morbidity and mortality.[2-4] The diagnosis[5] is based on the Paulus algorithm,[6] which includes B-type natriuretic peptide (BNP) determination and different echocardiographic measures. It is difficult to use in normal clinical practice, especially in outpatients. BNP has also shown utility for prognosis in patients with HF.[2,7,8]

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Left atrial (LA) function can be easily studied using speckle-tracking strain echocardiography.[9] LA function is divided into three phases: reservoir (filling during ventricular systole), conduit (passive emptying during early ventricular diastole), and active LA contraction (late ventricular diastole).[10] In a previous work with an earlier inclusion period of patients at our HF clinic, we found that impaired atrial strain was related to symptom onset in patients with HF.[11] In this group of outpatients with new-onset HF, LA strain was similarly reduced in patients with HFREF and those with HFPEF, but whereas in patients with HFREF, LV longitudinal strain was reduced, LV longitudinal strain showed no differences between patients with HFPEF and a non-HF group, suggesting earlier involvement of the LA in patients with HF.

LA strain was recently related to cardiovascular outcomes[12] and new-onset atrial fibrillation (AF)[13] in the general population. LV strain was also related to cardiovascular prognosis in patients with suspected HF.[14] The prognostic value of LA function has also been explored using other techniques. LA function measured using magnetic resonance as LA ejection fraction was related to clinical outcomes in patients with HF.[15] The assessment of LA work by computation as [LA stroke volume × blood density × (transmitral Doppler peak atrial velocity)^2] showed incremental prognostic value over LA size in

Background: *Left atrial (LA) dysfunction has been related to symptom onset in patients with heart failure (HF). However, the potential prognostic role of LA function has been scarcely studied in outpatients with new-onset HF symptoms.*

Methods: *Consecutive outpatients with suspected HF onset evaluated in a one-stop clinic were screened. HF diagnosis was performed following the actual guidelines. LA function was analyzed in patients with sinus rhythm by speckle-tracking echocardiography, determining peak LA strain-rate after the P-wave (LASRa) as a surrogate of atrial contractile function. Yearly prospective follow-up was conducted to report cardiovascular hospital admission or death. Patients with non-HF in sinus rhythm were followed as control group. Survival curves were estimated using the Kaplan-Meier method.*

Results: *154 outpatients were included (74±10 years old, 67% females) with a median follow-up of 44.4 months (P^{25-75} 31-58). Final diagnosis was 29.9% non-HF and 70.1%HF. 44.4% of patients with HF had AF (n=48) and 55.6% (n=60) sinus rhythm. The latter were divided by LASRa(s^{-1}) tertiles: highest -1.93±0.39, middle -1.08±0.21, lowest -0.47±0.18. At the end of follow-up, patients with AF had a low event-free survival (56.3%) similar to those with lower LASRa tertile (55.0%). The non-HF group had the best prognosis, the higher and middle LASRa tertiles showed intermediate prognosis (event-free survival 85, 75 and 70%, respectively)*

Conclusions: *The study of contractile LA function in outpatients with new onset-HF provides prognostic stratification. The early identification of patients at higher risk based on their atrial function, would allow focusing on them independently of their final diagnosis.*

INTRODUCTION

Heart failure (HF) with reduced ejection fraction (HFREF) can be easily diagnosed with echocardiography by a reduced left ventricular (LV) ejection fraction. HF with preserved ejection fraction (HFPEF) is more difficult to diagnose despite it is the most prevalent type of HF in outpatients[1] and has a high morbidity and mortality[2-4]. The diagnosis[5] is based on the Paulus algorithm[6] that includes natriuretic peptide type-B (BNP) determination and different echocardiographic measures. It is difficult to use in normal clinical practice, especially in outpatients. BNP has also shown its utility for prognosis of HF[2, 7, 8].

Left atrial (LA) function can be easily studied using speckle-tracking strain echocardiography[9]. LA function is divided in 3 phases: reservoir (filling during ventricular systole), conduit (passive emptying during early ventricular diastole) and active LA contraction (late ventricular diastole)[10]. In a previous work with an earlier inclusion period of patients in our HF clinic, we found that an impaired atrial strain was related to symptom onset of HF[11]. In this group of outpatients with new onset HF, LA strain was similarly reduced in patients with HFREF or HFPEF, but while in HFREF patients LV longitudinal strain was reduced, LV longitudinal strain showed no differences among HFPEF patients and the non-HF group, suggesting an earlier involvement of the LA in HF patients.

LA strain was recently related to cardiovascular outcomes[12] and new-onset atrial fibrillation (AF)[13] in the general population. LV strain was also related to cardiovascular prognosis in patients with suspected HF[14]. The prognostic value of LA function was also been explored with other techniques. LA function measured using magnetic resonance as LA ejection fraction was related to clinical outcomes in patients with HF[15]. The assessment of LA work by computation as [LA stroke volume x blood density x (transmitral Doppler peak atrial velocity)2] showed an incremental prognostic value over LA size in patients with chronic HF to predict death and HF hospitalization[16]. Finally, the measurement of an LA function index as [LA ejection fraction x VTI^{LVTO} x LA maximal volume] in patients with a first hospital admission for HF with reduced ejection fraction, significantly predicted adverse events in the first 6 months of follow-up[17]. However, the prognostic significance of an impaired LA strain in patients with HF, particularly in the outpatient setting, is unknown. Additionally, a more precise risk stratification of outpatients with potential symptoms of early HF that would allow us to focus on the higher risk patients is needed. We hypothesize that single study of LA function could stratify the cardiovascular risk of outpatients with new-onset HF. Therefore, we aimed to evaluate the usefulness of the analysis of atrial contractile function to predict cardiovascular outcomes in outpatients with HF onset.

METHODS

Study Design and Ethics

This is an observational study with a prospective screening of outpatients referred for diagnostic work up to our HF-clinic between March 2009 and March of 2014. A longitudinal follow-up was conducted to report death or hospital admission for a cardiovascular reason. The performance of the one-stop HF clinic[3] was previously described elsewhere. The present study represents the later phase of follow-up of outpatients included in our cohort of patients with new-onset HF; some of the patients included in the present study were also part of previous studies (which involved smaller numbers of patients and shorter duration of follow-up)[8,11]. Despite using similar and overlapped populations, the objectives of the previous studies were distinct and also complementary to those of the present study, as follows: in one previous study[11], the objective was to analyze the role of LA function in the differential diagnosis of outpatients with new-onset symptoms of HF, while in the other study[8], we examined the relation of blood biomarkers with prognosis (also including visits to the emergency department for cardiovascular reasons as an end point).

The investigation conforms with the principles outlined in the Declaration of Helsinki[18]. The study protocol was approved by the Ethics Committee of our institution and all participants provided written informed consent.

Patients

The cohort of consecutive patients visiting the HF-clinic for suspected new-onset of HF formed the population studied. At inclusion, diagnosis was performed following current recommendations[5,6] as non-HF, HFPEF or HFREF. The initial visit included physical examination, ECG, chest radiography, blood test with BNP measurement and a transthoracic echocardiography. Exclusion criteria were age <18 years, life expectancy <1 year and/or inability to perform the diagnostic circuit as previously describe[3]. Patients with final diagnosis of non-HF and sinus rhythm were included as a control group.

Echocardiography acquisition and analysis

A two-dimensional echocardiography study with conventional Doppler and tissue Doppler was performed using a commercially available system (Vivid 7, GE Healthcare, Milwaukee, WI). LV and LA dimensions were determined according to current recommendations19 and indexed by body surface (Du Bois method). LA deformation was analyzed in sinus rhythm patients from two-dimensional echocardiography using dedicated software (2D strain, EchoPACTM version 112, GE Healthcare, Milwaukee, WI). The frame rate was set between 60 and 80 frames per second to ensure adequate speckle-tracking. The onset to analyze the strain was determined by the onset of the P-wave on the ECG. LA longitudinal deformation was quantified and averaged from 6 segments of the LA from the apical 4 chamber view.

LA peak systolic strain-rate (LASRs) as a surrogate of LA reservoir function, LA peak strain-rate after atrial contraction (LASRa) as a surrogate of LA contractile function and LA peak strain-rate during early ventricular diastole (LASRe) as surrogate of conduit function were determined (Figure 1). Reproducibility analyses for LA strain measurements were performed by two investigators in 10 consecutive patients in sinus rhythm after all echocardiographic measurements had been completed. The new measurements were performed blinded to the initial results and the results of the other investigator. The measurements were performed in the first suitable video clip, but the electrocardiographic cycle to analyze was selected by the investigator at the time of the new measurement. Atrial strain in patients with AF was not measured due its high beat to beat variability. Global longitudinal LV strain was also quantified and averaged from six myocardial LV segments in the apical four-chamber view.

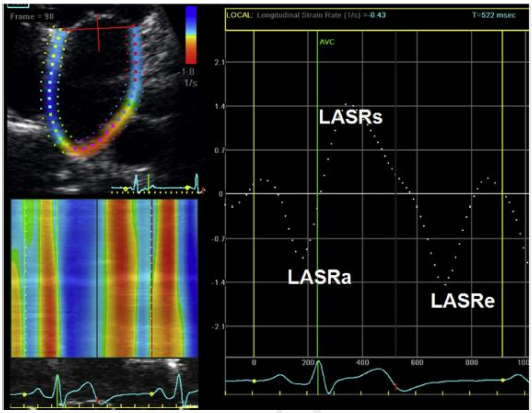


Figure 1 LA strain rate waves.

Follow-up

Cardiovascular events were prospectively reported during follow-up, annually, a telephonic interview and a medical history review were conducted by the research team. The duration of the follow-up was the interval between the date of the inclusion (initial visit in the outpatients HF-clinic) and the date of the last contact or death. Cardiovascular events were prospectively reported during follow-up. A telephonic interview and a medical history review of the centralized digital medical records of our health network referral area were yearly conducted by the research team. The duration of the follow-up was the interval between the date of the inclusion (initial visit in the outpatients HF-clinic) and the date of the last contact or death. A composite endpoint was defined to evaluate cardiovascular outcomes, including all-cause death or cardiovascular hospitalization (HF, acute coronary syndrome, arrhythmia, sudden death)

Statistical Analysis

The variables are shown as mean ± standard deviation, frequency distribution or proportions, as appropriate. Normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. A descriptive and comparative analysis was performed between the different diagnostic groups. The χ^2-test or Fisher tests were used to compare categorical variables and the t-student test for independent samples of quantitative variables. Anova and Bonferroni statistical tests were used to compare quantitative variables

between more than two groups. The receiver operating characteristic (ROC) curve was assessed to identify correlation of echocardiographic parameters with cardiovascular hospital admission or death. Survival curves for patient groups were estimated using the Kaplan–Meier product-limit estimator, and these were compared using the log-rank test. Pearson's test was used to correlate quantitative variables. Intra-observer and inter-observer intraclass correlations for LA strain analysis were performed using Cronbach's α method. A p-value lower than 0.05 (two sided) was considered statistically significant. Data were processed with SPSS version 19 (IBM, Armonk, N).

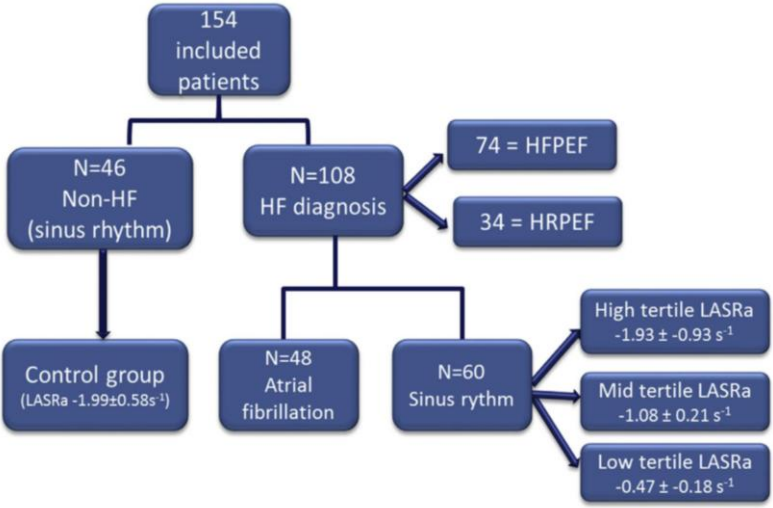


Figure 2 Distribution of the included patients in the different groups.

RESULTS

Demographics and clinical data

One hundred and fifty-four patients were included with a median follow-up of 44.4 months (P^{25-75} 31-58 months). Figure 2 shows the distribution of the included patients in the different groups. The mean age was 74±1 years, 67% were females and the most prevalent cardiovascular risk factor was systemic arterial hypertension (77%). Final diagnosis was HF in 70.13% (n=108) patients (68.5% HFPEF and 31.5% HFREF). NYHA functional class of HF patients at the moment of the inclusion was 1.8% I, 61.1% II and 37.1% III. Baseline and echocardiographic characteristics by diagnostic groups are shown in table 1.

Table 1 Baseline characteristics of the studied population according to final diagnosis

Baseline characteristics	HFPEF (*n* = 74)	HFREF (*n* = 34)	Non-HF (*n* = 46)	*P* value		
				Non-HF vs HFPEF	Non-HF vs HFREF	HFPEF vs HFREF
Age (y)	76.6 ± 7.2	74.2 ± 12.3	71.3 ± 11.4	0.013	0.560	0.731
Women	74.3 (55)	38.2 (13)	76.1 (35)	0.169	0.001	<0.001
Hypertension	86.5 (64)	73.5 (25)	63 (29)	0.009	0.756	0.401
Diabetes	31.1 (23)	41.2 (14)	23.9 (11)	1.000	0.305	0.096
Tobacco exposure	28.4 (21)	55.9 (19)	32.6 (15)	1.000	0.092	0.016
AF	39.2 (29)	55.9 (19)	0 (0)	<0.001	<0.001	0.162
HR (beats/min)	69.6 ± 12.6	81.3 ± 16.4	74.9 ± 10.2	0.099	0.088	<0.001
BNP (ng/mL)	159.4 ± 121.1	378.0 ± 558.7	35.8 ± 22.5	0.053	<0.001	0.001
LVDV (mL/m^2)	56.0 ± 19.0	98.6 ± 35.9	51.1 ± 23.0	0.969	<0.001	<0.001
LVEF (%)	59.8 ± 5.2	35.1 ± 9.7	60.8 ± 3.7	1.000	<0.001	<0.001
LV global strain (%)	−16.8 ± 3.62	−9.9 ± 4.5	−17.3 ± 3.9	1.000	<0.001	<0.001
LA volume (mL/m^2)	58.6 ± 23.3	58.8 ± 20.5	14.8 ± 2.2	<0.001	<0.001	1.000
LAS (%)	18.37 ± 6.85	17.31 ± 10.40	25.41 ± 6.09	<0.001	0.001	1.000
LASRs (sec^{-1})	0.94 ± 0.35	0.72 ± 0.44	1.43 ± 0.45	<0.001	<0.001	0.227
LASRa (sec^{-1})	−1.18 ± 0.68	−1.10 ± 0.60	−1.99 ± 0.58	<0.001	<0.001	1.000
LASRe (sec^{-1})	−0.72 ± 0.41	−0.67 ± 0.32	−0.90 ± 0.49	0.147	0.205	1.000
Diastolic dysfunction grade	1.6 ± 0.6	2.1 ± 0.8	0.8 ± 0.4	<0.001	<0.001	0.029

HR, Heart rate; *LAS*, global LA strain; *LVDV*, LV diastolic indexed volume; *LVEF*, LV ejection fraction.
Data are expressed as mean ± SD or as percentage (number).

AF was present at inclusion in 44.4% of HF patients. LVEF and global longitudinal LV strain showed no differences between non-HF and HFPEF and were significantly decreased in the HFREF group. LA volume was increased in both HF groups as compared to non-HF group. LA strain-rate was measured in sinus rhythm patients (n=116) and it was similarly decreased in both HF groups as compared to the control group.

Follow-up

All patients included were followed-up for a median time of 44.4 months (P^{25-75} 31-58 months). During follow-up, 48 patients had at least one event (death or hospital admission for cardiovascular reason). There were 25 deaths, 20 in the HF group (12 in the AF group, 8 in the sinus rhythm group) and 5 in the control group. 36 patients had at least one hospital admission for cardiovascular reasons (33 in the HF group and 3 in the control group). The most common cause of hospital admission was HF (61.1%, n=22), other causes were atrial fibrillation (n=8), atrial fibrillation and stroke (n=2), acute coronary syndrome with HF (n=1), sudden death (n=1) cardiogenic syncope (n=1).Time from inclusion to the first event was used to construct Kaplan-Meier survival curves.

ROC curves for the different prognostic echocardiographic parameters including LA indexed volume[20], LV global strain[14], LA strain and strain-rate, were constructed to predict events (Figure 3). The AUC and 95% confidence interval were as follows: LASRa 0.739

(0.630-0.848, p=0.001); LASRs 0.702 (0.587-0.817, P=0.004); LASRe 0.682 (0.562-0.802, p=0.010), LA strain 0.715 (CI 0.591-0.839, p=0.002); LA index volume 0.678 (0.555-0.801, p=0.011); LV longitudinal strain 0.635 (0.503-0.767, P=0.056).

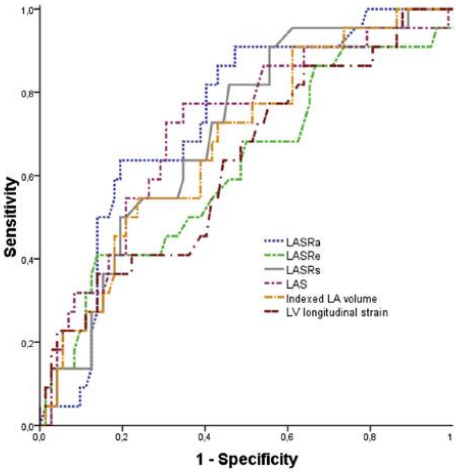


Figure 3 Receiver operating characteristic curves for prediction of cardiovascular events (death or hospital admission for cardio-vascular reason)

Due to its larger AUC, LASRa was the selected LA parameter to evaluate cardiovascular prognosis (cut-off value of LASRa for event prediction -1.400 s^{-1} [63.6% sensitivity and 65.3%specificity]). HF patients with sinus rhythm were divided according the LASRa by tertiles. HF patients with AF were followed as a separate group (Figure 2).

Table 2 shows the characteristics of the studied population in relationship to the LA function groups. Age and sex were similar between groups while cardiovascular risk

factors were less prevalent in the non-HF group. As anticipated, LV diastolic dysfunction was more impaired in the AF and low LASRa groups. In patients with sinus rhythm, LASRa had a moderate though significant, correlation with BNP (0.315, p=0.001), LA indexed volume (0.580, p<0.001), LV indexed volume (0.371, p<0.001), and LV longitudinal strain (0.334, p=0.001).

Table 2 Baseline characteristics of the studied population according to the status of LA contractile function

Baseline characteristics	Control group (*n* = 46)	High tertile of LASRa (*n* = 20)	Middle tertile of LASRa (*n* = 20)	Low tertile of LASRa (*n* = 20)	AF (*n* = 48)	Global *P* value
Age (y)	71.3 ± 11.4	76.9 ± 10.3	73.9 ± 10.6	73.9 ± 7.2	77.0 ± 8.7	0.057
Women	76.1 (35)	70.0 (14)	70.0 (14)	60.0 (12)	58.3 (28)	0.421
Hypertension	63.0 (29)	90.0 (18)	90.0 (18)	85.0 (17)	75.0 (36)	0.047
Diabetes	23.9 (11)	30.0 (6)	30.0 (6)	55.0 (11)	29.2 (14)	0.164
Smokers	32.6 (15)	30.0 (6)	25.0 (5)	40.0 (8)	43.8 (21)	0.568
HR (beats/min)	74.9 ± 10.1	72.3 ± 13.9	72.9 ± 11.7	65.5 ± 11.4	77.2 ± 16.6	0.025
BNP (ng/mL)	35.8 ± 22.5	92.5 ± 73.4	174.2 ± 157.0	388.1 ± 707.3	240.7 ± 175.9	<0.001
HFREF	–	20.0 (4)	25.0 (5)	30.0 (6)	39.6 (19)	0.386
LVDV (mL/m^2)	51.1 ± 23.0	65.2 ± 24.6	77.96 ± 30.2	87.73 ± 48.9	61.2 ± 24.9	<0.001
LVEF (%)	60.8 ± 3.7	56.1 ± 11.0	52.8 ± 14.3	48.5 ± 17.2	51.4 ± 12.0	<0.001
LV global strain (%)	−17.3 ± 3.9	−17.5 ± 4.1	−14.4 ± 5.5	−12.4 ± 4.3	−13.8 ± 5.2	<0.001
LA volume (mL/m^2)	31.6 ± 14.8	46.7 ± 15.2	54.5 ± 13.4	62.4 ± 21.3	63.8 ± 26.3	<0.001
LAS (%)	25.41 ± 6.09	22.35 ± 8.59	17.39 ± 3.64	14.59 ± 8.34	–	<0.001
LASRs (sec^{-1})	1.42 ± 0.45	1.20 ± 0.39	0.81 ± 0.14	0.65 ± 0.34	–	<0.001
LASRa (sec^{-1})	−1.99 ± 0.58	−1.93 ± 0.39	−1.08 ± 0.21	−0.47 ± 0.18	–	<0.001
LASRe (sec^{-1})	−0.91 ± 0.49	−0.86 ± 0.49	−0.61 ± 0.30	−0.67 ± 0.33	–	0.035
Diastolic dysfunction grade	0.8 ± 0.4	1.3 ± 0.6	1.5 ± 0.7	2.1 ± 0.6	1.9 ± 0.7	<0.001

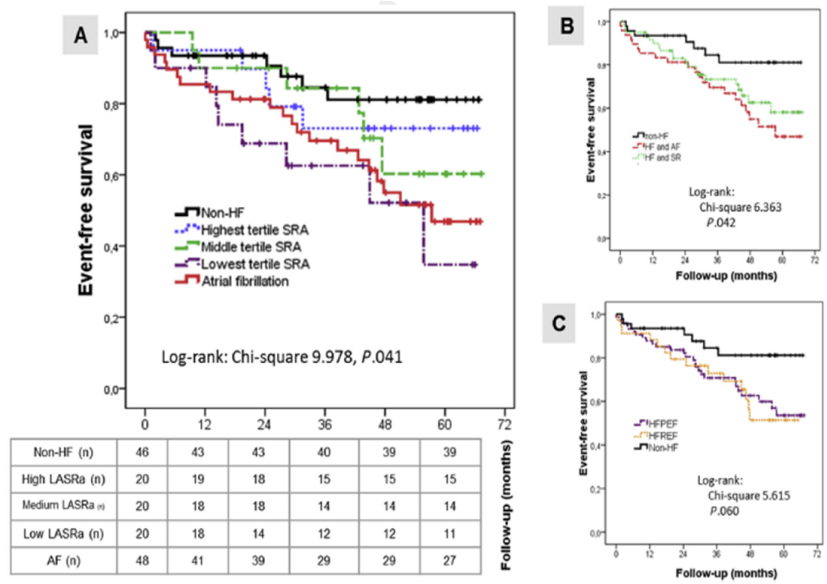
HR, Heart rate; *LAS*, global LA strain; *LVDV*, LV diastolic indexed volume.
Data are expressed as mean ± SD or as percentage (number).

During follow-up, 15 patients developed AF, 3 in the non-HF group (6.5%), none in the higher tertile of LASRa, 4 in the mid tertile of LASRa (20%) and 8 in the lower tertile of LASRa (40%).

Clinical outcomes

The cumulative rate of cardiovascular events was evaluated dividing the cohort according to their LA function

(LASRa tertiles or AF). Figure 4A shows Kaplan-Meier survival curves by groups (global Chi-squared 9.978, p=0.041). Patients with AF had a low event-free survival (56.3%) similar to those within the lower tertile of LASRa (55.0%). Patients in the non-HF group had the best prognosis (d prognosis (event-free survival 70 and 75%, respectively). Figure 4B shows Kaplan-Meier survival curves comparing non-HF patients, patients with HF in sinus rhythm and patients with HF and AF. Patients with HF and AF showed a trend to have lower event-free survival as compared to patients with HF in sinus rhythm but it was not statistically significant (respectively 56.3% vs. 66.7%, p=0.419)



Non-HF (n)	46	43	43	40	39	39
High LASRa (n)	20	19	18	15	15	15
Medium LASRa (n)	20	18	18	14	14	14
Low LASRa (n)	20	18	14	12	12	11
AF (n)	48	41	39	29	29	27

Figure 4 Kaplan-Meier survival curves. **(A)** Kaplan-Meier survival curve comparing patients with HF in sinus rhythm (SR) divided into tertiles of LASRa, patients with AF, and patients without HF. **(B)** Kaplan-Meier survival curve comparing patients with HF in sinus rhythm, HF and AF, and patients without HF. **(C)** Kaplan-Meier survival curve comparing patients with HFPEF or HFREF with the non-HF group. *SRA*, A-wave LA strain rate.

Figure 4C shows Kaplan-Meier survival curves comparing groups of patients with HFPEF or HFREF and those with non-HF; both HF groups had lower event-free survival than the non-HF group without differences between the two HF groups (HFPEF 63.5% vs. HFREF 58.8%, p=0.824; HFPEF vs. non-HF 84.4%, p=0.031; HFREF vs. non-HF, p=0.026).

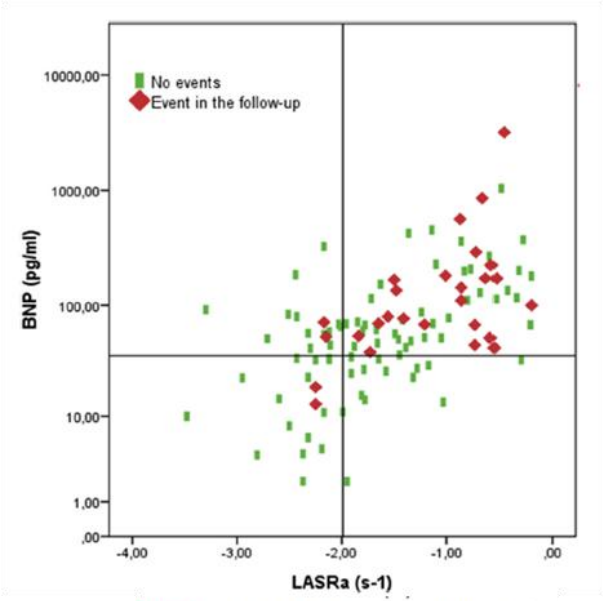


Figure 5 Distribution of events according to BNP and LASRa. Vertical and horizontal lines represent the mean values of BNP and LASRs in the non-HF group (−1.99 sec^{-1} and 35.8 ng/mL, respectively). The large majority (91.7% [n = 44]) of patients with events during follow-up are located in the right superior quadrant, corresponding to those patients with higher BNP levels and more abnormal LASRa (less negative values).

Finally, we constructed a scatterplot to show the event's distribution according to the patient's LASRa and BNP (the most frequently used biomarker to assess prognosis in HF patients) (Figure 5). The majority of the patients with events

(91.7%, n=44) were located in the quadrant with more abnormal LASRa (less negative values) and higher BNP.

Measurement variability of LA strain analysis

Intra-observer and inter-observer intraclass correlations were: LASRs 0.979, 0.953; LASRa 0.963, 0.960; LASRe 0.961, 0.943, LAS 0.984, 0.978.

DISCUSSION

In the present study, the analysis of LA function could predict cardiovascular outcomes in outpatients with HF onset. HF patients with AF showed slightly worse event-free survival than patients with HF in sinus rhythm; however, when patients with HF in sinus rhythm were divided according to their LA contractile function (as evaluated by LASRa), those with worse LA contractile function showed worse event-free survival and similar to that with HF and AF, independently of their LV ejection fraction.

The measurement of LA function as LA work[16] or LA function index[17] was previously related to cardiovascular prognosis in patients with chronic HF or HFREF respectively. In the general population a low global LA strain (considered as a surrogate of reservoir LA function) has been related to higher rate of cardiovascular events[12,14]. In our cohort of outpatients with HF onset, LASRs (a surrogate of reservoir function) was also related to cardiovascular events onset, but LASRa had the higher predictive value for cardiovascular

events prediction. In our cohort, 44.4% of HF patients had AF, previous studies have reported a higher rate of cardiovascular events among AF patients in general population[21], but especially in HF patients[22,23] independently of LV ejection fraction[24]. We have also found a slightly higher rate of cardiovascular events when comparing patients with HF and AF and patients with HF in sinus rhythm (56.3% vs. 66.7%, p=0.419 respectively) as it is shown in Figure 4B, but without statistically significant differences. However, when we compared patients with HF and AF with HF patients in sinus rhythm divided by tertiles of LASRa (figure 4A), AF patients had a similar prognosis to those in the lower tertile of LASRa.

Some previous studies have reported a worse prognosis in those patients with AF and low LA strain[25,26]. However, in our study we did not measure LA strain in patients with AF. Nonetheless, and regardless their LA strain value, patients in the AF group showed poor prognosis in our follow-up. During follow-up, new onset AF was more frequent in the group of patients with lower tertile of LASRa (40%) according to what we expected[13].

When we compared prognosis according to the final diagnosis of our cohort, HFPEF and HFREF patients had similar cardiovascular prognosis, and being worse than the non-HF group as previously reported in the outpatient and other clinical settings[2,8,27]. Despite that previous studies proposed LV strain to predict cardiovascular outcomes[14], in

our population, despite a lower LV longitudinal strain in groups of lower tertile of LASRa and in the AF group, its predictive value in the ROC analysis was lower than the atrial parameters and not statistically significant. It might be related to the characteristics of our cohort (new-onset HF in an outpatient setting) suggesting that LA dysfunction, with early involving in the HF, could be an earlier prognostic indicator.

BNP showed only a moderate correlation with LASRa, suggesting that the role of BNP as a prognostic marker could be lower than the one reported in patients with more advanced HF[8]. In an earlier phase of follow-up, we investigated the prognostic value of different biomarkers in the setting of outpatients with new onset of HF, finding that high sensitive troponin I and matrix metalloprotease 2 had the best prognostic value, on top of BNP values which showed a weaker prediction of events8. As shown in figure 5, most of patients with events during follow up (91.7%), had higher BNP levels and more abnormal LASRa. Considering that BNP has limited prognostic value among patients with new onset HF as compared to those with more advanced HF, the addition of LASRa to BNP determination could improve the prognostic stratification of this group of patients with new onset HF

Thus, LA function analysis could stratify the cardiovascular prognosis of outpatients with suspected HF. The LA seems to have a central role in HF syndrome[28]. In our study, including patients with new-onset HF, single study

of LA function can stratify their risk of cardiovascular hospital admission or death. In outpatients with new-onset HF, the presence of AF or low LASRa seems to be a marker of risk, meaning that these patients may benefit from a closer follow-up to reduce their morbidity and mortality.

The results of our study cannot be extrapolated to a general population, but we propose that the study of LA function could it be an outpatient tool to do in the first approach of outpatients referred to the clinic with dyspnea, providing important information of cardiovascular outcomes. The study of LA function might be especially important in those patients with preserved LV ejection fraction, if we consider that sometimes HFPEF is underdiagnosed and that most of HFPEF patients are old and had other comorbidities as lung disease or obesity that can be mistakenly identified as the primary cause of the dyspnea. Consequently, HFPEF patients can be sometimes treated as non-HF patients if their diagnostic clinical work-up is not fully completed including the determination of BNP levels.

Potential limitations

This is a pilot observational study. All patients were evaluated in an outpatient clinical setting due to suspected HF onset, so the study results cannot be extrapolated to a more general population without HF symptoms. New and larger studies are warranted to validate cut-off values of normal LA strain and to confirm our findings.

CONCLUSIONS

Patients with new-onset HF in sinus rhythm and severe LA contractile dysfunction show a low event-free survival and similar to that observed in patients with HF and AF. The analysis of LA function should be included in the initial evaluation of patients with suspected HF onset as it provides additional diagnostic and prognostic value to predict cardiovascular outcomes in outpatients with new-onset HF.

DISCLOSURES
None declared.

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DISCUSSION

In the set of papers included in this thesis, we studied a cohort of outpatients with new-onset HF symptoms diagnosed in a one-stop clinic. At the time of diagnosis, we performed a blood test (including BNP and metalloproteases) and a standard echocardiography (off-line analysis of myocardial deformation was subsequently performed). Then, a prospective follow-up was conducted to report cardiovascular events and correlate the initial clinical, echocardiographic and biochemical parameters with their cardiovascular prognosis.

The study of atrial and ventricular function in patients with HFPEF showed an early impairment of the LA function (reduced LA strain and presence of interatrial dyssynchrony) but with preserved LV function (as measured with standard techniques (LVEF) and with myocardial deformation). Moreover, the follow-up of our cohort of patients with new-onset HF (either HFPEF or HFREF) showed a similar midterm cardiovascular prognosis. High-sensitivity troponin I and MMP2 were selected as the biomarkers with higher prognostic value using the discriminant analysis. LA strain (strain-rate A wave as surrogate of the contractile function) was also useful to perform a prognostic stratification of our outpatients with new-onset HF.

1. CHARACTERIZATION OF THE INITIAL MECHANISMS INVOLVED IN HFPEF DEVELOPMENT USING ECHOCARDIOGRAPHIC TECHNIQUES

The definition of HFPEF syndrome remains controversial. Initially, HFPEF was considered as a precursor of HFREF[38]. Later on, it was suggested that there are different predisposing causes and different types of patients with HFPEF compared to the HFREF population[13, 59]. Likewise, diastolic dysfunction of the LV used to be confused with HFPEF, but isolated diastolic dysfunction can be found in asymptomatic patients without HF[9]. In fact, the prevalence of diastolic dysfunction in the general population has been reported to be up to 27%[42]. In our cohort, we also found a proportion of patients with diastolic dysfunction but without HF, so other factors may be involved in the clinical manifestations of the HFPEF syndrome.

Some previous studies observed a reduced myocardial deformation (strain) in patients with HFPEF[29, 31, 39]. That raised the question of LV systolic function being "normal" in these patients. In our cohort, LV function of patients with new-onset HFPEF, measured as LVEF (2D echocardiography) and with myocardial deformation (speckle-tracking strain), was completely within the normal range, showing no differences between HFPEF and non-HF patients. The findings of previous studies of reduced LV strain could be a

consequence of two main factors. First, some studies considered preserved LVEF ≥45%[39], while according to the guidelines[12, 17] the value must be > 50%. Those patients with LVEF of 45% to 50% would now be classified as patients with HF and mild reduction of the LV ejection fraction (HFmrEF); in previous guidelines[17] they were be classified as HFREF. New guidelines[12] have created this new subgroup of HFmrEF for those patients with LVEF 40% to 49%, considering them a grey area between HFREF and HFPEF.

Another factor is that the majority of patients included in previous studies had a longstanding clinical syndrome of HFPEF with several episodes of hospital admission due to HF[29, 31, 36]. Those patients with advanced HFPEF may have an impairment of the LV function that is not yet present in our cohort of outpatients with new-onset HFPEF. All patients included in our study were outpatients with new onset of HFPEF and LVEF > 50%. The heterogeneity of the inclusion criteria previous studies involving HFPEF patients makes it difficult to compare the results [Table4]. On the other hand, HFPEF is a heterogeneous syndrome, with several underlying aetiologic and pathophysiologic factors that also make it difficult to compare the results between the different trials.

Study	Year	Total number of patients (HFPEF patients)	LVEF	Origin	Objectives
Yu et al. (44)	2002	339 (73)	> 50%	Outpatients Retrospective	LV function study
Yip et al.(42)	2002	101 (29)	>45%	---	LV function study
Kawaguchi et al. (52)	2003	33 (10)	> 50%	Patients with hospital admission Prospective	LV function study
Vinereanu et al. (43)	2005	130 (30)	> 50%	Outpatients Prospective	LV function study
Wang et al.(20)	2008	50 (50)	>50%	Retrospective (origin non-specified)	LV function study(strain)
Phan et al. (21)	2009	93 (40)	> 50%	Outpatients Prospective	LV function study(strain)
Borlaung et al.(55)	2009	2042 (244)	> 50%	Outpatients Retrospective registry (Rochester Epidemiology Project)	LV function study
Yip et al. (22)	2011	287 (112)	> 50%	Patients with hospital admission Prospective	LV function study(strain)
Zile et al. (30)	2011	745 (745)	> 45%	Patients with hospital admission Prospective (I-PRESERVE registry)	Cardiac function and prognosis
Aizawa et al. (50)	2011	127(52)	> 50%	Outpatients Prospective	LV function study
Ohtani (51)	2012	855 (327)	> 50%	Outpatients Retrospective registry (Rochester Epidemiology Project)	LV function study and prognosis
Kraigher-Krainer (45)	2014	219 (219)	>45%	Retrospective(PARAMONT registry)	LV function study(strain)

Table 4: Previous studies describing LV function in HFPEF patients.

In recent years, the study of LA function in HF patients is becoming increasingly important[129]. In our cohort, patients with HFPEF presented an impairment of LA function (measured as deformation using speckle-tracking strain) similar to that observed in HFREF patients. Previous studies have also shown a reduction in LA strain (A-wave strain rate and global strain) in patients with HFPEF, compared to

patients with diastolic dysfunction without HF[51], but the comparison of LA strain between outpatients with HFPEF, HFREF or non-HF was not previously performed. According to the data obtained in our cohort, LA dysfunction could be one of the initial mechanisms involved in symptoms onset in HFPEF patients, even in the early phases of the disease. The magnitude of LA dysfunction in HFPEF patients was similar to that observed in HFREF patients, although the ventricular myocardium seemed to be unaffected (the LV strain of patients with HFPEF did not differ from that observed in the non-HF control group). Accordingly, the finding of an impairment of LA function may be considered to support early diagnosis of HFPEF. In our study, LA strain was the parameter best correlated with HF diagnosis, as also previously described by other groups[130]; however, LA strain analysis is not always available in routine clinic practice. As a practical approach, the presence of an enlarged atrium with preserved LVEF in a patient that complains of dyspnoea may be suspicious of HFPEF; in those cases, it is important to complete the study to confirm or rule out the HFPEF diagnosis.

Besides the presence of an early impairment of LA deformation in patients with new-onset HFPEF, we also observed the presence of interatrial dyssynchrony. Although the technique to determine interatrial dyssynchrony was

different, our findings are in keeping with the data previously presented by Eicher et al[57]. Their group of determined the interatrial dyssynchrony by applying pulsed Doppler on the mitral valve inflow, while we measured the time to maximum atrial peak strain. In our cohort, a linear correlation was found between interatrial dyssynchrony and BNP, suggesting a worse functional class in those patients with greater dyssynchrony. The group of patients with HFPEF was divided according to the presence of severe interatrial dyssynchrony (> 60 ms) or not. Patients with severe dyssynchrony presented higher levels of BNP and also more severe diastolic dysfunction. Despite these findings, we did not find differences in the atrial strain measurement between patients with severe dyssynchrony or not. This observation may suggest that interatrial dyssynchrony is an independent mechanism involved in the HFPEF syndrome that it is present already in the initial stages of the disease of some patients. If this was confirmed in more studies and larger population, a specific therapy to correct interatrial electrical dyssynchrony could be implemented[58].

2. PROGNOSIS OF PATIENTS WITH NEW ONSET OF HEART FAILURE (HFPEF vs. HFREF).

In our cohort of outpatients with de novo HF, both HFPEF and HFREF patients showed similar midterm cardiovascular outcomes. This similar prognosis was also reported in previous studies including retrospective cohorts[10, 59] or patients diagnosed after hospital admission[11, 14, 61]. These findings highlight the importance of performing an early diagnosis. Although the diagnosis of HFPEF is challenging, with early diagnosis, stricter control of cardiovascular risk factors and closer follow-up may improve patient prognosis.

We applied a discriminant analysis to determine which clinical, functional, structural and analytic parameters were related to cardiovascular prognosis in our cohort of patients with new-onset HF. The selected clinical factors were the presence of hypertension and male gender (worse prognosis). The classical echocardiographic variables related to worse prognosis were LA volume and E/e' ratio. Finally, the biomarkers with higher prognostic value were high-sensitivity troponin I and MMP2 followed by TIMP1 and haemoglobin. BNP was also related to the prognosis but with a more modest value than the other biomarkers. Both clinical and echocardiographic parameters obtained in this

analysis were previously related to HF prognosis in otherstudies[54, 59, 76].

In routine clinical practice, BNP is the biomarker most commonly used to diagnose HF[17]; it is also used as a prognostic marker, especially in patients admitted to hospital due to decompensated HF[87-89]. In our cohort, high-sensitivity troponin I was the biomarker with the strongest prognostic value, followed by MMP2. The most recent American guidelines on HF[92], emphasize the usefulness of troponin in HF patients. Likewise, the determination of metalloproteases, especially MMP2, may be useful for prognostic stratification; nevertheless, the high cost and limited availability restrict application in current routine clinical practice.

Later on, we related LA strain measurement to the cardiovascular prognosis. Previously, Cameli et al. described a stronger cardiovascular prognostic value (in the general population) of LA global strain as compared to LA volume or LA ejection fraction[56]. They proposed a reservoir function of the LA (LA global strain) as a predictor of cardiovascular outcomes in the general population[56]. In our cohort, LA strain parameters had a higher prognostic value for cardiovascular event prediction than LA volume or LV strain, as described by Cameli et al. Freed et al. also related LA reservoir function (measured with speckle-tracking

echocardiography) to a composite endpoint of hospital admission and death in a follow-up of 14 months; nonetheless, they included patients who were diagnosed after a hospital admission due to HF and they did not differentiate between patients with sinus rhythm or with atrial fibrillation[85].

In our cohort, the reservoir function (S wave of strain-rate) was also significantly related to cardiovascular prognosis but the A wave of the strain-rate (as surrogate of booster pump function of the LA) had the higher area under the ROC curve for cardiovascular event prediction. In the study by Freed et al., LA booster pump function was not evaluated due to the inclusion of patients with atrial fibrillation (in whom this function is not measurable). Furthermore, previous studies proposed the presence of AF as an independent factor for poor prognosis in patients with HF[131, 132]. In our cohort, we observed a no significantly worse prognosis in patients with HF and AF as compared to patients with sinus rhythm and HF. However, after dividing patients with HF and sinus rhythm according to their LA strain-rate A-wave value (as a surrogate of booster pump function), we observed that the group of patients in the lowest tertile of strain-rate had a similarly bad prognosis as that observed in the group of patients with HF and atrial fibrillation. This finding may suggest that LA dysfunction is related to worse

cardiovascular prognosis despite the maintenance of sinus rhythm.

To summarize, the presented data suggest that the study of the LA function may have important implications for HF diagnosis and prognosis, particularly in patients with HFPEF.

3. CONTRIBUTION TO CLINICAL PRACTICE

The published papers show a similar cardiovascular prognosis between HFPEF and HFREF patients, even if the diagnosis occurs in the early stages of the disease. This prognosis may be improved with an early diagnosis and subsequent close follow-up to achieve a better control of cardiovascular risk factors. Using non-invasive imaging, we have demonstrated that it is possible to perform an early diagnosis using speckle-tracking strain analysis to study LA function. The analysis of LA strain was useful to achieve the HF diagnosis, but it was also an important cardiovascular prognostic factor. The strain analysis may be cost-effective, as only a standard 2D transthoracic echocardiogram is necessary to perform an offline strain analysis. Nevertheless, the measurement of LA strain is not always possible in routine clinical practice. The presence of severe LA enlargement in a patient with preserved LVEF who complains of dyspnoea may be suspicious of HFPEF. The quantification of biomarkers at the moment of HF diagnosis also may be useful for prognostic stratification, especially high-sensitivity troponin I, as MMP2 is not usually available in routine clinical practice. Conversely, BNP seems to have a more limited prognostic value in our cohort of outpatients with new-onset HF.

The identification of the initial mechanisms involved in HFPEF syndrome may facilitate the identification of relevant cardiac structural phenotypes that can be a target for specific treatments. Atrial dysfunction seems to be related to HF symptoms onset; accordingly, the maintenance of the LA function, or its improvement if already impaired, may improve HF symptoms. In a pilot study, the correction of interatrial dyssynchrony with biatrial resynchronization using a biatrial pacemaker improved symptoms of patients with HFPEF and interatrial dyssynchrony[58].

Therefore, a better understating of the characteristics of HFPEF population with the combination of clinical, echocardiographic and biochemical parameters may help to achieve an early HFPEF diagnosis and to stratify prognosis, even at the time of the diagnosis. This also has the potential to open up a promising field for specific tailored therapies in HFPEF, where conventional medications and therapies have mostly failed until now.

4. LIMITATIONS

The main limitation of this research is the relatively small sample of the patient population. However, patients were rigorously diagnosed, following a step-by-step algorithm according to existing recommendations[17] at the time of inclusion. Based on the de Paulus algorithm[16], it was more restrictive for HFPEF diagnosis than the current recommendations[12]. Consequently, this is a homogeneous and carefully diagnosed cohort. Second, the control group was composed of patients referred to the one-stop clinic with a final diagnosis of non-HF; most of those patients complained of dyspnoea, and thus other confounding factors may be present. Nonetheless, cardiovascular outcomes differed significantly between the HF and non-HF groups.

Regarding echocardiography, the speckle-tracking strain study, especially for the LA analysis, might have some limitations despite its widespread use. There is no specific software for speckle-tracking strain analysis of the atrium, so the LV software is used in the LA. Another major problem is the lack of comparability between the different studies that included strain measurements; this is due to the absence of uniform strain values between the different companies producing the software used. Given the initial encouraging results of the strain analysis, it is expected that in coming

years a development and unification of the technique that allows its introduction in routine clinical practice will be developed[133, 134].

CONCLUSIONS

- HFPEF is a well-defined pathology different from HFREF.
- HFPEF can be characterized with echocardiography even in the early stages of the disease.
    - LA dysfunction and interatrial dyssynchrony are present already at the moment of symptoms onset. Accordingly, LA dysfunction may be one of the responsible mechanisms for the onset of symptoms.
    - LV function is normal in the initial stages of HFPEF, whether it is studied as LVEF (2D echocardiography) or with myocardial deformation (strain analysis).
- The fibrotic activity is already present at the initial stages of the HFPEF (increase of metalloproteases)

- The midterm cardiovascular prognosis of both types of HF(HFPEF and HFREF) in outpatients with new-onset symptoms is similar.
- The combination of biomarkers (especially high-sensitivity troponin I and MMP2) with clinical and echocardiographic parameters may be useful to stratify the prognosis of patients with new-onset HF at the time of the diagnosis.

- LA function is a good marker for diagnosis and prognosis in outpatients with suspected HF.

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CURRICULUM VITAE

Laura Sanchis was born in Castellón de la Plana (Spain) in 1983. After finishing high school, she moved to Valencia (Spain) to study Medicine. She finished the degree in Medicine and Surgery at the University of Valencia in 2007. Then, she was admitted at the Hospital Clinic (Barcelona, Spain) as a resident to specialize in Cardiology. After finishing her Residency in Cardiology in 2013, she stayed at Hospital Clinic as a predoctoral fellow in the Echocardiography Laboratory. Along this formative period she combined her research and learning activity with clinical work at the Hospital General of Cataluña (Sant Cugat, Barcelona, Spain) as a staff cardiologist and also as cardiologist at the Cardiology Intensive Care Unit of Hospital Clinic (Barcelona, Spain). In 2016, she completed a six months fellowship at the St. Antonius Ziekenhuis hospital (Nieuwegein, The Netherlands) focused in advanced echocardiography and echocardiographic guidance for percutaneous structural cardiac interventions in the Catheterization Laboratory.

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