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ORIGINAL ARTICLE

Haemodynamic forces predicting remodelling and outcome in patients with heart failure treated with sacubitril/valsartan

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Abstract

Aims A novel tool for the evaluation of left ventricular (LV) systo-diastolic function through echo-derived haemodynamic forces (HDFs) has been recently proposed. The present study aimed to assess the predictive value of HDFs on (i) 6 month treatment response to sacubitril/valsartan in heart failure with reduced ejection fraction (HFrEF) patients and (ii) cardiovascular events.

Methods and results Eighty-nine consecutive HFrEF patients [70% males, 65 ± 9 years, LV ejection fraction (LVEF) 27 ± 7%] initiating sacubitril/valsartan underwent clinical, laboratory, ultrasound and cardiopulmonary exercise testing evaluations. Patients experiencing no adverse events and showing ≥50% reduction in plasma N-terminal pro-B-type natriuretic peptide and/or ≥10% LVEF increase over 6 months were considered responders. Patients were followed up for the composite endpoint of HF-related hospitalisation, atrial fibrillation and cardiovascular death. Forty-five (51%) patients were responders. Among baseline variables, only HDF-derived whole cardiac cycle LV strength (wLVS) was higher in responders (4.4 ± 1.3 vs. 3.6 ± 1.2; $p = 0.01$). wLVS was also the only independent predictor of sacubitril/valsartan response at multivariable logistic regression analysis [odds ratio 1.36; 95% confidence interval (CI) 1.10–1.67], with good accuracy at receiver operating characteristic (ROC) analysis [optimal cutpoint: ≥3.7%; area under the curve (AUC) = 0.736]. During a 33 month (23–41) median follow-up, a wLVS increase after 6 months (ΔwLVS) showed a high discrimination ability at time-dependent ROC analysis (optimal cut-off: ≥0.5%; AUC = 0.811), stratified prognosis (log-rank $p < 0.0001$) and remained an independent predictor for the composite endpoint (hazard ratio 0.76; 95% CI 0.61–0.95; $p < 0.01$), after adjusting for clinical and instrumental variables.

Conclusions HDF analysis predicts sacubitril/valsartan response and might optimise decision-making in HFrEF patients.

Keywords Haemodynamic forces; Heart failure with reduced ejection fraction; Prognosis; Sacubitril/valsartan

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Introduction

Heart failure (HF) guidelines recommend angiotensin receptor-neprilysin inhibition (ARNI) as one of the pillars of drug treatment in HF with reduced ejection fraction (HFrEF) patients.[1] Sacubitril/valsartan has shown to be superior to enalapril in reducing all-cause/cardiovascular mortality and HF-related hospitalisations in outpatients and inpatients with HFrEF.[2–4] However, improvement in both clinical severity and neurohormonal activation is reported in just one third of

patients on ARNI.[5,6] The possibility to identify responders to ARNI based on clinical, biohumoral and imaging indexes may help to predict and/or monitor HF trajectories, thus tailoring therapeutic decision-making and follow-up [e.g., anticipating/delaying implantable cardioverter-defibrillator implantation, left ventricular (LV) assist devices or referral to HF transplant].[7] Additionally, ARNI response demonstrates significant inter-individual differences also in terms of LV reverse remodelling.[8,9]

Intracardiac fluid dynamics represent a novel field of imaging research that has been previously and extensively validated against the current gold standard of 4D-flow magnetic resonance imaging.[10–14] In particular, the analysis of haemodynamic forces (HDFs), defined as intraventricular pressure gradients averaged over the LV volume during the cardiac cycle, appears to be a valuable bedside tool to evaluate blood flow and cardiac mechanics.[15–18]

In this bicentric prospective observational study, including a population of HFrEF patients treated with ARNI, we aim to explore the predictors of response to treatment and cardiovascular events among clinical and biohumoral variables, including cardiopulmonary exercise testing (CPET) parameters and echocardiographic data with HDFs.

Methods

Study population

We prospectively enrolled 111 consecutive HFrEF stable outpatients (i.e., on optimal guideline-directed medical therapy and without HF-related hospitalisation in the previous 6 months) referred for evaluation to the Department of Cardiology of Fondazione Toscana Gabriele Monasterio, Pisa, Italy (n = 70), and the Department of Clinical and Experimental Medicine of the University Hospital of Pisa, Italy (n = 41), between 2017 and 2019. Patients enrolled were part of the Discover ARNI trial, which was registered with other purposes. HF diagnosis was based on typical HF signs or symptoms, and HFrEF was defined by an LV ejection fraction (LVEF) $\leq$ 40% in accordance with the latest European Society of Cardiology HF guidelines.[1] Exclusion criteria were more than moderate left-sided valve disease, arrhythmias not effectively controlled by anti-arrhythmic drugs or implantable defibrillator/pacemaker and inadequate acoustic windows. Fourteen subjects were excluded based on these criteria, and other 8 patients because of ARNI discontinuation, leading to a final study population of 89 subjects (Figure S1).

The Local Ethics Committees approved the protocol (ID Number 19204), and written informed consent was obtained from all patients. The study conformed to the principles of the Declaration of Helsinki.

Baseline multiparametric assessment

Baseline assessment consisted of clinical evaluation, complete laboratory analysis [including N-terminal pro-B-type natriuretic peptide (NT-proBNP) assessed via an electro-chemiluminescence monoclonal method, Roche Diagnostics Italia, Monza, Italy], CPET and rest transthoracic echocardiography, which were performed on the same day of enrolment. Further details are available in the supporting information.

Echocardiographic evaluation

All patients underwent a comprehensive transthoracic echocardiography examination (using Philips iE33 xMATRIX echocardiography system, Andover, MA, USA, or Hitachi Medical Systems LISENDO 880, Tokyo, Japan) at rest, according to the international recommendations.[19–21] The protocol is described in detail in the supporting information, including speckle tracking echocardiography (STE). Every recorded image consisted of at least 3 or 5 cardiac cycles in sinus rhythm or atrial fibrillation (AF), respectively.

Beyond standard echocardiographic assessment, we non-invasively estimated pulmonary artery wedge pressure (PAWP) using a previously validated equation, which includes the following variables: tricuspid regurgitation velocity (TRV), LVEF, right ventricular (RV) fractional area change, left atrial (LA) volume index (LAVi), E/e', inferior vena cava and mean pulmonary artery pressure (mPAP).[22] Cardiac output (CO) was calculated by multiplying stroke volume by heart rate. Then, pulmonary vascular resistance (PVR) was calculated as (mPAP − PAWP)/CO.[22]

HDF analysis

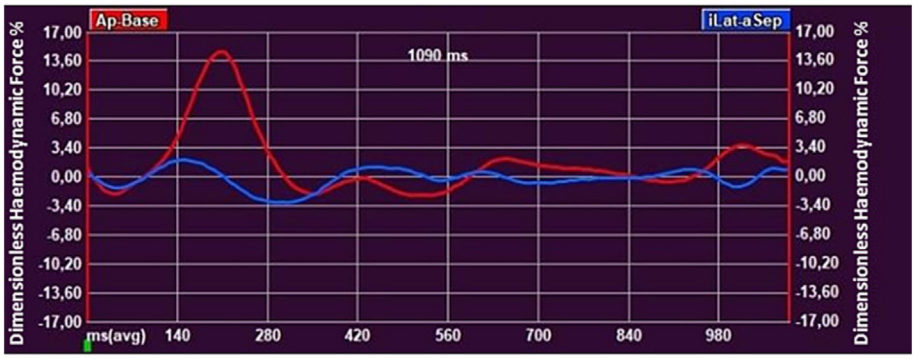
HDFs were obtained by offline analysis of echocardiographic DICOM files with a dedicated software (QStrain Echo v.1.3, Medis Medical Imaging, Leiden, the Netherlands). First, the software performed STE analysis of LV in the three routinely acquired apical scans: four-chamber, two-chamber and three-chamber views. Then, HDFs could be detected through endocardial velocities, LV geometry and aortic and mitral orifices areas, obtained after measuring the internal diameter of the valve annulus in parasternal long-axis view[12,16] as depicted in Figure S2.

Tissue velocities were derived directly from STE.[15] The average velocity of blood on the open part of the boundary (e.g., the mitral area during diastole) was estimated by mass conservation. HDFs in the LV occur along three planes: basal–apical, septal–lateral and inferior–anterior directions.[13] We analysed only the longitudinal component of the HDFs (i.e., basal–apical direction), which is the most widely reproducible and detectable force in all patients.[12,16] The instantaneous value of HDFs was normalised by the corresponding value of LV volume to compare patients with different LV

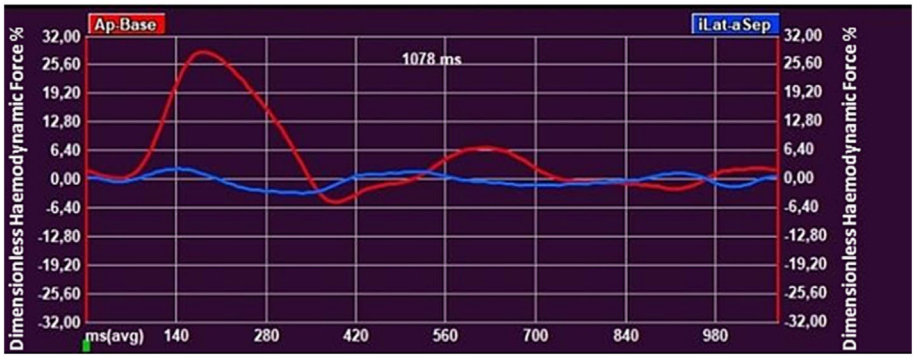
sizes. It was then divided by blood density and gravity acceleration, obtaining a dimensionless value corresponding to the force expressed as a percentage of gravity acceleration.[12,16] *Figure* 1 displays different time profiles of HDFs. In the present study, we used the longitudinal HDF time profile to extract a few characteristic parameters:

- whole cardiac cycle LV strength (wLVS): the mean amplitude of the longitudinal force along the entire cardiac cycle, expressed as root mean square and including both positive and negative values;
- systolic impulse: the mean amplitude of the longitudinal force during the positive systolic phase;

Figure 1 Haemodynamic force (HDF) to predict angiotensin receptor-neprilysin inhibitor (ARNI) response and adverse events in patients with heart failure with reduced ejection fraction (HFrEF). (Upper panel) Time profiles of HDFs in an HFrEF patient who resulted an ARNI responder (left) versus a non-responder (right). We analysed only the longitudinal component of the HDFs (red curves), ignoring the septal–lateral direction (blue curves). (Lower panel) Time-dependent receiver operating characteristic curves illustrating the accuracy of whole cardiac cycle left ventricular strength (wLVS) and ΔwLVS in predicting ARNI response (left) and the composite clinical endpoint (right), respectively. Δ indicates the difference measured between the 6 month ARNI-response protocol and baseline evaluation. LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain.



Baseline evaluation
LVEF: 25%
LVGLS: 10%
wLVS: 4.6%



6-month ARNI-response
LVEF: 39%
LVGLS: 15%
wLVS: 7.9%
ΔwLVS: 3.3%

- systolic peak: the peak amplitude of the longitudinal force during the positive systolic phase;
- time to systolic peak: time to reach the systolic peak (expressed in milliseconds);
- systolic LV strength (sLVS): the mean amplitude of longitudinal force during the systole, expressed as root mean square and including both positive and negative values; and
- systolic impulse duration: the duration of longitudinal force during the systole, expressed as a percentage of the whole cardiac cycle.

Six-month ARNI response and clinical follow-up

The primary aim of the study was the identification of the predictors of ARNI response. After the initiation of sacubitril/valsartan, the frequency of the follow-up visits was performed at the discretion of the attending cardiologist. Most patients were visited every month in each centre until the drug was up-titrated to the maximum tolerated dose [average time to maximum up-titration 1.5 months, interquartile range (IQR) 1.0–3.5], and side effects were reported. A 6 month follow-up visit was scheduled for each patient, and at this time point, all parameters acquired at baseline were re-assessed. As per protocol, we excluded from the analysis eight patients who discontinued the drug due to hypotension (n = 5), worsening renal function (n = 2) or hyperkalaemia (n = 1).

We defined an ARNI responder as a patient taking the drug (i) without HF admissions, death or heart transplant and (ii) with a ≥50% reduction in NT-proBNP levels[5] and/or an increase of ≥10 points in LVEF[23] after a 6 month treatment period.

The secondary aim of the study was an exploratory survival analysis after completing the ARNI-response protocol. All subjects were followed by an exhaustive review of medical directories as well as by phone calls for a composite endpoint, including all-cause death, HF-related hospitalisation (defined as an in-hospital stay $>$ 24 h due to HF as the primary diagnosis on the discharge letter) and new-onset AF. When multiple events occurred, patients were censored at the time of the first event. Follow-up events were adjudicated by an independent trained investigator blinded to the clinical data.

Statistical analysis

The sample size to address the primary aim was previously calculated to provide a statistical power of 90% at a 5% significance level with a medium effect size (f = 0.25) and considering two groups in a 1:1 fashion (ARNI responders vs. non-responders). We estimated a minimum sample size of 80 subjects. Continuous measures were expressed as the mean value ± standard deviation or median and IQR for normally or skewed distributed variables, respectively. *T*-test or Mann–Whitney test was used to compare two independent samples, whereas paired *T*-test or Wilcoxon test was used for paired sample comparisons (repeated measures in the same subject before and after ARNI administration), according to variable distributions. Categorical variables were presented as percentages and compared using the chi-square test or the McNemar test to analyse two independent or paired samples, respectively.

Time-dependent receiver operating characteristic (ROC) analysis was used to calculate the area under the curve (AUC) and the cut-off point with the highest Youden index. Stepwise multivariable linear regression models were employed to predict ARNI response using parameters acquired during baseline evaluation as independent variables. Variance inflation factor $>$ 5 was used to exclude multi-collinearity between selected variables. We evaluated survival probabilities using Kaplan–Meier curves in ARNI responders versus non-responders and according to the best performing HDF-derived variable.

We then tested Cox proportional-hazards regression analysis to identify the independent predictors of the composite endpoint and used forward stepwise selection (entry and removal value of $p < 0.01$ and $p > 0.10$, respectively) to prevent overfitting. We selected a total of 10 variables with potential prognostic significance based on clinical experience and prior publications: age, gender, ΔNT-proBNP, Δpeak VO_2, ΔLA reservoir strain, ΔLVEF, ΔLV global longitudinal strain (LVGLS), ΔRV free-wall longitudinal strain, ΔPAWP and ΔwLVS, where Δ indicates the difference in each variable measured at baseline and after 6 month treatment with ARNI. Again, variance inflation factor $>$ 5 was used to exclude multi-collinearity between selected variables. To test the proportional-hazards assumption, we analysed the interaction between time and covariates in the model. If the assumption was violated, we included the relevant interaction terms alongside the original predictors in the model. A bootstrap resampling procedure was used to confirm or exclude the best fitting variables from the original regression model (1000 repeats with forward selection, entry and removal values of $p < 0.01$ and $p > 0.10$, respectively). Variables selected in $>$70% of all repeats were included in the final model.

A random sample of 20 patients was re-analysed by the same observer who performed the analysis. Two independent readers were blinded to clinical data to measure the reproducibility of HDF-derived variables. All tests were two-sided, with a p-value of $<$0.05 considered significant. Data were analysed with SPSS Version 25.0 (IBM Corp., Armonk, NY, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The characteristics of the study population at baseline and 6 months after sacubitril/valsartan initiation are shown in Table S1. At baseline, echo-derived estimation of PAWP was >15 mmHg in most patients (*n* = 79/89, 89%); ~50% had mild pulmonary hypertension (mPAP ≥ 25 mmHg, *n* = 47/89, 53%); no subject had increased PVR (PVR > 3 mmHg). Overall, a mild but significant reduction in LV volumes, an increase of LVEF (*p* = 0.03) and LVGLS (*p* = 0.03) and a significant de-

Table 1 Clinical characteristics of the study population (ARNI responders vs. non-responders).

Variable	ARNI responders (*n* = 45)	ARNI non-responders (*n* = 44)	*p*-value
Baseline evaluation			
Age, years	63 ± 8	67 ± 10	0.11
Male	33 (73)	30 (68)	0.60
BMI, kg/m^2	27 ± 5	26 ± 3	0.43
BSA, m^2	1.9 ± 0.3	1.9 ± 0.2	0.42
Current smoker	24 (53)	17 (38)	0.21
Hypertension	17 (38)	13 (32)	0.40
Diabetes mellitus	11 (28)	8 (18)	0.33
Dyslipidaemia	23 (52)	23 (53)	0.81
Ischaemic aetiology	16 (36)	18 (41)	0.22
COPD	7 (16)	9 (21)	0.52
NYHA class	2 (1 to 3)	2 (1 to 3)	0.83
Pacemaker	1 (2)	3 (7)	0.50
ICD	21 (47)	13 (29)	0.11
CRT-D	16 (36)	15 (34)	0.74
CRT-P	4 (9)	3 (7)	0.62
SBP, mmHg	117 ± 18	123 ± 19	0.22
DBP, mmHg	69 ± 13	70 ± 11	0.80
Heart rate, b.p.m.	68 ± 12	65 ± 9	0.13
Haemoglobin, g/dL	13.5 ± 1.6	13.8 ± 1.3	0.41
K^+, mEq/L	4.5 ± 0.5	4.3 ± 0.7	0.14
eGFR, mL/min/1.73 m^2	70 ± 13	69 ± 12	0.24
NT-proBNP, ng/L	1712 (879 to 2978)	1566 (726 to 2240)	0.12
Beta-blocker	43 (96)	43 (98)	0.71
ACEi or ARB (pre-ARNI)	40 (89)	40 (91)	0.83
MRA	36 (80)	40 (90)	0.24
Diuretics	34 (75)	33 (75)	0.91
ARNI initial dose, mg			
24/26	28 (63)	30 (69)	0.62
49/51	16 (35)	13 (29)	0.54
97/103	1 (2)	1 (2)	0.92
Peak VO_2, mL/kg/min	15 ± 4	16 ± 4	0.31
6 month ARNI-response protocol			
BMI, kg/m^2	26 ± 4	26 ± 4	0.61
BSA, m^2	1.9 ± 0.2	1.9 ± 0.2	0.52
NYHA class	2 (1 to 3)	2 (1 to 3)	0.72
SBP, mmHg	109 ± 19	114 ± 20	0.11
DBP, mmHg	65 ± 15	68 ± 12	0.80
Heart rate, b.p.m.	69 ± 13	67 ± 10	0.43
Haemoglobin, g/dL	13.6 ± 1.6	13.5 ± 1.5	0.51
K^+, mEq/L	4.6 ± 0.6	4.4 ± 0.7	0.11
eGFR, mL/min/1.73 m^2	68 ± 16	67 ± 17	0.92
NT-proBNP, ng/L	537 (371 to 850)	1228 (617 to 1783)	**<0.0001**
ARNI dose, mg			
24/26	7 (15)	14 (32)	0.13
49/51	11 (25)	16 (36)	0.32
97/103	27 (60)	14 (32)	**0.01**
Peak VO_2, mL/kg/min	17 ± 4	14 ± 4	**0.02**
Post-protocol clinical follow-up			
Cardiovascular death	0	3 (7)	0.10
HF hospitalisation	2 (4)	17 (38)	**0.0001**
New-onset atrial fibrillation	3 (7)	12 (27)	**0.01**
Composite endpoint	5 (11)	29 (66)	**<0.0001**

Note: Results are expressed in number (%), mean (SD) or median (interquartile range), Bold *p*-values emphasise the statistically meaningful tests. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronisation therapy defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; VO_2, oxygen consumption.

crease in NT-proBNP levels (p = 0.01) were observed at 6 months. Likewise, HDF-derived wLVS increased (p = 0.02), whereas time to systolic peak decreased ($p < 0.0001$). There were no missing echocardiographic data, and good intraobserver and interobserver reproducibility was documented for all HDF-derived parameters (Table S2).

ARNI responders versus non-responders

Out of 89 patients, 45 responded to ARNI (51%) according to the study criteria. Among responders, no patient experienced cardiovascular death or heart transplant, 38/45 (84%) had ≥50% reduction in NT-proBNP levels, 25/45 (56%) showed an increase of ≥10 points in LVEF and 13/45 (29%) met both criteria. No significant difference was found between responders and non-responders at baseline for clinical severity, aetiology, cardiopulmonary indices and medical treatment (*Table* 1). At 6 months, ARNI responders showed higher LVEF and lower NT-proBNP as per protocol, with increased peak VO_2. In non-responders, fewer patients reached the highest ARNI dose (p = 0.01 vs. responders).

The echocardiographic characteristics of responders versus non-responders are summarised in *Table* 2. Responders and non-responders did not differ in structural, functional and haemodynamic echo-derived assessment at baseline. Only the HDF-derived wLVS and sLVS were significantly different, showing higher values in responders (all $p < 0.05$). At the end of the 6 month ARNI-response protocol, responders displayed significantly reduced LA and LV volumes, with simultaneous improvement of LA reservoir strain, LVEF, LVGLS and diastolic function (all $p < 0.05$). Likewise, RV free-wall longitudinal strain increased, whereas echo-derived systolic pulmonary artery pressure, mPAP and PAWP decreased in responders, differently from non-responders (all $p < 0.01$). All the HDF-derived parameters (except for the systolic impulse duration and time to systolic peak) were significantly higher in responders versus non-responders, and wLVS displayed the highest significant difference.

ARNI-response predictors

Multivariable logistic regression analysis using baseline parameters represented wLVS as the only independent predictor of ARNI response at 6 months [odds ratio 1.36; 95% confidence interval (CI) 1.10–1.67; p = 0.004] after adjusting for clinical, functional and conventional echocardiographic parameters (*Table* 3). ROC analysis showed a significant accuracy of wLVS ≥ 3.7% in predicting ARNI response (AUC = 0.736, 95% CI 0.607–0.840; $p < 0.0001$; *Figure* 1). Also, wLVS independently predicted the up-titration to the highest ARNI dose (Table S3).

Follow-up and survival analysis

After the 6 month ARNI-response protocol, patients entered a clinical follow-up (median 33, IQR 23–41 months). ARNI non-responders experienced a significantly higher proportion of adverse events, considering the composite endpoint and the single components of HF hospitalisation and new-onset AF, whereas the difference in cardiovascular death was not statistically significant between the two subgroups (*Table* 1). Kaplan–Meier analysis for the composite endpoint displayed a significantly higher survival probability in ARNI responders versus non-responders ($p < 0.0001$ by log-rank test; *Figure* 2A). At Cox proportional-hazards multivariable regression analysis, ΔNT-proBNP, Δpeak VO_2, ΔRV free-wall longitudinal strain, ΔPAWP and ΔwLVS were found to be all independent predictors of the composite endpoint, even after adjusting for clinical, functional and conventional echocardiographic parameters (*Table* 4). After including time-dependent covariates, we found no significant improvement in model fit (p = 0.100). Stepwise regression of 1000 bootstrap samples showed that all the independent predictors selected entered in >70% of the models (72% to 85%). At time-dependent ROC analysis, the accuracy of ΔwLVS ≤ 0.5% in predicting the composite endpoint was excellent (AUC = 0.811, 95% CI 0.69–0.90; $p < 0.0001$; *Figure* 1). Kaplan–Meier analysis for the composite endpoint also showed a significantly higher survival probability in patients with ΔwLVS > 0.5% versus those having ΔwLVS ≤ 0.5% ($p < 0.0001$ by log-rank test; *Figure* 2B). We also conducted a sensitivity survival analysis including only cardiovascular death and HF hospitalisation (Table S4), which confirmed the prognostic role of ΔwLVS.

Discussion

The analysis of HDFs by echocardiography from this exploratory bicentric observational study provides relevant information on the different responses (reverse remodelling and neurohormonal improvement) to ARNI treatment in HFrEF patients. HDF-derived wLVS emerged as an accurate predictor of the efficacy of ARNI response. Moreover, wLVS variation at 6 months (ΔwLVS) was also an independent predictor of adverse cardiovascular events, especially HF hospitalisation and new-onset AF.

The PARADIGM-HF trial demonstrated that the benefit of ARNI in HFrEF is associated with a significant reduction in plasma NT-proBNP levels,[2] which, in turn, is a well-known index of reverse remodelling.[24] The hypothesis of a direct link between ARNI and reverse remodelling has been increasingly studied. Januzzi et al. highlighted a significant improvement in LV volume and function, as well as a reduction in LAVi and the ratio of early transmitral Doppler velocity/early diastolic annular velocity (E/e') in patients treated with ARNI.[23] Previous studies

Table 2 Echocardiographic characteristics of the study population (ARNI responders vs. non-responders).

Variable	ARNI responders (n = 45)	ARNI non-responders (n = 44)	p-value
Baseline evaluation			
Maximum LAVi, mL/m^2	42 ± 24	49 ± 20	0.21
Minimum LAVi, mL/m^2	24 ± 20	30 ± 20	0.22
LA reservoir strain, %	20 ± 12	17 ± 7	0.11
LVMi, g/m^2	140 ± 34	133 ± 21	0.31
LVEDVi, mL/m^2	118 ± 22	117 ± 18	0.94
LVESVi, mL/m^2	86 ± 23	84 ± 16	0.73
LVEF, %	27 ± 6	28 ± 5	0.52
Cardiac output, L/min	3.9 ± 1.1	3.8 ± 1.2	0.71
LVGLS, %	9 ± 3	9 ± 2	0.71
E/A ratio	1.3 ± 0.7	1.5 ± 0.8	0.30
Deceleration time, ms	187 ± 60	202 ± 84	0.41
E/e′ ratio	12 ± 5	13 ± 6	0.32
S′ wave, cm/s	10 ± 3	11 ± 3	0.33
TAPSE, mm	18 ± 5	19 ± 4	0.83
RVFAC, %	37 ± 8	38 ± 9	0.72
RV free-wall longitudinal strain, %	17 ± 7	17 ± 3	0.51
Systolic PAP, mmHg	39 ± 12	43 ± 14	0.11
Diastolic PAP, mmHg	16 ± 5	15 ± 5	0.50
Mean PAP, mmHg	25 ± 7	24 ± 7	0.50
Pulmonary vascular resistance, WU	1.4 ± 0.6	1.7 ± 0.7	0.22
PAWP, mmHg	18 ± 5	19 ± 5	0.53
Haemodynamic longitudinal forces			
Whole cardiac cycle LV strength, %[a]	4.4 ± 1.3	3.6 ± 1.2	**0.01**
Systolic impulse, %	4.9 ± 2.7	4.0 ± 2.2	0.14
Systolic peak, %	11.1 ± 5.1	9.2 ± 4.6	0.14
Time to systolic peak, ms	178 ± 39	176 ± 41	0.81
Systolic LV strength, %	5.3 ± 2.3	4.2 ± 2.1	**0.03**
Systolic impulse duration, % of cardiac cycle	32 ± 9	36 ± 10	0.12
6 month ARNI-response protocol			
Maximum LAVi, mL/m^2	35 ± 19	54 ± 23	<**0.0001**
Minimum LAVi, mL/m^2	19 ± 16	36 ± 17	<**0.0001**
LA reservoir strain, %	24 ± 9	13 ± 7	<**0.0001**
LVMi, g/m^2	120 ± 20	139 ± 22	<**0.0001**
LVEDVi, mL/m^2	98 ± 21	126 ± 27	<**0.0001**
LVESVi, mL/m^2	64 ± 20	92 ± 24	<**0.0001**
LVEF, %	35 ± 9	27 ± 4	<**0.0001**
Cardiac output, L/min	4.3 ± 1.1	3.7 ± 1.2	**0.02**
LVGLS, %	12 ± 3	9 ± 3	**0.02**
E/A ratio	0.8 ± 0.3	1.7 ± 1.1	<**0.0001**
Deceleration time, ms	239 ± 75	185 ± 60	**0.001**
E/e′ ratio	10 ± 3	13 ± 6	**0.03**
RV S′ wave, cm/s	12 ± 3	11 ± 3	0.12
TAPSE, mm	20 ± 6	18 ± 5	0.12
RVFAC, %	39 ± 10	37 ± 9	0.31
RV free-wall longitudinal strain, %	22 ± 8	16 ± 5	<**0.0001**
Systolic PAP, mmHg	35 ± 6	46 ± 13	<**0.0001**
Diastolic PAP, mmHg	13 ± 5	15 ± 5	0.14
Mean PAP, mmHg	20 ± 7	24 ± 7	**0.01**
Pulmonary vascular resistance, WU	1.4 ± 0.5	1.7 ± 0.8	0.14
PAWP, mmHg	13 ± 5	18 ± 5	**0.001**
Haemodynamic forces			
Whole cardiac cycle LV strength, %[a]	5.2 ± 1.3	3.7 ± 1.4	<**0.0001**
Systolic impulse, %	5.8 ± 2.8	4.1 ± 2.4	**0.006**
Systolic peak, %	13.3 ± 5.4	9.4 ± 5.5	**0.01**
Time to systolic peak, ms	154 ± 48	149 ± 43	0.63
Systolic LV strength, %	6.5 ± 2.7	4.4 ± 2.5	**0.001**
Systolic impulse duration, % of cardiac cycle	33.3 ± 6	36 ± 10	0.14

Note: Bold p-values emphasise the statistically meaningful tests.
Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; LA, left atrial; LAVi, left atrial volume index; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVGLS, left ventricular global longitudinal strain; LVMi, left ventricular mass index; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RV, right ventricular; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.
[a]Expressed as root mean square.

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Table 3 Multivariable logistic regression analysis for predicting response to ARNI therapy using baseline evaluation.

Variable	Odds ratio (95% CI)	*p*-value
Age, years	0.95 (0.87 to 1.05)	0.33
Male	0.29 (0.04 to 1.94)	0.21
Ischaemic aetiology	0.55 (0.27 to 1.13)	0.14
NT-proBNP, ng/L	1.00 (0.99 to 1.01)	0.90
Peak VO_2, mL/kg/min	1.09 (0.59 to 1.39)	0.61
LA reservoir strain, %	0.92 (0.89 to 1.02)	0.11
LVEF, %	1.14 (0.92 to 1.41)	0.22
LVGLS, %	1.29 (0.91 to 1.84)	0.13
RV free-wall longitudinal strain, %	1.08 (0.73 to 1.26)	0.24
PAWP, mmHg	0.95 (0.87 to 1.03)	0.12
Whole cardiac cycle LV strength, %	1.36 (1.10 to 1.67)	**0.004**

Note: Bold *p*-values emphasise the statistically meaningful tests.
Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; RV, right ventricular; VO_2, oxygen consumption.

on small populations found similar LV morphological and functional improvements.[6,25] More recently, the EVALUATE-HF study offered insights into the effects of sacubitril/valsartan on cardiac chamber geometries.[26] However, there was no appreciable difference between enalapril and sacubitril/valsartan in LVEF. In the PROVE-HF study, patients treated with ARNI had statistically significant improvements in LVEF from baseline to 6 months, reducing multiple atrial and ventricular parameters of remodelling.[26] Our results are consistent with these findings, but most LV morphology and function indices, including HDFs, significantly improved only in the ARNI responders.

We also observed in these patients a protective role of ARNI on LA remodelling and function, confirmed by the lower incidence of new-onset AF in this group than in non-responders. The PARADIGM-HF trial showed no difference in new-onset AF incidence between groups treated with ARNI or enalapril. However, the multicentre, observational, prospective registry SAVE THE RHYTHM described a decreased arrhythmic burden in patients with paroxysmal AF and a reduced incidence of de novo AF in those with no history of arrhythmia.[27] The incidence of cardiovascular deaths (3%) and HF hospitalisations (21%) in our cohort were similar to those reported in larger clinical trials.[2,28,29] Notably, the prevalence of adverse cardiovascular events was significantly lower in ARNI responders versus non-responders, stressing the importance of predicting drug response.

Shorter disease duration, non-ischaemic aetiology of HFrEF and female gender have been related to more significant improvement in biohumoral and echocardiographic parameters following optimal medical therapy, including ARNI.[30,31] In our population, there were no significant differences in baseline clinical evaluation between responders and non-responders. Similarly, baseline echocardiographic features were comparable in the two groups, except for HDF-derived parameters (i.e., wLVS and sLVS). In a prospective echocardiographic study including strain imaging, therapy with sacubitril/valsartan created a state of gradual and chronic LV unloading, favouring reverse remodelling and restoration of Starling force properties.[32]

HDF analysis identifies subclinical abnormalities in LV systolic and diastolic function when more conventional volumetric and deformation measures remain intact, including LVGLS.[18,33,34] Thus, it is conceivable that the same parameters could further refine, compared with STE tools, the stratification of patients with overt HFrEF, as there is a tight, reciprocal connection between fluid dynamics and cardiac function.[17,35] Actually, the interplay between blood flow and cardiomyocytes was demonstrated to influence the morphogenesis of embryonic hearts,[36] as well as the pathological adaptation of adult hearts.[17,37] Notably, wLVS was the only independent predictor of ARNI response at baseline among several variables, including peak VO_2 at CPET, effectively detecting cardiovascular functional impairment in patients with HF.[38,39] As wLVS was significantly higher at baseline evaluation in ARNI responders, HDFs could identify those patients with less advanced HF that could benefit the most from ARNI introduction and up-titration. Indeed, wLVS independently predicted up-titration to the highest ARNI dose after adjusting for demographic, clinical or biohumoral parameters. Moreover, ΔwLVS resulted as an independent predictor of the composite endpoint, along with ΔNT-proBNP, Δpeak VO_2, ΔRV free-wall longitudinal strain and ΔPAWP, promoting its use as a prognostic discriminator if confirmed in larger cohorts. In this respect, the reproducibility of HDF-derived parameters and the relatively short time of analysis using a dedicated vendor-independent software (i.e., comparable with the time dedicated to conventional STE assessment and easily evaluable during the same session) might expedite its use in clinical settings and promote the development of larger registries to confirm our results.

Limitations

This is a pilot, hypothesis-generating study; therefore, it is impossible to establish causality in the relationships between response to sacubitril/valsartan and echocardiographic modifications. Due to a small sample size and a relatively short follow-up, further research is needed to confirm the usefulness and accuracy of HDFs in identifying initial cardiac abnormalities and predicting the response to medical therapy. Moreover, there is no univocal definition of ARNI efficacy. The criteria proposed in this paper are based on large registries evaluating biohumoral[5] or echocardiographic[23] effects of ARNI and have been used in other studies.[40] Furthermore, the response to treatment is also supported by CPET data, which had not been included in the preliminary established criteria of ARNI response in our study. Beyond ARNI, sodium-glucose co-transporter 2 inhibitors (SGLT2i) are known to reduce NT-proBNP levels and improve cardiac function and prognosis. Unfortunately, data regarding treatment with SGLT2i were not available.

Figure 2 Survival analyses. Kaplan–Meier survival analysis for the composite endpoint (all-cause death, hospitalisation due to worsening heart failure and new-onset atrial fibrillation) after a median follow-up of 32.5 months. The patients are stratified into angiotensin receptor-neprilysin inhibitor (ARNI) responders and non-responders (A) and according to Δwhole cardiac cycle left ventricular strength (ΔwLVS > 0.5% vs. ΔwLVS > 0.5%) (B). Δ indicates the difference measured between the 6 month ARNI-response protocol and baseline evaluation.

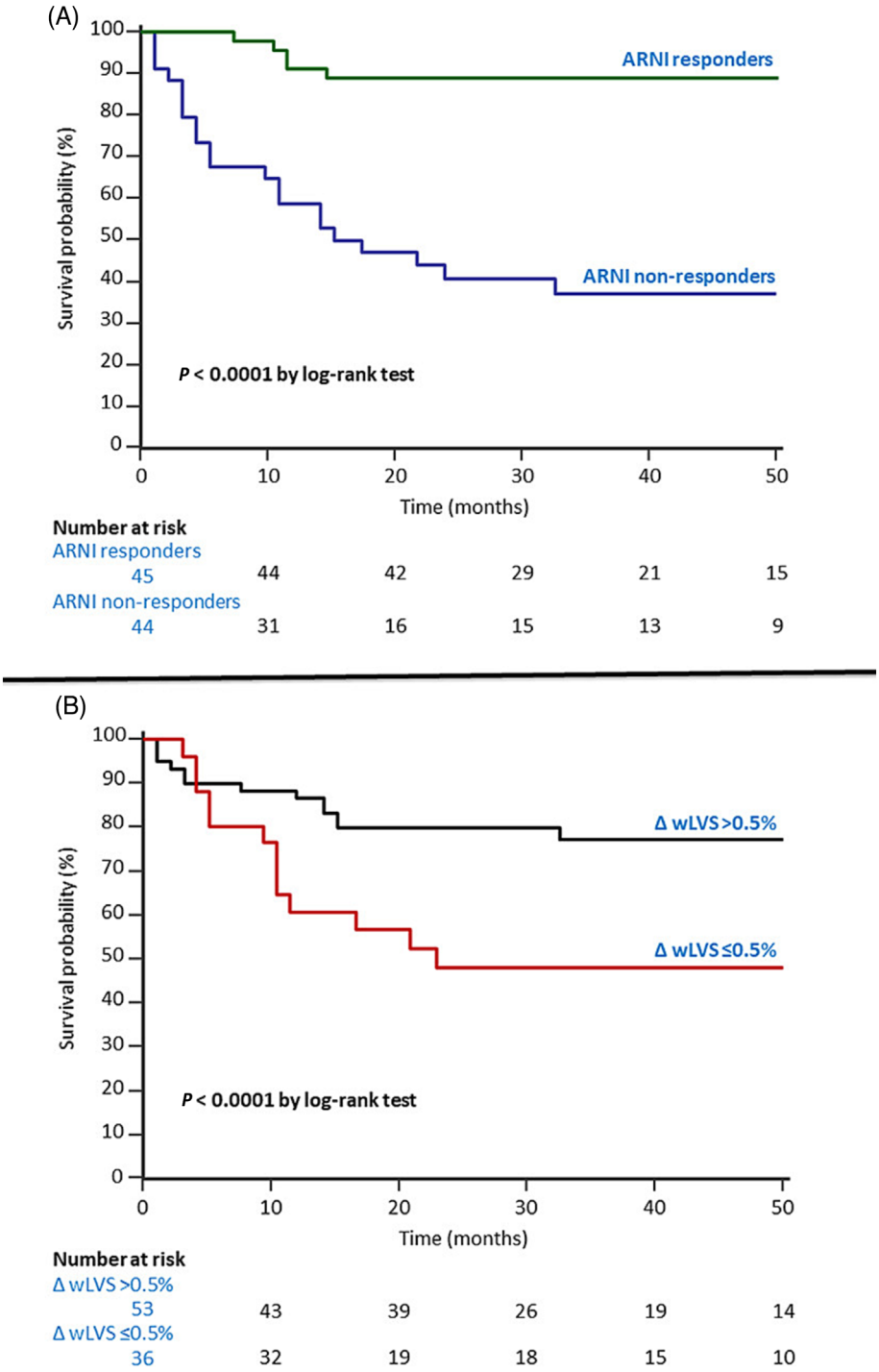

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Table 4 Cox proportional-hazards multivariable regression analysis for predicting the composite endpoint (cardiovascular death, hospitalisation for heart failure and new-onset atrial fibrillation).

Variable	Hazard ratio (95% CI)	*p*-value
Age, years	1.02 (0.89 to 1.11)	0.13
Male	1.09 (0.84 to 1.44)	0.24
Ischaemic aetiology	1.23 (0.98 to 1.51)	0.11
ΔNT-proBNP, ng/L	1.00 (1.00 to 1.01)	**0.001**
Δ Peak VO_2, mL/kg/min	0.81 (0.64 to 0.96)	**0.01**
ΔLA reservoir strain, %	1.00 (0.91 to 1.11)	0.90
ΔLVEF, %	0.94 (0.85 to 1.04)	0.23
ΔLVGLS, %	0.97 (0.79 to 1.18)	0.72
ΔRV free-wall longitudinal strain, %	0.82 (0.67 to 0.98)	**0.004**
ΔPAWP, mmHg	1.19 (1.08 to 1.32)	**0.001**
ΔWhole cardiac cycle LV strength, %	0.76 (0.61 to 0.95)	**0.01**

Note: Δ indicates the difference from 6 month evaluation to baseline, Bold *p*-values emphasise the statistically meaningful tests.
Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; RV, right ventricular; VO_2, oxygen consumption.

Conclusions

The analysis of HDFs helps to predict both the ARNI response and the risk for adverse cardiovascular outcomes in patients with HFrEF. Identifying patients with a high likelihood of ARNI response could lead to a more prompt, effective drug prescription and, hopefully, a more logical follow-up and referral to device implantation. Confirming these findings in more extensive studies could provide clinicians with new bedside tools to highlight early abnormalities in cardiac function and tailor medical/device therapy.

Conflict of interest statement

No conflict of interest to declare.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographics of the study population (n = 89) at baseline and after 6 months following initiation of sacubitril-valsartan.
Table S2. Reproducibility analysis of HDF-derived parameters.
Table S3. Multivariable logistic regression analysis for prediction of up-titration to the highest ARNI dose using baseline evaluation.
Table S4. Cox proportional-hazards multivariable regression analysis for predicting cardiovascular death and hospitalization for heart failure.
Figure S1. Enrolment flowchart. ^High frequency of premature ventricular complexes (>40% of all beats) despite the use of rate and/or rhythm control therapy. *Patients underwent spirometry before exercise, and those with more than moderate airflow obstruction (FEV1/FVC < 0.70 and FEV1 < 50% of predicted FEV1) and/or restrictive pattern (<80% of predicted FVC) were excluded. ARNI: angiotensin receptor-neprilysin inhibitor; CPET: cardiopulmonary exercise testing; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.
Figure S2. Hemodynamic forces (HDFs) evaluation: software workflow. HDFs were obtained by offline analysis of echocardiographic DICOM files with a dedicated software (QStrain Echo Prototype v.1.3, Medis Medical Imaging, Leiden, The Netherlands). From left to right, in progressive order: (1) selection of the conventional three apical windows (4-chamber, 2-chamber and apical long-axis view); (2) 3-point endocardial contour drawing (basal lateral + medial mitral annular insertion and apex) and processing (with correct tracing evaluation), for each window; (3) manual identification and trace (line) of mitral (2-chamber view) and aortic (apical long-axis view) annulus; (4) HDFs derivation.

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