

Original Investigation Reports

Determination of hemodynamic forces by Cardiac Magnetic Resonance as a marker of cardiovascular events.

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ABSTRACT

Introduction: in the Alto Valle of Rio Negro (RN) in 2017, a healthcare issue was identified where hospitals do not routinely use thrombolytics (TBL) for immediate treatment of ST-Segment Elevation Acute Coronary Syndrome (STEMI) and instead refer patients for primary percutaneous coronary intervention (PCI).

Objective: to formulate an early reperfusion project that includes pre-hospital/hospital thrombolysis and PCI under the "Infarction Code" (IC) protocol to reduce the years of potential life lost (YPLL) observed in this population and to increase patient engagement.

Materials and Methods: the project was formulated using the methodology of socio-sanitary project development from a perspective of macromanagement.

Results: prioritizing PCI as the main strategy, STEMI patients from hospitals in the Eastern Health Zone should be referred to Sanatorio Juan XXIII (Level A1) or Clínica Roca (Level A2). Patients from the Western Health Zone should be referred to Fundación Médica (Level A1) or Policlínico Modelo de Cipolletti (Level A2), with direct access to the hemodynamics room. The arrival times from Catriel and El Cuy are at the threshold for PCI within 120 minutes; therefore, these patients should receive (unless contraindicated) fibrin-specific TBL followed by referral for a pharmaco-invasive strategy.

Conclusions: the situation in the Alto Valle of RN requires immediate, collective, and coordinated actions among different stakeholders to enable network-based treatment of STEMI under the IC protocol, aiming to increase the average life years gained (LYG) and to enhance patient engagement.

ABBREVIATIONS

MRI: Magnetic resonance imaging
BB: Bright-blood sequence in MRI
FT: Feature tracking
HDF: Hemodynamic forces
LGE: Late gadolinium enhancement
CLBBB: Complete left bundle branch block
LVEF: Left ventricular ejection fraction
RVEF: Right ventricular ejection fraction
LV GLS: Left ventricular global longitudinal strain
LV GCS: Left ventricular global circumferential strain
LV GRS: Left ventricular global radial strain
HF: Heart failure
AMI: Acute myocardial infarction
CHF: Congestive heart failure
HFPEF: Heart failure with preserved ejection fraction
CD: Cardiac death
IQR: Interquartile range
CRT: Cardiac resynchronization therapy

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by the presence or history of typical symptoms and/or signs secondary to a structural or functional alteration of the heart, leading to a reduction in output or an increase in filling pressures, whether in rest or in strain.¹

There are multiple etiologies leading to this development, and their characterization is essential. From HF with preserved ejection fraction to HF with decreased ejection fraction, the continuum of this syndrome presents multiple phenotypes, in which ventricular remodeling behaves not just as adaptation to the injury, but also as its consequence.^{2,3}

For this reason, physicians need to have tools available, enabling an adequate assessment for decision-making. One of the key aspects for this is the impact on myocardial structure compromise and its consequences on ventricular function, quality of life and survival of cardiovascular patients.

Currently, we have ventricular function and structure analysis tools, which anticipate changes in fiber strain. Examples are myo-

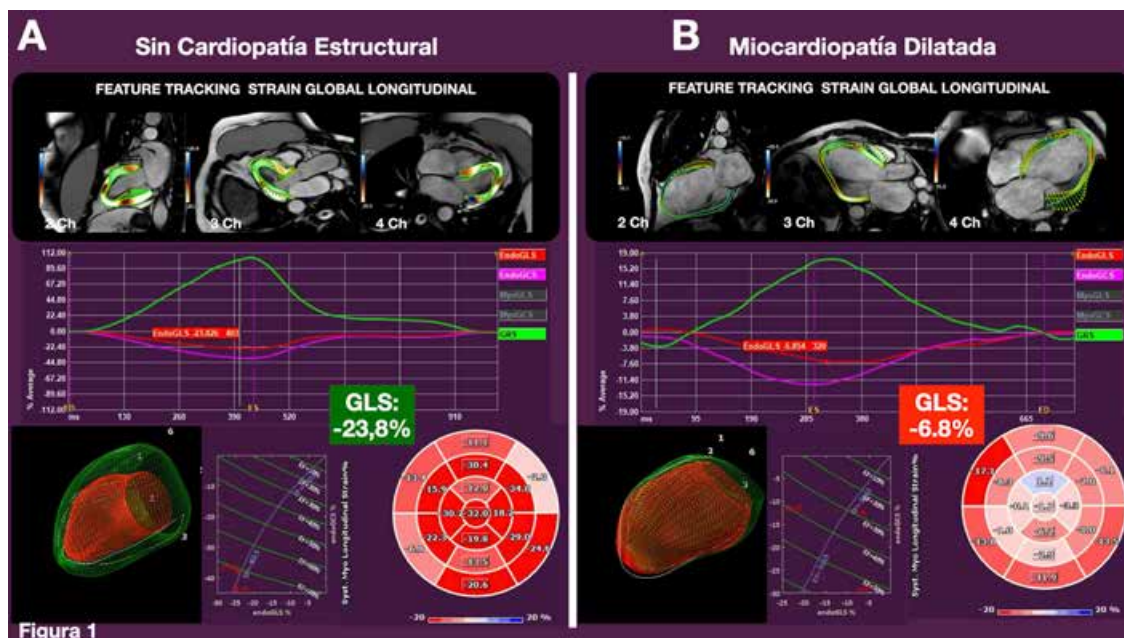


FIGURE 1.

Myocardial strain assessment by feature tracking in patients with and without structural disease

In the figure, we present two contrasting scenarios to illustrate GLS: a patient without structural pathology (A) and another with dilated cardiomyopathy (B). In the above section, we observe the endocardial delimitation made in bright-blood sequences for estimation by FT in 2-, 3- and 4-chamber views. In the central section, we show the global graph results of strain by curves: the red curve represents GLS, the purple one GCS and the green one GRS. Finally, the inferior part of the graph:

- From left to right: 3D model of left ventricular structure.
- A graph relating GLS (%) with GCS (%) jointly with LVEF, enabling a fast interpretation of the strain-function relation, very useful for the follow-up.
- Polar map for regional assessment of GLS by segments.

GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain; LVEF: left ventricular ejection fraction.

cardial strain measured by transthoracic echocardiography and/or magnetic resonance imaging (MRI). It is also possible to estimate the onset of mechanical contraction by myocardial mechanical synchrony evaluation with Phase analysis with gated SPECT in myocardial perfusion studies. These elements have proven to generate incremental prognostic value for the method they accompany, and subsequently, they may prove their impact on regional and global myocardial function.^{4,5,6} Recent studies have introduced the evaluation of left ventricular hemodynamic forces (HDF) as a promising method for mechanical and noninvasive evaluation of the interaction between the left ventricle and intracardiac blood movement, which could be valuable in the study of different cardiomyopathies. The HDFs evaluated by MRI allow to contemplate the intimate interaction of the blood pool with endocardial tissue, analyzed by myocardial movement and represented by left ventricular wall motion velocity, reconstructed by myocardial global longitudinal strain (GLS) and the amount of blood going through the valves (applying the principle of conservation of mass). The average gradients of intraventricular pressure may be estimated by a mathematical model that, taking advantage of the balance of the moment, integrates left ventricular geometry and the movement of the wall with the areas of the aortic and mitral valve orifices. Projected in specific directions within the left ventricle, this HDF may be broken down into longitudinal and transversal components. This concept of myocardial mecha-

nical functional estimation is validated by 3D phase contrast or 4DFlow, and has the potential to facilitate the determination of intraventricular gradients, not requiring to make patients undergo invasive procedures.⁷ It is for this reason that this study was set out to assess hemodynamic forces in a population of patients who underwent MRI to determine its capacity and usefulness as a cardiovascular prognostic marker.

METHODS

An analysis was made retrospectively of patients who underwent conventional MRI due to different indications, in an institution of outpatient diagnosis. The follow-up of patients by a post-study phone interview and analysis of digital clinical history between years 2015 and 2023. In follow-up, major cardiovascular events were analyzed, such as myocardial infarction (AMI), heart failure admission (HFA) and cardiovascular death (CD), as well as the composite endpoint of AMI + HFA + CD.

Image acquisition

Philips Achieva and Prodrive MRI devices were used, of 1.5 T, for anatomical assessment and volume quantification. The acquired images were synchronized by ECG of permanent registry and active coordination of apnea. Late gadolinium enhancement (LGE) images were obtained approximately 10 minutes after administering contrast.

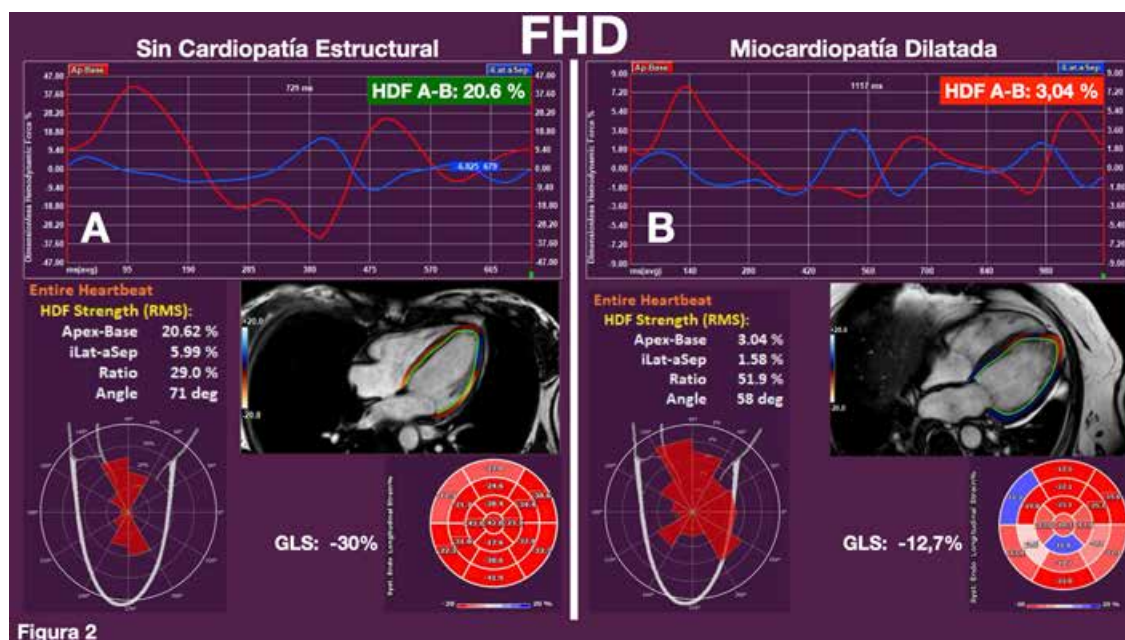


FIGURE 2.

Assessment of hemodynamic forces (HDF) in patients with and without structural disease

Assessment of hemodynamic forces (HDF) in a patient with no structural disease (A) and another with dilated cardiomyopathy (B). In both cases, graphs are shown that represent the evolution of HDFs over the cardiac cycle, both in the apex-base direction (red) and lateral-septal direction (blue). Quantitative analysis and visualization: quantitative variables of HDF are shown, along with a polar map (at the left in every case). This polar map shows the intensity weighted of the forces and its orientation in degrees and dimensions, outlining the left ventricle. We observe a noticeable difference between the two examples. In the patient with dilated cardiomyopathy (B), the representation of HDF is less linear in regard to the 90° axis, indicating a decrease both in the apex-base and lateral-septal HDFs. Supplementary information: the figure also includes screen captures of BB images in 4-chamber views. Myocardial strain assessment by FT technique of GLS is shown, as well as its results in the polar map in both cases. This information, along with the aortic and mitral valve areas, allows the estimation of HDF by MRI.

HDF: apex-to-base hemodynamic forces; **Lateral-to-septal HDF:** septal-to-lateral hemodynamic forces; **BB:** bright blood sequence; **FT:** feature tracking; **GLS:** global longitudinal strain; **MRI:** magnetic resonance imaging.

Image analysis

The following parameters were analyzed: end diastolic volume (EDV), end systolic volume (ESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF) by BB images. LGE images were quantified automatically with signal intensity (SI) >6 of the mean on the myocardium following the model of 17 segments of the AHA, excluding the apex.

Strain analysis and HDF by feature tracking

By Feature Tracking (FT) technique, the endocardial edges were defined in the telesystolic and telediastolic frame. Then, by continuous monitoring with the post-processing software, myocardial shortening was estimated in the cardiac cycle (myocardial strain), thus calculating GCS on the long axis and GRS on the short axis. Diffusion-weighted imaging (DWI) was estimated: this is a parameter to assess regional ventricular function by FT, assessing wall movement toward the inside of the chamber and contractility (Figure 1).^{6,8}

Analysis of ventricular hemodynamic forces

Once GLS measurements in 2-, 3- and 4-chamber views were obtained by the HDF add-on tool of the software, we proceeded to manually draw aortic annulus dimensions in 3-chamber views and mitral annulus in 4-chamber views, automatically es-

timating inlet and outlet area of the left ventricular blood pool.

By this process, different measurement parameters are determined, such as amplitude ones, contemplating the three hemodynamic forces: namely, once force from the apex to the base, one force from the lateral to the septal wall, and one force from the inferior to the anterior wall, although the latter are annulled, so they are not expressed.

Simultaneously, temporality parameters are measured; these measures are associated to cardiac cycle events, derived from the hemodynamic forces, and finally orientation parameters, that are measures associated to the direction of the vector of the left ventricular forces. Provide a comparison between longitudinal forces (apex-base) and transversal forces (septal-lateral/anterior-inferior) (Figure 2).⁹

The apex-to-base, lateral-to-septal FHDs are reported as quantitative means, adjusted by LV volume, adjusted to gravity and blood flow density. These parameters are presented as percentages, allowing a comparison between individuals.^{9,10} They may be observed in real time, in a dynamic way, according to the selection of the phase of the cardiac cycle of interest by software interphase with a polar map of weighed intensity, which reflects the orientation of the vector in degrees and the respective orientation in regard to the overlapped outlined figure of the left ventricle.

TABLE 1.
Characteristics of the population in the study

Characteristics of the population	Total of patients (N° 126)
Age (years)	53 ($\pm$ 1575)
Male gender (%)	78 (62)
Hypertension (%)	73 (58)
Smoking (%)	13 (103)
Diabetes Mellitus (%)	16 (127)
Dyslipidemia (%)	46 (365)
Previous TCA (%)	7 (56%)
Functional parameters in MRI	
LVEF (%)	538 ($\pm$ 149)
RVEF (%)	495 ($\pm$ 108)
Amount in % of late gadolinium enhancement	39 ($\pm$ 78)
LV Global Longitudinal Strain	-193 ($\pm$ 64)
RV Global Longitudinal Strain	-318 ($\pm$ 385)
Parameters of hemodynamic forces by MRI	
Apex-to-base HDF	169 ($\pm$ 10)
Lateral-to-septal HDF	3 ($\pm$ 138)
Vector angle HDF	731 ($\pm$ 45)
AB/SL HDF	207 ($\pm$ 143)
Clinical follow-up	
Non-cardiac death (%)	2 (16)
Admission due to HF (%)	15 (119)
Acute myocardial infarction (%)	3 (24)
Cardiac death (%)	9 (71)
Composite endpoint (CD.HFA.AMI) (%)	24 (19)

TCA: transcatheter coronary angioplasty; RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; HDF: hemodynamic forces; HF: heart failure; CD: cardiac death; HFA: heart failure admission; AMI: acute myocardial infarction; RV: right ventricle; LV: left ventricle.

Statistical analysis

The data analyzed of quantitative variables are presented as mean and standard deviation for those with normal distribution, and median with interquartile ranges (IQR) for those with non-normal distribution. The differences between groups were analyzed by t-test or Mann-Whitney for continuous variables and X2 or Fisher's exact test for categorical variables. Pearson correlation coefficient was used to examine the association between continuous parameters. Survival multivariate analyses with Cox proportional hazards model were carried out to evaluate the hazard ratio (HR) and 95% confidence interval (95% CI). Kaplan-Meier curves were estimated for the apex-base HDF and lateral-septal HDF variables. The statistical analysis was carried out with the commercial software Wizard Pro-2 Mac OS, SPSS, and open-source Jamovi.

TABLE 2.
Clinical and MRI characteristics according to groups

Variable	Apex-to-base HDF > 75% (N° 105)	Apex-to-base HDF < 75% (N° 21)	Significance
Age	54 (IQR 427-663)	62 (IQR 55-67)	P=003
CLBBB (%)	48	286	P<001
CRBBB (%)	48	0	P=031
Hypertension	628	333	P=001
Smoking	76	238	P=003
Dyslipidemia	352	428	P=051
Diabetes Mellitus	95	286	P=002
RVEF	525 (49-56)	36 (267-48)	P<001
LVEF	60 (54-65)	28 (21-41)	P<001
LGE percentage amount	0 (0-3)	5 (0-19.3)	P=001
LV GLS	-218 (24-191)	-96 (117 - 79)	P<001
RV GLS	-297 (338-266)	-228 (299-171)	P<001
Apex-to-base HDF	164 (126 - 224)	62 (45-65)	P<001
Composite event	10 (952%)	14 (66%)	P<001

CLBBB: complete left bundle branch block; CRBBB: complete right bundle branch block; RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; LGE: late gadolinium enhancement; HDF: hemodynamic forces; GLS: global longitudinal strain; LV: left ventricle; RV: right ventricle.

RESULTS

Study population

A total of 137 patients underwent MRI during the follow-up period between years 2015 and 2023, of whom 126 could complete the MRI re-evaluation and the FT technique for HDF analysis. The main clinical and MRI characteristics are summarized in *Table 1*. The mean age of patients was 53.7 years ($\pm$ 15.7), of whom 78 (62%) were males. The pre-established composite event had a 19% incidence (n=24). The apex-to-base HDF presented a cutoff value of 7.5% to identify patients who would develop a major event, with an area under the ROC curve of 0.829 (95% CI 0.725-0.934), $p<0.0001$, 91% sensitivity and 59% specificity (*Figure 3A*); 66% of patients (N=14) with apex-to-base HDF <7.5% presented a composite event, while only 9.5% (N=10) presented it, with apex-to-base HDF >7.5% (*Table 2*). The time median for the appearance of a major event was 104 months for the group with apex-to-base HDF, in comparison with 89 months in the depressed HDF group (*Figure 3B*).

Analysis of ROC curves of HDF variables was also conducted, as lateral-septal and vector angle. The two variables presented significant ROC curves, with the lateral-septal HDF presenting an AUC of 0.787 (95% CI 0.680-0.893), $p<0.0001$, with a cutoff value of 2.44%, and vector angle HDF presenting an AUC of 0.720 (95% CI 0.593-0.846), $p=0.001$, cutoff value of 69. Given the slight superiority of apex-base HDF to classify patients, it was decided to continue with it as the comparison variable in the study.

In *Table 2*, the significant differences presented by patients are shown, both in terms of clinical history and MRI parameters.

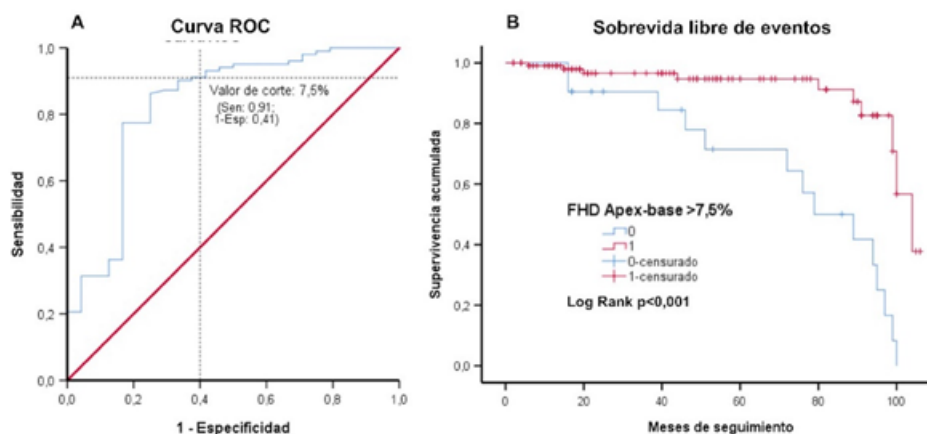


FIGURE 3.

Analysis for the determination of the cutoff point of apex-to-base HDF optimizing risk prediction of incidence of a composite event

A. ROC curve: it was used to determine the sensitivity and specificity of a cutoff point of 7.5% of apex-to-base HDF, selected as it maximizes the incidence of the composite event.

B. Kaplan-Meier (Log-Rank) survival analysis: it allowed to manifest the evolution of two population groups discriminated by a cutoff point of apex-to-base HDF of more than 7.5%.

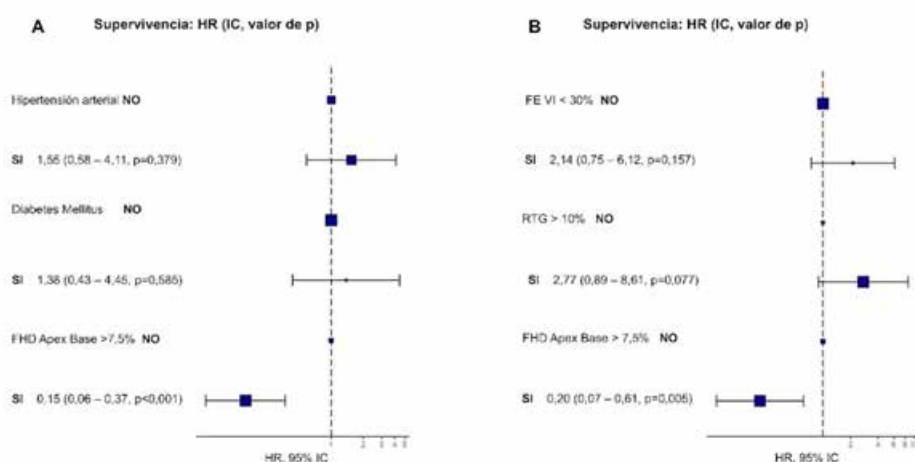


FIGURE 4.

Multivariate analysis of clinical predictors and of MRI for the development of composite event

A. Impact of apex-to-base HDF of more than 7.5% in relation to classical cardiovascular risk factors.

B. Impact of apex-to-base HDF of more than 7.5% in relation to risk markers acknowledged in literature with severe ventricular dysfunction (LVEF <30%) and significant necrotic load (LGE 10% of the left ventricle).

HR: hazard ratio; CI: confidence interval.

A multivariate analysis was made to learn the value of hemodynamic forces in comparison with clinical history and previously validated MRI parameters. Given the low numbers of events, the use of a variable was estimated for each 10 patients that presented the event, so it was compared with another two variables only. In a multivariate analysis that included the clinical risk factors described in the bibliography for the development of major events, the presence of apex-base HDF lower than 7.5% presented an adjusted hazard ratio value of 6.49 (95% CI 2.73-15.45, $p < 0.001$); while the other predictors were not significant (Figure 4A).

Another multivariate analysis that included the main measurement of MRI according to the risk cutoff determined by bibliography (LVEF <30% and LGE >10%) showed that the presence of apex-base HDF lower than 7.5% presented an adjusted hazard ratio value of 4.90 (95% CI 1.69-14.68, $p = 0.005$); while the other predictors were not significant (4B).

DISCUSSION

In this population, analyzed retrospectively, it was observed that HDF presented a statistically significant capacity at the time of separating patients with appearance of composite adverse event in comparison with conventional clinical risk factors and with measurements estimated by MRI such as LVEF and LGE.

Cardiovascular assessment is constantly evolving, transcending LVEF as the only risk parameter. Adding dynamic fluids analysis, such as flow mechanics vortices, offers a new perspective on the complex hemodynamic interaction and cardiovascular disease load. This approach conceptualizes the intrinsic relationship between myocardial tissue and blood flow with the early consequences of ventricular remodeling.^{11,12} The introduction of HDF assessment in clinical practice through MRI may entail an advancement in the assessment of patients in heart failure.¹³ The novelty of this model lies in its capacity to estimate the main characteristics of the hemodynamic force vector from the dynamics of endocardial tissue, not requiring the direct measurement of blood flow velocity within the left ventricle.⁷

This approach could be applicable in the follow-up of patients with heart failure with preserved ejection fraction (HFpEF), or those with marked compromise in the left ventricular architecture, dyssynchronous and with severe deterioration of LVEF, due to its capacity to evaluate cardiac dynamics, in the identification of dyssynchrony pattern and the response to cardiac resynchronization therapy (CRT).^{2,14}

In patients with advanced heart failure and complete left bundle branch block (CLBBB), Eriksson J. et al. analyzed the impact of cardiac dyssynchrony by HDF. Its findings revealed signifi-

cant differences in filling patterns and flow distribution between patients with CLBBB and dyssynchrony, suggesting HDF could be useful to predict the response to CRT.¹⁵ The author highlights the substantial alteration of systolic and diastolic patterns, both in quantity and quality. The delay and mechanical asynchronous activation, often accompanied by widened QRS, generate an increase in transversal HDF (lateral-septal HDF), leading to dissipation of the energy generated. The alignment generated by CRT, measured by HDF, is an important marker of response to the treatment.¹⁵

It is known that currently, MRI has consolidated as an invaluable tool in the comprehensive evaluation of cardiac function. Its advantages include thorough tissue characterization, high spatial resolution, and thorough functional evaluation. MRI allows to categorize the causes of ventricular dysfunction, differentiate it from other diseases as infiltrative and pericardial disorders, and to provide prognostic information by techniques like late gadolinium enhancement and parametric mapping.^{16,17} In this regard, HDFs show a significant correlation with LGE extent, particularly the apex-base and lateral-septal HDFs, suggesting a direct connection between HDF and fibrosis and myocardial remodeling. This finding is supported by the recent study published by Shao et al., where 63 patients with type 2 diabetes and 50 healthy volunteers were evaluated. In this study, in spite of left ventricular ejection fraction (LVEF) and myocardial strain not showing statistically significant differences between groups, a noticeable alteration was observed in the HDFs of diabetic patients. This suggests that HDFs could work as an early and sensitive marker of subclinical myocardial dysfunction, even in the absence of alterations detectable by conventional parameters.¹⁸

The findings of our study, just as with the study by Shao et al., would be in line with the idea that HDFs could provide more accurate functional information, and more sensitive to changes, in comparison with the conventional parameters of MRI.

Limitations

This registry was based on the observation of an outpatient population of general and derived character for different evaluations, which may present selection biases in the population. The rate of events in relation to the sample could be small, and it would be a challenge to continue recording data to increase it for a future analysis.

CONCLUSIONS

In our study, the presence of apex-base HDF of less than 7.5% was associated significantly to a greater incidence of the composite event in regard to patients with a value of more than 7.5%.

The functional analysis of HDF could enhance the value of conventional MRI, providing a new instrument for control and functional monitoring of patients with suspicion or impact of cardiovascular disease.

It is necessary to perform a greater number of studies, with selected populations and longitudinal follow-up, to determine the true prognostic and diagnostic power of this novel technique.

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