

ORIGINAL ARTICLE



Left Ventricular Flow Analysis

Novel Imaging Biomarkers and Predictors of Exercise Capacity in Heart Failure

See Editorial by Bax and Kwong

BACKGROUND: Cardiac remodeling, after a myocardial insult, often causes progression to heart failure. The relationship between alterations in left ventricular blood flow, including kinetic energy (KE), and remodeling is uncertain. We hypothesized that increasing derangements in left ventricular blood flow would relate to (1) conventional cardiac remodeling markers, (2) increased levels of biochemical remodeling markers, (3) altered cardiac energetics, and (4) worsening patient symptoms and functional capacity.

METHODS: Thirty-four dilated cardiomyopathy patients, 30 ischemic cardiomyopathy patients, and 36 controls underwent magnetic resonance including 4-dimensional flow, BNP (brain-type natriuretic peptide) measurement, functional capacity assessment (6-minute walk test), and symptom quantification. A subgroup of dilated cardiomyopathy and control subjects underwent cardiac energetic assessment. Left ventricular flow was separated into 4 components: direct flow, retained inflow, delayed ejection flow, and residual volume. Average KE throughout the cardiac cycle was calculated.

RESULTS: Patients had reduced direct flow proportion and direct-flow average KE compared with controls ($P<0.0001$). The residual volume proportion and residual volume average KE were increased in patients ($P<0.0001$). Importantly, in a multiple linear regression model to predict the patient's 6-minute walk test, the independent predictors were age ($\beta=-0.3015$; $P=0.019$) and direct-flow average KE ($\beta=0.280$, $P=0.035$; R^2 model, 0.466, $P=0.002$). In contrast, neither ejection fraction nor left ventricular volumes were independently predictive.

CONCLUSIONS: This study demonstrates an independent predictive relationship between the direct-flow average KE and a prognostic measure of functional capacity. Intracardiac 4-dimensional flow parameters are novel biomarkers in heart failure and may provide additive value in monitoring new therapies and predicting prognosis.

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CLINICAL PERSPECTIVE

Cardiac magnetic resonance imaging plays a central role in the diagnosis and prognostication of patients with heart failure. In this current study, we investigated the clinical utility of 4-dimensional flow imaging compared with conventional imaging and clinical prognostic markers. The left ventricular flow was divided into 4 functional components and the kinetic energy of each flow component calculated throughout the cardiac cycle. We found that in patients with either ischemic or dilated cardiomyopathy, there was a decrease in the volume and kinetic energy of the direct flow component compared with healthy controls. The degree of derangement in the direct flow parameters worsened as the left ventricular ejection fraction declined. The direct-flow average kinetic energy correlated negatively with the conventional remodeling parameters of left ventricular end-diastolic and end-systolic volumes, patient symptoms (as measured by a validated questionnaire), and B-type natriuretic peptide levels ($P < 0.0001$). This is the first study that found in a multiple linear regression model that the direct-flow average kinetic energy was predictive of the patient's functional capacity, as measured by the distance covered during a 6-minute walk test. Conventional imaging parameters including left ventricular ejection fraction were not predictive of the patient's functional capacity. These results suggest that intracardiac 4-dimensional flow parameters are novel biomarkers in heart failure and warrant further investigation in longitudinal studies as a marker of prognosis in patients with heart failure.

Heat failure (HF) is a global health burden with significant morbidity and mortality.¹ It is a complex multifactorial syndrome that is initiated by a myocardial insult, which activates cardiac remodeling—a process encompassing numerous transcriptional, cellular, and architectural changes within both cardiac myocytes and surrounding extracellular structures.² The ability of the heart to remodel in response to stimuli is important for cardiovascular adaptation in altered physiological conditions, such as pregnancy.³ However, in pathological remodeling, this initially beneficial plasticity response becomes maladaptive with a propensity toward hypertrophy, ventricular dilatation, systolic dysfunction, and electrophysiological changes resulting in ventricular arrhythmias and HF.^{2,3}

Fluid dynamic studies indicate that the morphological structure of a compliant vessel is inextricably linked

to the flow within it.⁴ Hence, as ventricular flow is altered in the early stages of remodeling,⁵ it is probable that the flow itself can influence disease progression.⁴ Insights into and quantification of left ventricular (LV) blood flow and kinetic energy (KE) are now afforded by 3-dimensional, time-resolved magnetic resonance imaging (4-dimensional [4D] flow).⁶ Previous studies have demonstrated altered LV flow patterns in seemingly compensated dilated cardiomyopathy (DCM) patients,⁵ as well as higher KE in severe HF.⁷ However, no studies have found relationships between intracardiac blood flow parameters and the functional ability of patients with HF.

BNP (brain-type natriuretic peptide) produced by cardiac myocytes in response to volume expansion and pressure overload is a powerful prognostic HF marker.⁸ Functional capacity in HF, as represented by the distance covered during a 6-minute walk test (6MWT), is also a predictor of mortality and morbidity,⁹ as is the presence of symptoms as assessed with a standardized questionnaire (Minnesota Heart Failure Questionnaire).¹⁰

Cardiac phosphorus magnetic resonance spectroscopy allows noninvasive measurement of the phosphocreatine-to-ATP concentration ratio (PCr/ATP), which is a sensitive marker of myocardial energetics. Impaired myocardial energetics (decreased PCr/ATP) in DCM patients are predictive of mortality.¹¹ However, the relationship between derangements in myocardial energetics and LV blood flow is unknown.

Much remains to be understood about cardiac remodeling²; the aim of this study was to investigate the relationship between ventricular morphology, function, and blood flow during cardiac remodeling. In this study, patients were included with 2 of the commonest causes of HF—ischemic heart disease (IHD) and DCM.¹ We hypothesized that increasing derangements in LV blood flow would relate to (1) conventional cardiac remodeling markers, (2) increased levels of biochemical remodeling markers, (3) altered cardiac energetics, and (4) worsening patient symptoms and functional capacity.

Further, we hypothesized these changes to be independent of the cause of the myocardial damage, instead reflecting the self-propagating nature of cardiac remodeling and that 4D flow parameters would be more powerful predictors of the functional consequences of cardiac remodeling than conventional imaging parameters.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of a lack of ethical approval to share datasets beyond the host institution's research team.

Study Population

This study was approved by the National Research Ethics Committee. Each participant gave written informed consent. Hundred participants were recruited; 34 DCM, 30 ischemic cardiomyopathy (IHD), and 36 healthy controls. See Methods in the [Data Supplement](#) for inclusion/exclusion criteria.

Cardiac Magnetic Resonance Protocol

Imaging was performed at 3.0 T (Trio; Siemens Healthcare, Erlangen, Germany) using a 32-channel cardiac coil. Standard cine and strain imaging were performed (see Methods in the [Data Supplement](#)).^{12,13}

4D flow acquisitions were free breathing, using a retrospectively ECG triggered, respiratory navigator gated, 3-dimensional, 3-directional, time-resolved phase-contrast magnetic resonance imaging sequence with a 52-ms measurement temporal resolution and 3×3×3 mm³ voxel size, with velocity encoding 100 cm/s.

Cardiac Magnetic Resonance Data Analysis

LV volumes were analyzed using cmr42 (Circle Cardiovascular Imaging, Inc, Calgary, Canada) as described previously.¹² LV sphericity index was calculated by division of the horizontal long-axis length by the maximum diameter at end diastole.

Tagged images were analyzed for midventricular peak systolic circumferential strain and diastolic strain rate using Cardiac Image Modeller software (CIMTag2D v7; Auckland, New Zealand).¹³

4D Flow Data Analysis

LV blood flow was analyzed using methodology described by Eriksson et al,¹⁴ consisting of endocardial segmentation at end diastole and end systole, with pathline generation from each segmented voxel. The position of pathlines at end systole divides them into 4 functional flow components as described previously^{5,14}: (1) direct flow: blood that enters and exits the LV in the analyzed cardiac cycle; (2) retained inflow: enters the LV but does not exit during the analyzed cycle; (3) delayed ejection flow: starts within the LV and exits during the analyzed cycle; and (4) residual volume: blood that remains in the LV for at least 2 cardiac cycles. Each component volume was calculated as a proportion of the total end-diastolic volume. LV segmentation was performed in Segment (version 1.9R2842) and flow visualization in EnSight (CEI, Inc, NC).

Each component's KE was calculated throughout the cardiac cycle using $KE = \frac{1}{2} \cdot \rho_{\text{blood}} \cdot V_{\text{pathline}} \cdot v_{\text{pathline}}^2$, where ρ_{blood} is blood density; V_{pathline} the blood volume represented by 1 pathline, and v_{pathline} the pathline velocity. The KE for each component is the sum of KE for each of its pathlines. Two different measurements of KE are reported within this study: (1) KE at end diastole and (2) average KE. (1) KE at end diastole: as in previous studies, KE for each component was recorded at end diastole, as these reflect the preservation of the inflowing KE before the rapid systolic ejection of blood.⁵ (2) Average KE: this was calculated for each flow component to assess whether the inclusion of all time frames provided additional information. The average KE was calculated by adding the KE values for the entire flow component's pathlines throughout the cardiac cycle. This summed value was then divided by 30

to reflect the average KE for that flow component per time frame. Using the average KE values, the proportion of the direct-flow average KE was derived by dividing the direct-flow average KE by the total average KE for all components. The same calculation was performed with the residual volume average KE to derive the proportion of the residual volume average KE. Both measures of KE (KE at end diastole and average KE) were additionally normalized to the end-diastolic volume.

Phosphorus Magnetic Resonance Spectroscopy

Twenty-five patients with DCM and 10 controls underwent phosphorus magnetic resonance spectroscopy at 7T (Magnetom; Siemens, Germany), as previously described by our group in controls and patients (see Methods in the [Data Supplement](#)).^{15,16} IHD patients were not included in this study because of the regionality of the LV dysfunction.

Statistical Analysis

Statistics were analyzed using SPSS 22 (Chicago, IL). Normality testing utilized the D'Agostino and Pearson omnibus normality test; data are presented as mean±SDs, unless otherwise specified. One-way ANOVA with post hoc Tukey or Kruskal-Wallis *H* with post hoc Dunn multiple-comparison tests were performed as appropriate. Correlation was assessed using the Pearson or Spearman method. *P* <0.05 was considered significant. Multiple linear regression models were created, using stepwise entry and the dependent variable as the patient 6MWT result. Variables with *P* <0.05 that had the strongest relationship with 6MWT were included in the model. Linear model fit was assessed by visually checking the linearity assumption. Residuals were normally distributed. Standardized (β) values are reported.

RESULTS

Participant Characteristics

Demographic and clinical data are shown in Table 1. There were no significant differences in age or heart rate between groups. Blood pressure tended to be lower in the patients, likely reflecting HF and pharmacotherapy (Table 1 in the [Data Supplement](#)). As expected, patients with IHD and DCM patients had higher BNP levels compared with controls (*P*<0.0001). Mean distance walked was 20% less in DCM and 25% less in patients with IHD compared with controls (*P*<0.0001).

Myocardial Structure and Function

Results for LV volumes and function are summarized in Table 2. The 2 patient groups, as expected, had significantly increased LV volumes and decreased systolic function compared with controls (*P*<0.0001). Both patient groups had a more spherical ventricle with impaired systolic strain compared with controls (*P*<0.0001). There were no significant differences between the patient groups.

Table 1. Baseline Characteristics

	Controls (n=36)	DCM (n=34)	IHD (n=30)	P Value, DCM vs Controls	P Value, IHD vs Controls
Demographics					
Age, y	57±12	57±14	63±12	1.0	0.125
Men, n (%)	25 (70)	22 (65)	28 (93)	0.89	0.062
BMI, kg/m ²	25±4	28±4	28±4	0.04	0.007
Systolic BP, mmHg	134±20	128±18	120±15	0.375	0.007
Diastolic BP, mmHg	78±10	72±12	69±9	0.044	0.003
Heart rate, bpm	64±14	65±14	65±14	0.988	0.967
Prognostic markers					
BNP, pmol/L	7±5	51±105	77±108	<0.0001	<0.0001
6MWT, m	624±77	500±84	470±101	<0.0001	<0.0001
MHFQ	...	18±19	22±22

Values are mean±SDs or percentages. 6MWT indicates 6-min walk test; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; and MHFQ, Minnesota Heart Failure Questionnaire.

Changes in Flow Components

Flow visualizations are shown in Figure 1 and Movies in the [Data Supplement](#). The changes in proportion of the flow components, compared with controls, were similar between the DCM and IHD groups Figure 2. DCM was associated with a 71% and IHD a 63% decrease in the direct flow component proportion compared with controls ($P<0.0001$). This decrease in direct flow corresponded to a similar increase in the residual volume component in both DCM (63% increase) and IHD patients (70% increase) compared with controls ($P<0.0001$).

Changes in KE Profiles

KE values for all 4 flow components differed significantly for the DCM and IHD groups compared with controls but not between the patient groups Figure 3. In controls, the efficient direct flow component possessed the

greatest KE; in patients with DCM and IHD, this was decreased (DCM average KE, 60% decrease, and IHD, 56% decrease, versus controls; $P<0.0001$; Figure 3B), and the KE of the other 3 flow components increased compared with controls. These KE changes were seen for both KE at end diastole and the average KE, but the magnitude of change differed depending on which KE measure was assessed (Figure 3A and 3B).

The proportion of the direct-flow average KE compared with the total average KE of all flow components was the highest for the control group (64±8%), compared with DCM of 23±14% and IHD of 29±19% ($P<0.0001$). The residual volume average KE proportion was significantly higher in the 2 patient groups (DCM, 17±11%; IHD, 15±12%) compared with controls (4±2%; $P<0.0001$).

The derangement in the proportion and KE values of the flow components progressed as the LV ejection fraction (LVEF) decreased, as illustrated in Figure 4. The

Table 2. Cardiac Magnetic Resonance Results in Controls, IHD Patients, and DCM Patients

Variable	Controls (n=36)	DCM (n=34)	IHD (n=30)	P Value, DCM vs Controls	P Value, IHD vs Controls
LV end-diastolic volume, mL	159±31	273±118	231±68	<0.0001	<0.0001
LV end-diastolic volume-indexed BSA, mL/m ²	82±14	135±52	116±33	<0.0001	<0.0001
LV end-systolic volume, mL	53±13	182±108	146±65	<0.0001	<0.0001
LV stroke volume, mL	106±20	90±25	85±22	0.012	0.001
LVEF, %	67±4	36±11	39±12	<0.0001	<0.0001
Cardiac output, L/min	6.7	5.6	5.2	0.003	<0.0001
LV mass, g	113±35	137±46	137±30	0.010	0.081
LV mass index, g/m ²	58±15	69±20	68±13	<0.0001	0.038
LV sphericity index	1.7±0.2	1.4±0.2	1.4±0.2	<0.0001	<0.0001
Midventricular circumferential systolic strain, % (negative)	19±3	10±4	12±4	<0.0001	<0.0001
Midventricular diastolic strain rate, s ⁻¹	83±19	48±21	53±18	<0.0001	<0.0001

Values are mean±SDs or percentages. BSA indicates body surface area; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; LV, left ventricle; and LVEF, left ventricular ejection fraction.

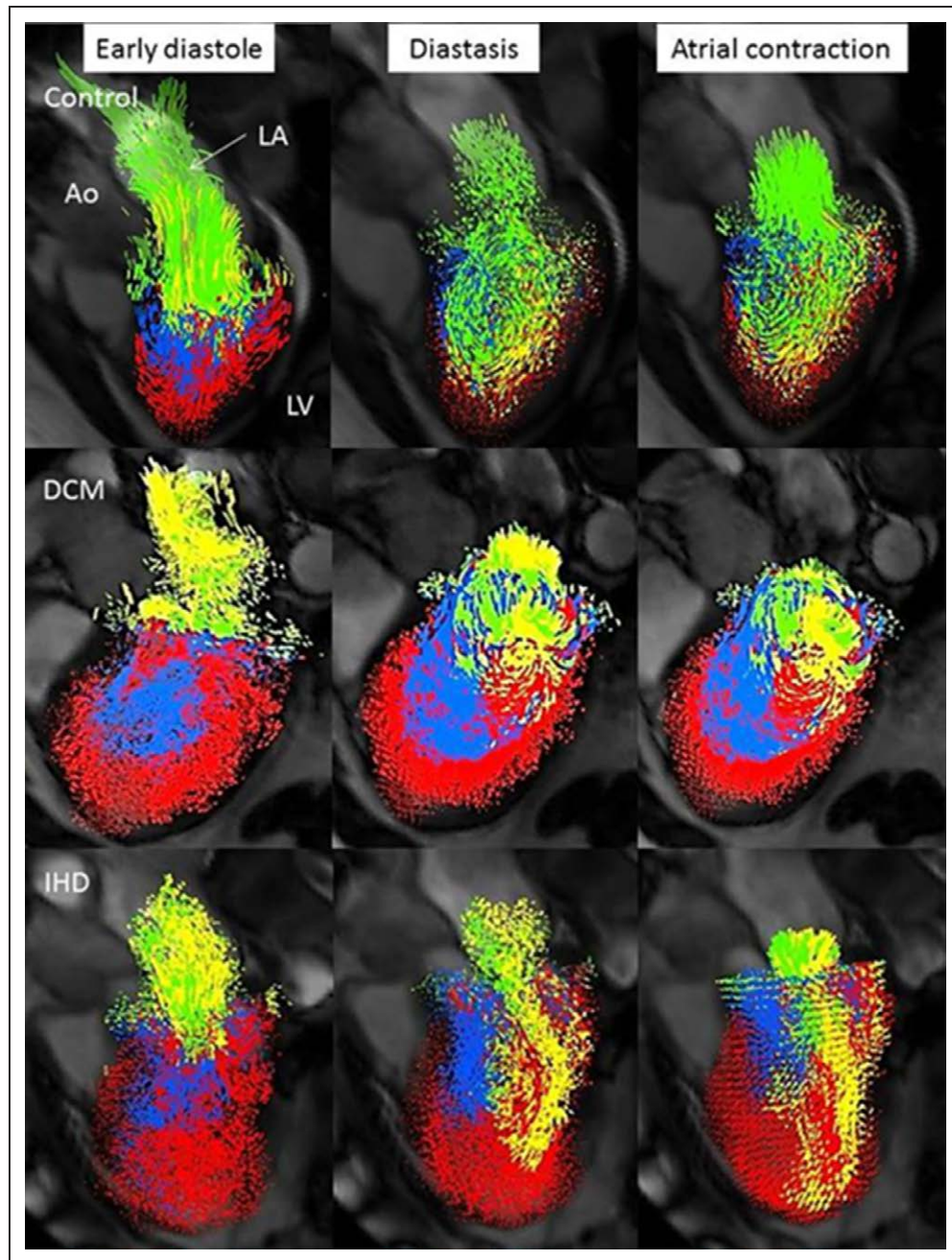


Figure 1. Representative diastolic left ventricular (LV) visualizations in a control (direct flow, 35%; residual volume, 29%), dilated cardiomyopathy (DCM; direct flow, 10%; residual volume, 55%), and ischemic cardiomyopathy (IHD) patient with an anteroapical infarct (direct flow, 8%; residual volume, 56%).

Despite similar proportions of residual volume between the IHD and DCM patients, the distribution differs, with a global distribution in the DCM patient and a more localized distribution in the IHD patient, corresponding to the area of infarction. Direct flow, green; retained inflow, yellow; delayed ejection flow, blue; and residual volume, red. Ao indicates aorta; and LA, left atrium.

proportion of the direct flow decreased in line with the ejection fraction. However, the decrease in direct-flow KE occurred only with the development of more advanced HF, with an ejection fraction of $\leq 44\%$ (Figure 4B and 4C). The proportion and KE of the residual volume component increased steadily as LV impairment worsened (Figure 4J through 4L). As with the direct flow, the change in the KE of the residual volume, in this case an increase, occurred with more advanced HF, with ejection fraction of $\leq 44\%$.

Association of Novel 4D Flow Parameters With Classical Remodeling and Prognostic Markers

The correlation coefficients for the direct flow and residual volume KE across all participants are shown in Table 3. Direct-flow KE correlated negatively with the conventional remodeling parameters of LV end-diastolic volume, LV end-systolic volume, and positively with

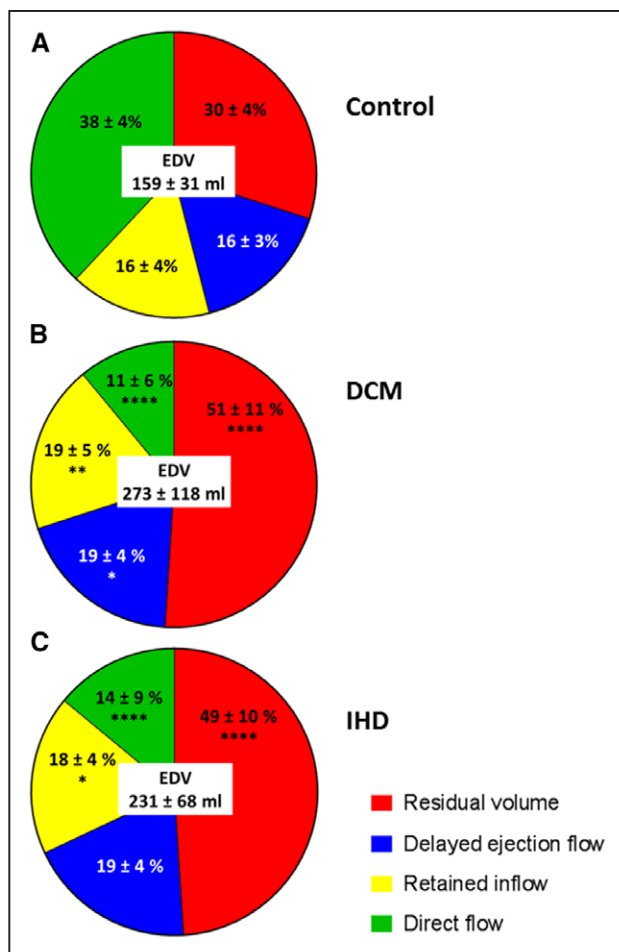


Figure 2. Left ventricular flow components.

Flow components by percentage of the end-diastolic volume (EDV) for (A) control, (B) dilated cardiomyopathy (DCM), and (C) ischemic cardiomyopathy (IHD). Data are mean±SD. All comparisons between DCM and IHD patients were nonsignificant. **** $P < 0.0001$, ** $P < 0.01$, * $P < 0.05$ compared with corresponding component in controls.

LVEF ($P < 0.0001$). Residual volume KE correlated negatively with the LVEF and positively with the LV end-diastolic volume and LV end-systolic volume ($P < 0.0001$). Both the direct flow and residual volume KE correlated, but in opposite directions, with the patients' symptoms (Minnesota Heart Failure Questionnaire), their functional capacity (6MWT), and biochemical evidence of cardiac remodeling (BNP).

KE values for direct flow and residual volume according to distance covered during the 6MWT are shown in Table 4. The direct-flow average KE was found to be different depending on the distance walked ($P = 0.008$).

To assess whether remodeling parameters were predictive of the patient's functional capacity, as represented by the 6MWT, a multiple linear regression model was created. The independent variables entered into the model were age, height, LVEF, BNP, direct-flow average KE, and peak systolic circumferential strain. Importantly, the independent predictors of the 6MWT were found to be age ($\beta = -0.315$; $P = 0.019$) and direct-flow average

KE ($\beta = 0.280$; $P = 0.035$; overall R^2 of the model, 0.466; Table II in the [Data Supplement](#)). To avoid colinearity of predictors, the other prognostic remodeling parameters of end-systolic volume and end-diastolic volume were substituted into the model above instead of LVEF, but in these subsequent models, age and direct-flow average KE remained the only independent predictors. Thus, direct-flow average KE was, but traditional remodeling parameters were not, independent predictor of functional capacity in these HF patients.

Associations Between Myocardial Energetics and 4D Flow Parameters in DCM

In keeping with previous studies,¹¹ we found a reduced PCr/ATP ratio in DCM compared with controls (PCr/ATP, 1.54 ± 0.39 versus 1.95 ± 0.25 ; $P = 0.005$; Figure 5A). The PCr/ATP ratio correlated with the classical remodeling parameters of LVEF ($r = 0.527$; $P = 0.01$; 95% CI, 0.11–0.72), LV end-diastolic volume ($r = -0.587$; $P = 0.0002$; 95% CI, -0.79 to -0.15), and LV end systolic volume ($r = -0.601$; $P = 0.0001$; 95% CI, -0.80 to -0.21), as well as the peak systolic circumferential strain ($r = 0.507$; $P = 0.003$; 95% CI, 0.19–0.74). In addition, the PCr/ATP ratio correlated with 4D flow parameters (Figure 5B through 5F) including the proportion of the direct-flow average KE ($r = 0.45$; $P = 0.007$; 95% CI, 0.05–0.73) and proportion of the residual volume average KE ($r = -0.41$; $P = 0.014$; 95% CI, -0.67 to -0.03).

DISCUSSION

In this work, the relationships between ventricular morphology, prognostic markers, and novel 4D flow parameters during cardiac remodeling because of dilated and ischemic cardiomyopathy were assessed using cardiac magnetic resonance. We demonstrate that the average KE of the direct flow and residual volume correlate with conventional remodeling parameters and prognostic markers, suggesting a role as novel cardiac remodeling imaging biomarkers. Importantly, we show that the direct-flow average KE is predictive of the patient's functional capacity, whereas the LVEF and LV volumes were not. We demonstrate that changes in flow components and KE, as seen previously in DCM patients,⁵ are similar in ischemic cardiomyopathy, despite a different myocardial insult cause. Finally, we demonstrate that in DCM, there is a relationship between the impaired myocardial energetics and the KE of the LV flow components.

Consequences of Alterations in LV Flow Components and KE

In health, most inflow volume and hence KE of blood from the left atrium (direct flow and retained inflow) is because of direct flow, which preserves its KE as

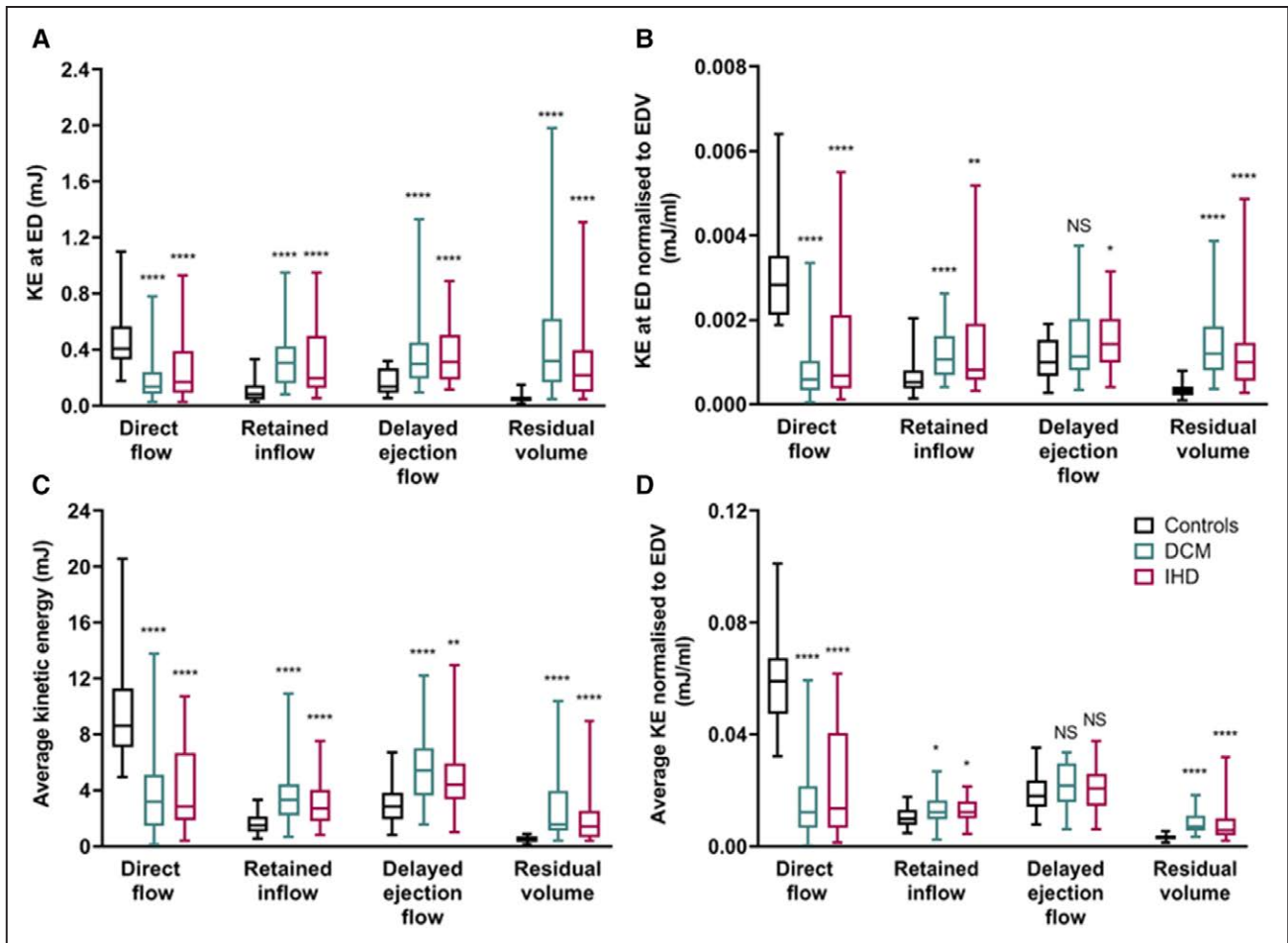


Figure 3. Kinetic energy (KE) profiles. A, KE at end diastole; (B) KE at end diastole normalized to end-diastolic volume (EDV); (C) average KE throughout the cardiac cycle; and (D) average KE normalized to EDV. Bars show minimum and maximum values. All comparisons between dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (IHD) patients were nonsignificant (NS). ED indicates end diastole. **** $P < 0.0001$, *** $P < 0.001$ compared with corresponding component value in controls.

it transits the LV.¹⁷ We identified that in DCM and IHD, the majority of the inflowing volume and KE is because of the retained inflow component. Hence, instead of immediate ejection as part of the direct flow, the KE possessed by the retained inflow resides within the LV for at least 1 cardiac cycle before ejection. The KE of this blood has several possible fates in the receiving ventricle, it may (1) be transferred as KE to the blood already residing in the LV (delayed ejection flow and residual volume), (2) be converted into potential energy that is either stored within the elastic recoil of the myocardium or causes an elevation in ventricular pressure, or (3) be dissipated in the form of friction/heat.⁵ With any of these fates, energy is dissipated or converted into less efficient configurations within the ventricle, and the KE of the LV residing components is increased compared with the situation in health.

Many processes that occur as a consequence of cardiac remodeling have initial advantageous effects that become deleterious over time; it may be that increasing the residual volume in ventricular dysfunc-

tion initially confers an advantage such as acting as a buffer to redistribute KE, so as to reduce transfer of KE to potential energy that would result in elevated ventricular pressure. However, when either the myocardium remodels becoming less compliant or the LV pressure exceeds a certain level, the conversion of KE to potential energy declines and may explain why we see the sharp rise in the residual volume average KE once end-stage remodeling is reached, suggesting failure of any compensatory mechanisms. The KE of the residual volume may also have a role in prevention of blood stasis and thrombus formation, as suggested by a Doppler study that found lower apical blood velocities in patients with thrombus compared with those without.¹⁸

Relation to Earlier Studies

Previous work by Eriksson et al⁵ and Kanski et al⁷ found that patients with HF have higher KE values compared with controls. Eriksson et al⁵ studied patients with clinically compensated DCM and found similar but less pro-

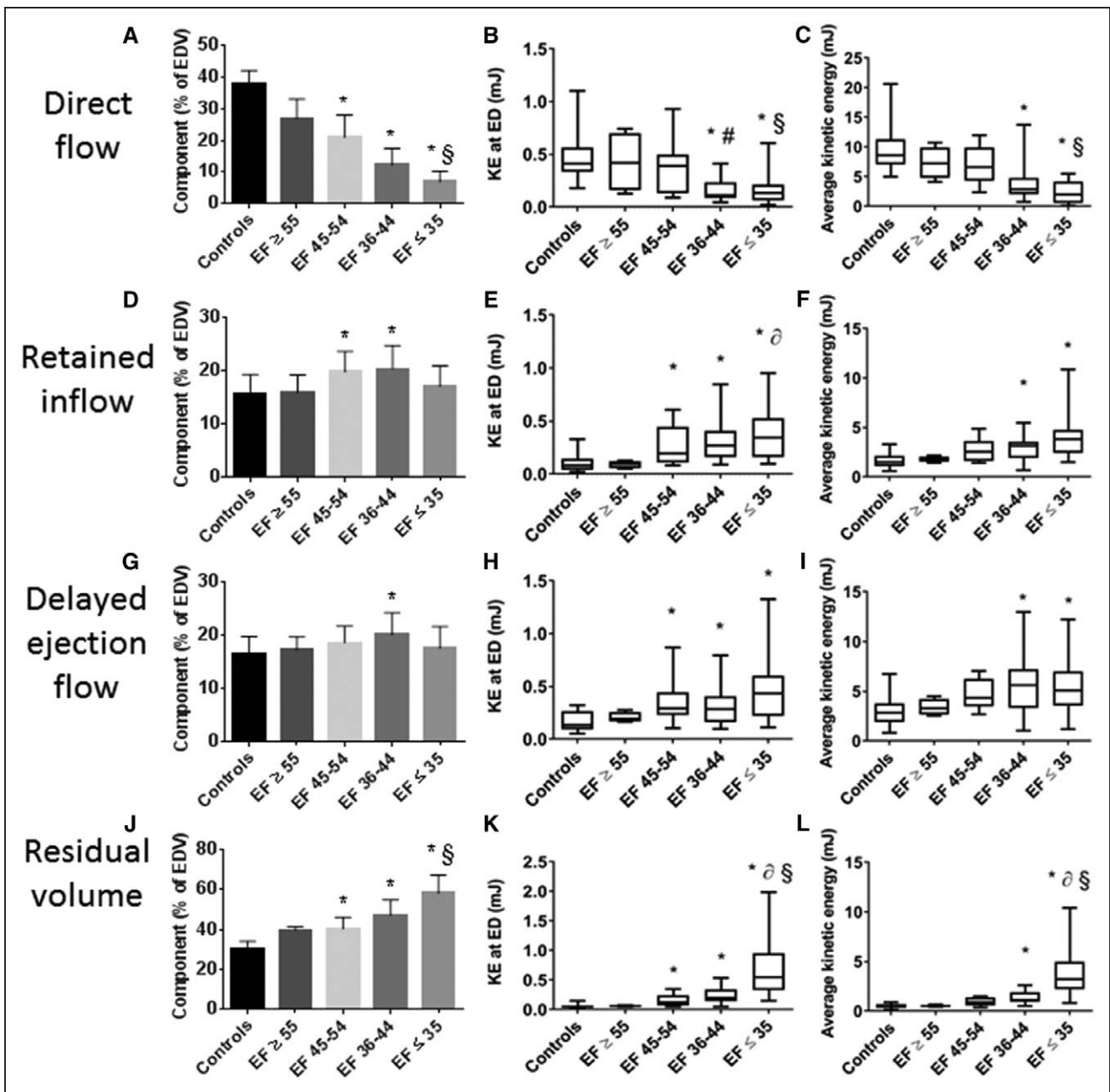


Figure 4. Differences in flow component percentage, kinetic energy at end diastole (ED), and average kinetic energy according to left ventricular ejection fraction (LVEF).

LVEF, >55% (n=4); ejection fraction (EF), 45% to 54% (n=11); EF, 36% to 44% (n=21); EF, ≤35% (n=28). **A, D, G, and J,** Bars show mean value, and error bars indicate SD. **B, C, E, F, H, I, K,** and **L** bars show minimum and maximum values. EDV indicates end-diastolic volume; and KE, kinetic energy. **P*<0.05 compared with controls; §*P*<0.05 LVEF ≤35% compared with ≥55%; ∂*P*<0.05 LVEF ≤35% compared with ≥55%; #*P*<0.05 LVEF 36% to 44% compared with 45% to 54%.

nounced alterations in the flow component volumes with reduced direct flow and increases in the other flow components. This study looked at KE values at end diastole and found, as we did, an increase in KE of the retained inflow, delayed ejection flow, and residual volume. Unlike our results, they did not see a difference in the KE of the direct flow between the DCM patients and controls, but their patients had better systolic function (mean LVEF, 42%, and preserved stroke volume versus our values of LVEF, 36% DCM and 39% IHD,

with reduced stroke volume), which may explain this difference.

Kanski et al⁷ evaluated the average KE of the total ventricular blood volume in patients with HF. They found no difference in diastolic average KE between patients and controls but higher average systolic KE. They did not find any relationship between the patients' symptoms or functional capacity and the total KE. This lack of association is likely because of consideration of the blood volume as a whole rather than as flow compo-

Table 3. Correlations Between Ventricular Remodeling Parameters, Prognostic Markers, KE at Both End Diastole and Average KE for Direct Flow and Residual Volume

Variable	Direct-Flow KE at ED		Direct-Flow Average KE		Residual Volume KE at ED		Residual Volume Average KE	
	r	P Value (95% CI)	r	P Value (95% CI)	r	P Value (95% CI)	r	P Value (95% CI)
LV EDV	-0.35	<0.0001 (-0.50 to -0.14)	-0.41	<0.0001 (-0.52 to -0.18)	0.78	<0.0001 (0.64 to 0.85)	0.88	<0.0001 (0.79 to 0.92)
LV ESV	-0.55	<0.0001 (-0.65 to -0.37)	-0.64	<0.0001 (-0.70 to -0.46)	0.89	<0.0001 (0.81 to 0.91)	0.93	<0.0001 (0.86 to 0.95)
LV EF	0.66	<0.0001 (0.50 to 0.75)	0.79	<0.0001 (0.65 to 0.84)	-0.88	<0.0001 (-0.90 to -0.79)	-0.86	<0.0001 (-0.90 to -0.76)
MHFQ	-0.56	<0.0001 (-0.70 to -0.40)	-0.63	<0.0001 (-0.73 to -0.50)	0.60	<0.0001 (0.43 to 0.73)	0.58	<0.0001 (0.42 to 0.71)
6MWT	0.46	<0.0001 (0.28 to 0.62)	0.60	<0.0001 (0.45 to 0.72)	-0.50	<0.0001 (-0.63 to -0.33)	-0.43	<0.0001 (-0.57 to -0.23)
Circumferential systolic strain	-0.56	<0.0001 (-0.69 to -0.39)	-0.73	<0.0001 (-0.80 to -0.59)	0.78	<0.0001 (0.69 to 0.86)	0.77	<0.0001 (0.66 to 0.84)
BNP	-0.45	<0.0001 (-0.57 to -0.20)	-0.58	<0.0001 (-0.64 to -0.34)	0.53	<0.0001 (0.29 to 0.62)	0.51	<0.0001 (0.22 to 0.60)

Correlations are performed with Pearson or Spearman correlation as appropriate. 6MWT indicates 6-min walk test; BNP, brain-type natriuretic peptide; ED, end diastole; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; KE, kinetic energy; LV, left ventricle; and MHFQ, Minnesota Heart Failure Questionnaire.

nents as in our study. Interestingly, in Fontan patients, Sjöberg et al¹⁹ found that the peak diastolic, but not systolic, KE indexed to stroke volume was lower in Fontan patients than controls. These varying results depending on the cause of myocardial injury suggest that there is still much to be understood about intracardiac KE.

Potential Clinical Utility of Intracardiac KE Assessment

To our knowledge, our work is the first to demonstrate that the KE of both the direct flow and the residual volume flow components correlated with conventional, established prognostic markers for HF, including BNP levels, HF symptoms, and functional capacity. These results support a clinical utility for KE evaluation in the management and follow-up of patients with HF. Current volumetric-based cardiac imaging techniques have limited ability to provide prognostic information for this patient cohort. In the future, it is hoped that by incorporating more advanced imaging techniques, such as

4D flow KE assessments, the predictive ability of cardiac imaging to provide prognostication in patients with HF can be further refined and aid appropriate targeting of new therapies to those patients most at risk of complications. However, before generalized use of 4D flow for clinical assessments occurs, our results require further validation in a larger multicenter study to fully establish the reproducibility between centers and the clinical potential of this technique.

Candidate Pathophysiological Mechanisms for Transduction of Blood Flow Abnormalities to Cardiac Remodeling

Blood flow within the LV is subject to the laws of mechanics including that of Laplace; ventricular wall stress is proportional to ventricular pressure and cavity radius and inversely proportional to the wall thickness.² If KE conversion to potential energy causes increased LV pressure, especially diastolic pressure, this would result

Table 4. Results for Direct Flow Percentage and KE Values and Residual Volume Percentage and KE Values According to Distance Covered During 6MWT

	6MWT, <450 m (n=17)	6MWT, 451–550 m (n=31)	6MWT, >551 m (n=16)	P Value
Direct flow (percentage of EDV)	9.8±4.4	13.6±8.7	13.7±8.9	0.264
Direct-flow KE at ED, mJ	0.17±0.12	0.24±0.25	0.24±0.15	0.456
Direct flow average KE, mJ	2.41±1.32	3.93±2.80	5.71±3.95	0.008
Residual volume (percentage of EDV)	53.7±9.3	49.0±11.6	48.0±9.4	0.261
Residual volume KE at ED, mJ	0.40±0.29	0.35±0.41	0.44±0.38	0.745
Residual volume average KE, mJ	2.23±1.51	2.23±2.43	2.27±1.59	0.989

Values are mean±SDs. 6MWT indicates 6-min walk test; ED, end diastole; EDV, end-diastolic volume; and KE, kinetic energy.

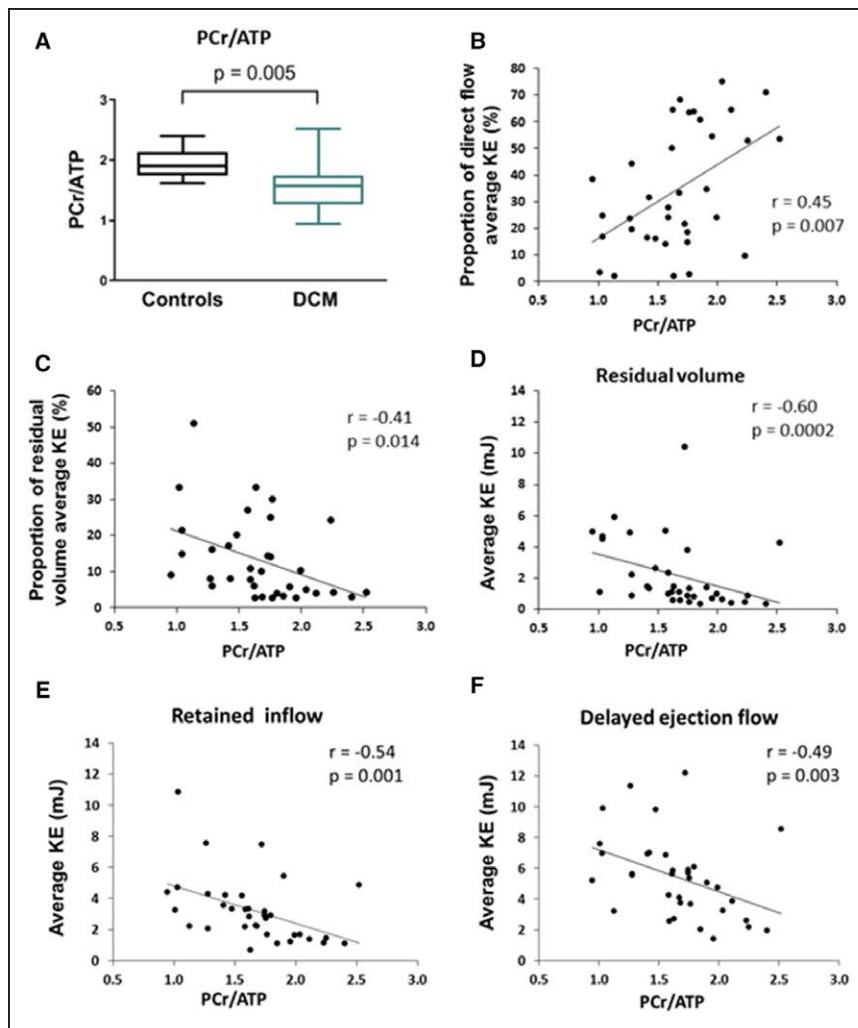


Figure 5. Myocardial energetics results and correlations in dilated cardiomyopathy (DCM) patients.

A, Phosphocreatine-to-ATP concentration ratio (PCr/ATP) in controls compared with DCM. Correlations between PCr/ATP ratio and **(B)** proportion of direct-flow average kinetic energy (KE); **(C)** proportion of residual volume average KE; **(D)** residual volume average KE; **(E)** retained inflow average KE; and **(F)** delayed ejection flow average KE.

in increased ventricular wall stress/stretch, which may be important in the activation of cardiac remodeling pathways.³ Translating stretch stimuli to downstream signaling requires numerous complex pathways including transient receptor potential channels, integrins, as well as the sarcomere-spanning protein titin.²⁰ Once cardiac myocytes have sensed mechanical stretch, they convert this into intracellular growth signals and changes in gene expression.²¹

A common early feature of cardiac remodeling is an increase in wall thickness to reduce wall stress and decrease oxygen demand; however, when the wall stress is sustained, the myocardium slowly transitions to a state of decompensation and subsequent HF. Part of the cardiac myocyte response to mechanical stress is to reactivate a pattern of gene expression similar to that required during fetal growth, which includes BNP.² Reexpression of fetal genes during remodeling provides further evidence for the potential influence of cardiac blood flow on morphological changes; in fetal cardiac development, mechanical signals from blood flow, via induction of gene expression, promote ventricular cell enlargement and contractility.²²

Additional support for the importance of intracardiac blood flow on myocardial cellular processes is provided by tissue samples obtained before and after implantation of a LV assist device in patients with HF, which demonstrated reverse remodeling changes including regression of cell thickening/elongation and reversion of gene expression controlling calcium cycling.²³

Myocardial Energetics and Intraventricular Blood Flow

Myocardial energetics were associated with the proportion of the direct-flow average KE. This suggests that, as well as the direct-flow KE, the KE of the components that remain within the LV for at least 1 cycle are also important. One explanation for this may relate to altered cardiac substrate metabolism as a consequence of reactivation of the fetal gene program by abnormal LV stretch (caused by the KE of the LV residing components). Hence, it may be that the activation of this gene program shifts myocardial metabolism from dominant fat to dominant glucose metabolism.²⁴ Metabolizing glucose requires less oxygen per unit of ATP generated

than metabolizing fat, but a mole of glucose has significantly lower chemical potential energy than a mole of fat. This metabolic shift might impair ATP generation in advanced HF.²⁵ In support of this, mechanical unloading of failing hearts with LV assist devices is associated with at least partial normalization of cardiac metabolism.²⁶

Study Limitations

4D flow acquisitions were at rest, and although associations were found with the patients' functional capacity, these relationships and understanding of blood flow changes in HF may elucidate additional mechanisms if assessed during pharmacological or exercise stress.

An alternative selection method for the variables to include in the multiple linear regression model could have been used, such as setting the significance level higher (eg, $P < 0.2$) or using index criteria. However, these methods were not used because this would have resulted in more eligible variables, which with the limited sample size available may have resulted in overfitting of the data. However, we acknowledge that the selection method used means other relevant variables may have been excluded from the current model, which should be investigated further in future studies with larger sample sizes. In addition, the results are primarily unadjusted, and the sample size has limited ability to fully adjust for covariates. The lack of significance of covariates in the analysis cannot exclude these as parameters of importance and may instead be because of a small effect that the limited study size sample was unable to detect. This will require future larger sample size studies to investigate further.

Potential selection bias based on recruitment from patients under tertiary-level care, as well as for controls who volunteered for the study, may also confound the applicability of these results beyond the present study cohort. In addition, the patients enrolled for this study were recruited on the basis of systolic HF and were mostly well-compensated patients. Therefore, as such, it was perhaps not surprising that the results for patients with IHD and DCM were similar, despite the differing original myocardial insult. No patients with HF-preserved ejection fraction were recruited to this study. Further studies enrolling a cohort of patients with HF-preserved ejection fraction would be of benefit to understand whether novel 4D flow parameters may be of clinical utility in this patient population.

This study has highlighted important relationships between classical remodeling parameters and novel 4D flow markers, but, in line with its proof-of-principle concept, cross-sectional and observational nature, it cannot assess the causality of these relationships. In addition, the exploratory nature of this study means that multiple parameters have been assessed at once and therefore mass significance is a potential limitation.

Although we found with statistical modeling the direct-flow average KE to be a superior predictor of patients' functional capacity compared with volumetric parameters, assessment of the applicability of this result to all patients with different causes of HF is beyond the scope of this study design.

Clinical Implications

Therapies for HF, including angiotensin-converting enzyme inhibitors and β -blockers, have significantly reduced morbidity and mortality.¹ However, the incidence of HF and burden of disease continues to increase, and the need for new therapies remains.² Despite numerous phase I and phase II studies describing potential novel therapies, few of these compounds have been successfully translated in clinical trials. The reasons for this failure are multifactorial including the difficulty of achieving adequate power to demonstrate a mortality benefit and the inability to identify effective therapies in phase II trials, which may be compounded by the use of surrogate end points that are a consequence of remodeling rather than an active part of the process.²⁷ Therefore, the identification in this study of novel 4D flow imaging biomarkers that may be mechanistic in the cardiac remodeling process, rather than surrogate markers, warrants further investigation with longitudinal therapeutic intervention studies, potentially providing an early efficacy signal indicating prognostic benefit more strongly than traditional remodeling markers.

Conclusions

In patients with HF, the direct-flow average KE was the only imaging-based independent predictor of functional capacity. 4D flow parameters are novel imaging biomarkers that provide additional information about disease severity and cardiac remodeling over conventional imaging parameters. We speculate that 4D flow parameters may become a powerful surrogate for clinical end points in future HF studies.

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Disclosures

None.

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