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ORIGINAL PAPER

The ventricular residence time distribution derived from 4D flow particle tracing: a novel marker of myocardial dysfunction

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Abstract

4D flow cardiac magnetic resonance (CMR) imaging allows visualisation of blood flow in the cardiac chambers and great vessels. Post processing of the flow data allows determination of the *residence time distribution* (RTD), a novel means of assessing ventricular function, potentially providing additional information beyond ejection fraction. We evaluated the RTD measurement of efficiency of left and right ventricular (LV and RV) blood flow. 16 volunteers and 16 patients with systolic dysfunction (LVEF < 50%) underwent CMR studies including 4D flow. The RTDs were created computationally by seeding virtual 'particles' at the inlet plane in customised post-processing software, moving these particles with the measured blood velocity, recording and counting how many exited per unit of time. The efficiency of ventricular flow was determined from the RTDs based on the time constant (RTDc = − 1/B) of the exponential decay. The RTDc was compared to ejection fraction, T1 mapping and global longitudinal strain (GLS). There was a significant difference between groups in LV RTDc (healthy volunteers 1.2 ± 0.13 vs systolic dysfunction 2.2 ± 0.80, p < 0.001, C-statistic = 1.0) and RV RTDc (1.5 ± 0.15 vs 2.0 ± 0.57, p = 0.013, C-statistic = 0.799). The LV RTDc correlated significantly with LVEF (R = − 0.84, P < 0.001) and the RV RTDc had significant correlation with RVEF (R = − 0.402, p = 0.008). The correlation between LV RTDc and LVEF was similar to GLS and LVEF (0.926, p < 0.001). The ventricular residence time correlates with ejection fraction and can distinguish normal from abnormal systolic function. Further assessment of this method of assessment of chamber function is warranted.

Keywords 4D flow · Cardiac magnetic resonance · Dilated cardiomyopathy

Abbreviations

CMR	Cardiac magnetic resonance imaging
RTD	Residence time distribution
LV	Left ventricular
RV	Right ventricular
EF	Ejection fraction
GLS	Global longitudinal strain
4D	Four dimensional
DCM	Dilated cardiomyopathy
ECV	Extracellular volume

Background

Cardiac magnetic resonance imaging including 4D flow allows for accurate assessment of blood flow patterns within the ventricle [1]. Alterations in blood flow are seen in heart failure [2, 3], and 4D flow derived measures of cardiac efficiency may provide sophisticated diagnostic and prognostic information. By post processing the underlying flow data, we have determined the *residence time distribution* (RTD) of blood transiting the ventricle, a novel means of assessing ventricular function.

The residence time distribution was originally devised to assess efficiency of chemical reactors and here reflects the cumulative distribution of the time it takes for a blood

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volume to transit a cardiac chamber and exit [4]. RTDs are used to characterise mixing and flow within chemical reactors, and to compare the behaviour of reactors to ideal models. While mixing is not a key component of cardiac function, some mixing is inevitable and blood flow and stasis have important implications in cardiac physiology and disease. The RTD differs from ejection fraction as it is a measure of the time taken for blood 'particles' to transit the ventricle, evaluating blood flow rather than cardiac mechanics. The RTD may therefore provide a novel tool to assess myocardial dysfunction and ventricular efficiency.

In this prospective study, we analysed left and right ventricular 4D flow in a healthy cohort and in patients with reduced left ventricular systolic function. The aim of the study was to calculate the RTD of blood transiting the left and right ventricles (as a marker of cardiac efficiency), and to compare the relationship between the RTD and left ventricular ejection fraction. We also compared the RTD with a measure of tissue function (global longitudinal strain) and tissue composition (T1 mapping), to compare the ability of the techniques to discriminate normal from abnormal myocardial function.

Methods

This is a single centre, prospective cross-sectional study. All research was performed at the Baker Heart and Diabetes Institute, Melbourne, Australia between August 2015 and April 2017. The study was approved by the Alfred Hospital Ethics Committee (Melbourne, Australia) and carried out under their guidelines. Prior to inclusion in the study written informed consent was obtained from all participants.

Study population

Thirty-two participants were included in the study. As a reference group 16 healthy volunteers (9 male, 7 female) with a mean age of 43 ± 11 years were included (Table 1). The healthy volunteers were normotensive with a low pretest probability of cardiovascular disease (without history of diabetes, renal impairment, smoking) and normal CMR findings (ventricular size, ejection fraction, mass index, no late gadolinium enhancement).

Patients with dilated cardiomyopathy (DCM) were included if they had a history of symptomatic heart failure, and a dilated left ventricle with an ejection fraction (LVEF) < 50%. We enrolled 16 patients (10 males, 6 females) in this group with a mean age of 53 ± 14 years (Table 1).

A blood sample was drawn from each subject at the time of CMR (healthy volunteers and cases) to measure hematocrit, and estimated glomerular filtration rate (eGFR).

Table 1 Demographics and clinical data

	Healthy controls	DCM	p-value
Number	16	16	–
Age (years)	43 ± 11	54 ± 14	0.03
Gender	9 M/7 F	10 M/6 F	–
LV EDV (mL/m^2)	94 ± 15	120 ± 54	0.088
LVSV (mL)	107 ± 27	75 ± 22	0.001
LVEF (%)	59 ± 5	35 ± 9	< 0.001
RVEDV (mL/m^2)	91 ± 16	78 ± 21	0.082
RVSV (mL)	96 ± 22	62±21	< 0.001
RV EF	63 ± 30	43 ± 12	0.021
Native T1 (ms)	1497 ± 52	1568 ± 65	0.004
ECV (%)	20.9 ± 1.6	23.6 ± 3.4	0.011
GLS (%)	− 19.8 ± 2.4	− 11.2 ± 3.4	< 0.001

Cardiac magnetic resonance imaging

We performed all CMR examinations on a clinical 3T MRI scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). Detailed imaging parameters are presented in Supplementary 1. Ventricular function and T1 mapping post processing was performed using the CVI42 software (CVI42; Circle Cardiovascular Imaging, Inc., Calgary, Canada), and 4D flow was analysed using Siemens prototype software.

Velocity vectors were exported from the Siemens software, allowing post processing of 4D flow data sets using a bespoke program constructed by the investigators using MATLAB (Mathworks, Natick, Massachusetts, USA).

Evaluation of cardiac structure, LV function and regional myocardial fibrosis

After acquisition of scout images, cine imaging of the heart in standard 4-, 3-, and 2-chamber long-axis views and five short-axis views through the left ventricle was performed using an ECG-gated balanced steady-state free precision (SSFP) sequence in expiration. A stack of contiguous short-axis steady-state free precession cine images was acquired, extending from the mitral valve annulus to the LV apex (8-mm slice thickness, no gap), to enable volumetric analysis of the left ventricle using the summation of disk method. This sequence allowed analysis of the ventricular volumes and ejection fractions, and left ventricular mass.

Evaluation of diffuse fibrosis

Myocardial T1 times were estimated of by means of a prototype SASHA sequence (Siemens Healthineers, Erlangen,

Germany). This sequence automatically generated pixel maps of T1 times that were used during post-processing with motion correction algorithm applied to the raw images.

Each sequence was acquired within an end-expiration breath-hold using an electrocardiogram-triggered single-shot acquisition with a balanced steady-state free precession readout in a single mid short-axis slice. Native T1 (pre-contrast) and post contrast T1 times were measured in the myocardium and left ventricular blood pool using a region of interest (ROI) on the T1 pixel map, T1 measurements were taken at the mid short-axis level, both by including the entire myocardium (excluding artefact) and by taking a region within the septum. Any mid-wall fibrosis (typical of DCM) was included, with the consideration that this represents a continuum with diffuse interstitial fibrosis [5].

Extracellular volume (ECV) measures were then obtained from previously measured native and non-corrected post contrast T1 as previously described [6].

Evaluation of global longitudinal strain

Global longitudinal strain was calculated using feature tracking on the cine images on the CVI42 software. The myocardium was defined according to AHA segments by placing a marker across the mitral valve annulus and from the annulus to the apex on long axis images, and by marking endocardial and epicardial borders in the short axis volumetric stack and three apical cine images (4 chamber, 2 chamber, 3 chamber). Markers were placed at both RV insertion points on the short axis images. The feature-tracking algorithm within the CVI42 software calculated strain.

4D flow

Three-dimensional (3D) anatomical imaging was performed in combination with the acquisition of spatially registered three-directional intraluminal velocity information (time-resolved 3D, 4D). Data were acquired using a sagittal oblique 3D volume covering the entire thoracic aorta including the transverse arch and the supra-aortic vessels and the including coverage of the whole heart. Voxel size was $3.0 \times 3.0 \times 3.0$ mm, TR 42.5 ms, number if time frames = 20, velocity encoding 2.0 m/s.

ECG gating was used to assess blood-flow information as a function of the cardiac cycle, and respiratory gating were used to avoid artifact from respiratory motion. Acquisition of 4D flow images took between 6 and 12 min.

Post processing was performed using Siemens prototype software. All images were corrected for background phase, phase aliasing and for motion. Post-processing the images took approximately 5 min to define the planes, and 10 min of computer processing.

Residence time distribution

Residence time distributions were created from the velocity vector data sets. A virtual 'particle seeding' plane was created in the Siemens software at the mitral or tricuspid valve level, with the location identified from orthogonal magnitude images. A second plane was set at the proximal ascending aorta or main pulmonary artery. Particles were seeded uniformly over that part of the plane that was determined to be inside the blood flow. These particles were then advected (i.e. 'moved') with the measured blood velocity over five complete cardiac cycles.

The velocity vectors and plane locations measured in the 4D flow imaging were exported to MATLAB. The particles were followed to the exit plane and counted as they crossed the plane (either the ascending aorta or main pulmonary artery). Particles that did not cross the plane were discarded from analysis. Raw RTD graphs were created within MATLAB and accumulated over five heartbeats, with examples shown in for a normal heart (Fig. 1a) and a heart with reduced LVEF (Fig. 1b).

The $E(t)$ curves represent the proportion of the total exiting particles that crossed the exit plane in the time-slice given along the horizontal axis, and is the usual representation of a residence time distribution.

These data can also be plotted as a fraction of the total particles remaining in the ventricle as a function of time (i.e. heartbeats) (see Fig. 2a, b for normal and reduced LVEF). An exponential decay function (of the form $y = Ae^{-Bt}$) was fitted to these latter plots and efficiency of ventricular flow was then determined based on the time constant (RTDc = 1/B) of the exponential decay curve.

Statistical analysis

All data were analysed using SPSS Statistics software (version 23.0; SPSS Inc., Chicago, IL). Data are presented as mean ± standard deviation (SD) unless otherwise stated, and $p < 0.05$ was considered statistically significant. Paired Student's t tests were used to compare continuous data. Pearson correlation co-efficients were used to assess the relationship between RTDc and EF. Accuracy was assessed using the C-statistic derived from receiver operating characteristic (ROC) curve analysis, and compared using the method described by De Long et al. [7] Intra observer and inter observer agreement was assessed using intra class correlation coefficients (ICC) in sixteen randomly selected cases. Two-way mixed ICCwith absolute agreement were used to compare the RTDc for LV and RV. An ICC value greater than 0.85 was considered excellent.

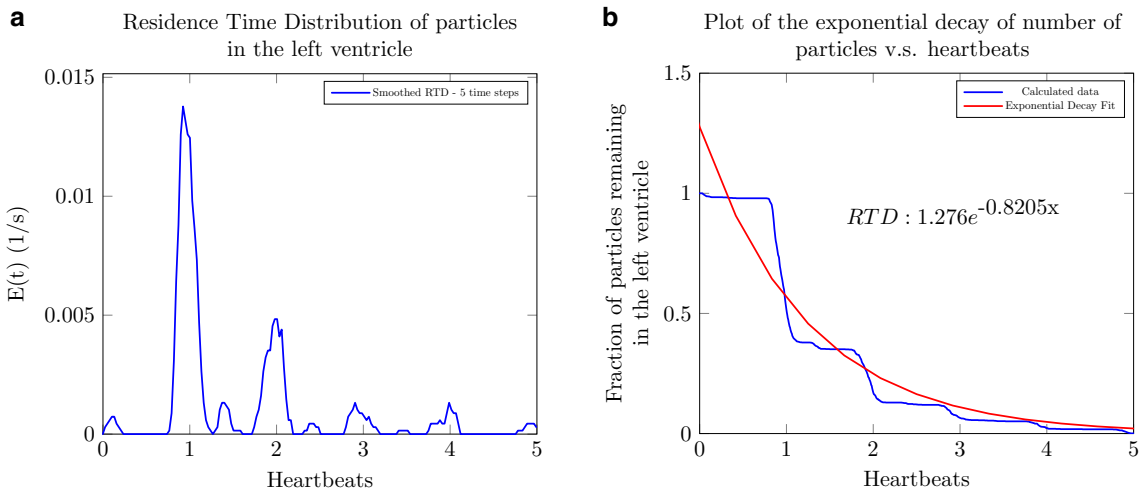

Fig. 1 **a** Example left ventricular residence time distribution, LVEF = 60%. **b** Example exponential decay curve from residence time distribution, LVEF = 60%

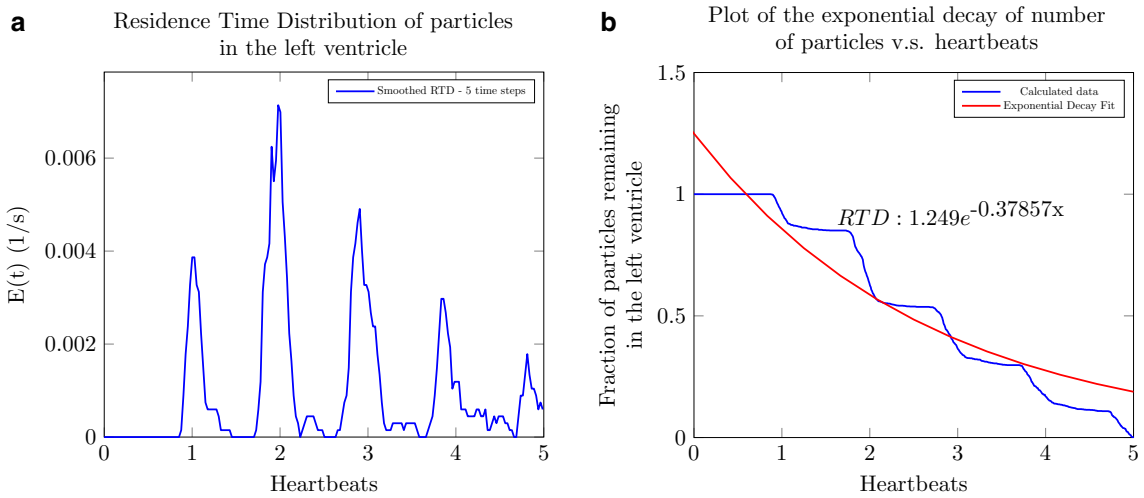

Fig. 2 **a** Example left ventricular residence time distribution, LVEF = 38%. **b** Example exponential decay curve from residence time distribution, LVEF = 38%

Results

The RTDc is essentially equivalent to the mean number of heartbeats taken for particles to transit the reference chamber. In the LV the agreement between RTDc and mean heart beat number was strong (ICC 0.923, $p < 0.001$). We therefore analysed the data using the RTDc to aid in visualising the RTD concept.

Relationship of residence time distribution and left ventricular ejection fraction

We assessed the RTD in both the LV (LV RTDc) and RV (RV RTDc) by comparing with the ejection fraction of the corresponding ventricle LVEF and RVEF respectively.

There was a significant difference between the LV RTDc in healthy volunteers and DCM (1.2 ± 0.13 vs 2.2 ± 0.80,

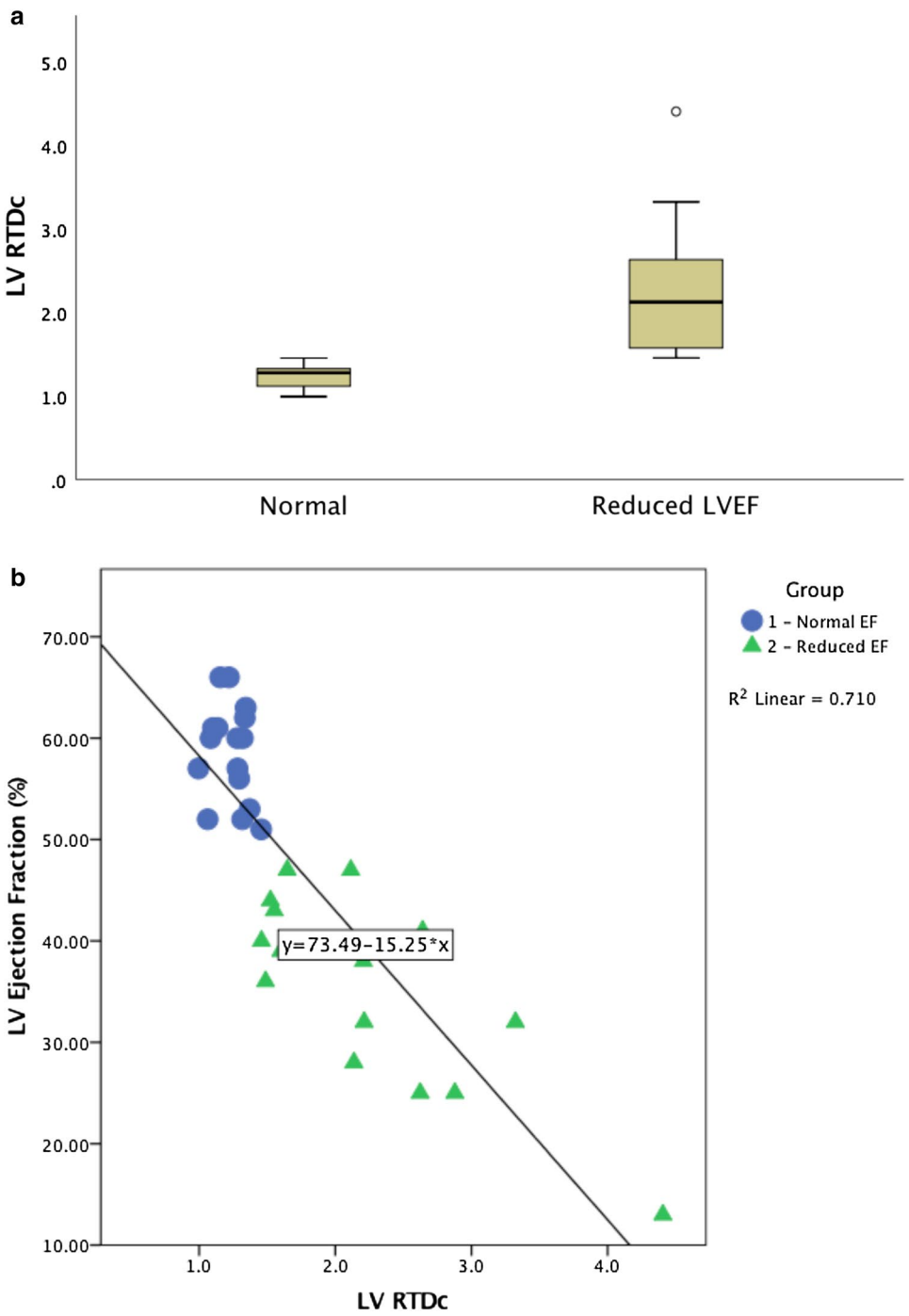

Fig. 3 **a** Box plot of left ventricular residence time distribution constant (LV RTDc, y axis) according to group (x-axis). **b** Correlation of LV ejection fraction (y-axis) with residence time distribution constant (LV RTDc, x-axis). The healthy controls are displayed as blue circles, dilated cardiomyopathy as green triangles

$p < 0.001$, Fig. 3a), with a C-statistic of 1 in the study cohort (Fig. 3a). LV RTDc had a strong negative correlation with LVEF ($R = -0.843$, $p < 0.001$, Fig. 3b) across both groups.

Relationship of residence time distribution and right ventricular ejection fraction

In the right ventricle we compared the mean RTDc between the groups defined by left ventricular function. In healthy volunteers the RV RTDc was 1.5 ± 0.2 compared to 2.1 ± 1.1, $p = 0.01$ (Fig. 4a). There was a modest negative correlation between the RV RTDc and RVEF ($R = -0.402$, $p = 0.023$, Fig. 4b). There was a strong correlation between LV and RV RTDc ($R = 0.763$, $p < 0.001$). In healthy volunteers, the standard deviation of both the LV and RV RTDc was small. In contrast to the LV RTDc, there was a wider variability of RV RTDc in the reduced LV group, with several patients having similar RV RTDc to the healthy control group.

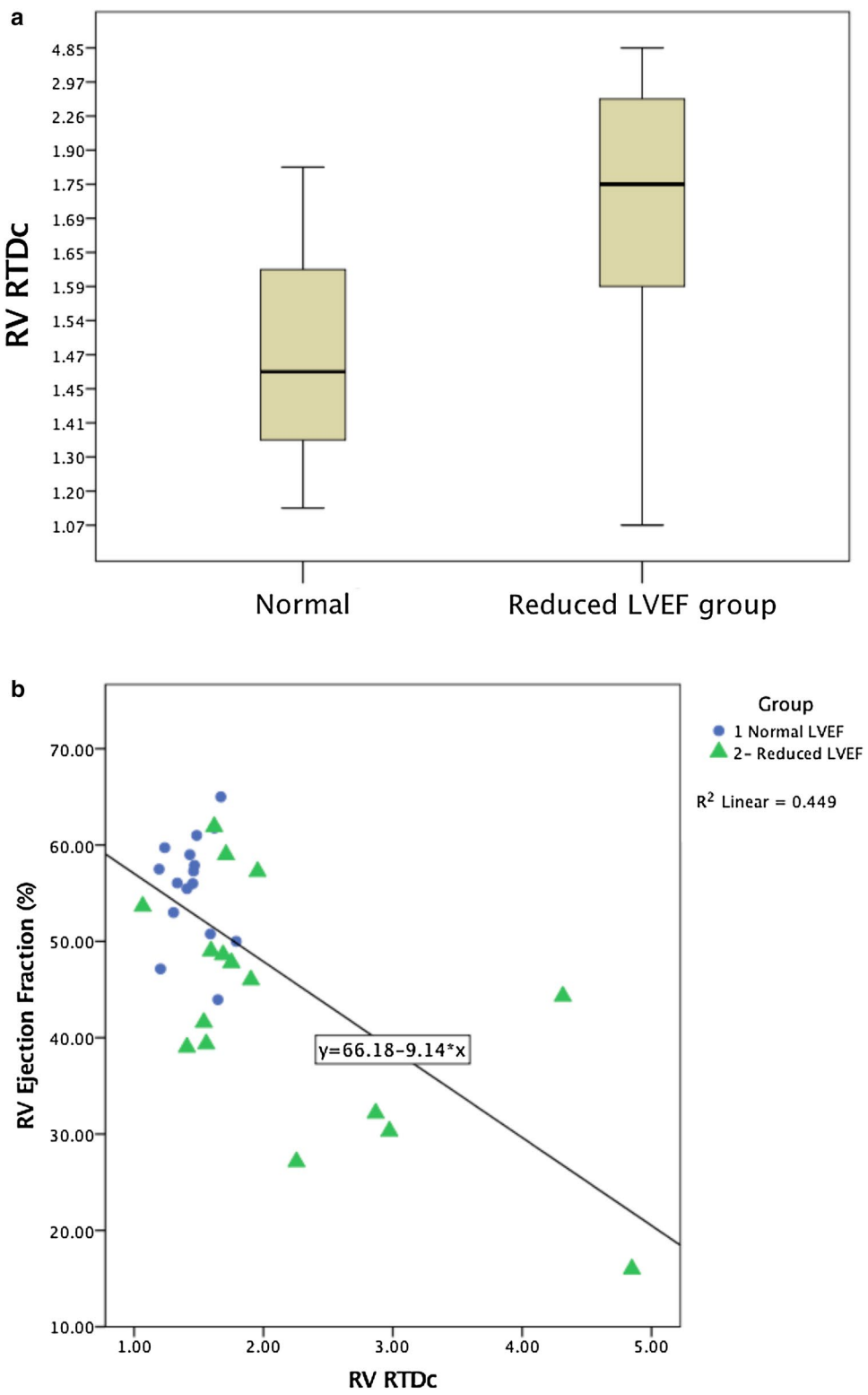

Fig. 4 **a** Box plot of right ventricular residence time distribution constant (RV RTDc, y axis) according to group (x-axis). **b** Correlation of RV ejection fraction (y-axis) with residence time distribution constant (x-axis). The healthy controls are displayed as blue circles, dilated cardiomyopathy as green triangles

Diagnostic utility of residence time distribution, global longitudinal strain and T1 mapping

There was a strong correlation between RTD and GLS ($R = 0.786$, $p < 0.001$) and strong negative correlation between GLS and LVEF ($R = -0.926$, $p < 0.001$).

There was a weak correlation between RTDc T1 mapping parameters. The correlation between RTDc and native T1 time was $R = 0.474$, $p = 0.013$ and between RTDc and ECV was $R = 0.442$, $p = 0.021$.

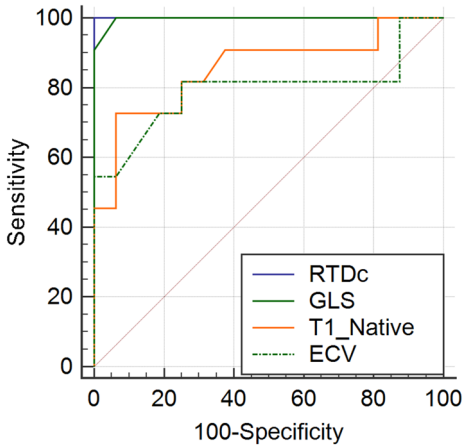

Fig. 5 Receiver operator characteristic curves comparing residence time distribution, global longitudinal strain and T1 mapping methods of discriminating normal controls from dilated cardiomyopathy

Table 2 Inter and intra-observer agreement (ICC, p-value)

n = 16	Intra-observer	Inter-observer
LV RTDc	0.901 (p < 0.001)	0.881 (p < 0.001)
RV RTDc	0.768 (p = 0.004)	0.728 (p = 0.008)

The correlation between LVEF and native T1 was −0.607, p = 0.001, and LVEF and ECV was −0.556, p = 0.03.

The capacity of the RTD, GLS and tissue mapping to distinguishing normal from reduced LVEF was assessed. The C-statistic from analysis of the area under the curve of the receiver operator characteristic curve was 1.00 for the RTDc, 0.997 for GLS, 0.855 for Native T1 and 0.795 for ECV. All values were significant to p < 0.01 (Fig. 5).

While there was no statistically significant difference between the ROC curve for RTD and GLS (p = 0.4795), there was a strong trend to a difference between RTD and T1 native (p = 0.08), RTD and ECV (p = 0.05), GLS and T1 native (p = 0.08) and GLS and ECV (p = 0.05).

Inter-observer and intra-observer variability

After approximately 1 h of training for a clinician with experience in cardiac imaging, inter-observer variability was excellent in the LV and moderate in the RV. Inter and intra-observability measures are presented in Table 2.

Discussion

In this study we have described the residence time distribution, a novel method of assessing cardiac function and efficiency derived from 4D flow using cardiac magnetic resonance. The RTDc was lower in participants with normal LV function when compared to participants with established systolic dysfunction. In healthy volunteers with presumed normal cardiac function the RTD constant fell within a narrow range (mean 1.24, range 1.0–1.45). All participants with reduced ejection fraction in this study had RTDc above this range, (from 1.45 to 4.48).

Excellent agreement was seen in the inter and intra-observer variability measures of the RTDc in the LV, and moderate agreement in the RV. The stronger agreement in LV measures is likely to be a reflection of the increased difficulty in accurately defining the tricuspid annular plane.

In healthy volunteers, the greatest proportion of blood was seen to transit the ventricle in the first cardiac cycle, whereas there was a delay in transit in heart failure, with a greater volume exiting during the second cycle (Fig. 2). A delay in the transit of blood particles is a marker of inefficiency, with a loss of the kinetic energy created by diastolic suction of blood into the left ventricle, and a requirement in systole to provide the momentum to re-establish flow.

In addition, the RTDc correlated with LVEF across the broad range of ejection fractions. While this correlation was not as strong in the right ventricle, we can only surmise whether this is due to reduced accuracy in the RV (again reflecting the challenge of defining the tricuspid plane), or a different relationship between RTDc and the ejection fraction of the right and left ventricle. Dilated cardiomyopathy is not always biventricular, and the RTDc of the right ventricle may provide an insight into the degree of involvement of the right ventricle in the pathologic process and may also reflect a greater conduit function of the right ventricle as compared to the left.

While ejection fraction is an effective method of analysing the left ventricle, providing functional and prognostic information [8], it is often a late sign of dysfunction, and finding markers of dysfunction earlier in the pathophysiologic process could improve clinical outcomes. A theoretical advantage of the RTDc over ejection fraction in cardiomyopathy is that the RTDc should not be influenced by functional mitral regurgitation, which commonly occurs in more advanced cardiomyopathy [9, 10] and may lead to an overestimation of cardiac function based on ejection fraction.

Furthermore, the right ventricle and atria provide additional challenges for the accurate assessment of function, and advanced methods of cardiac function analysis are highly sought after [11]. The possibility that increased resident time is associated with increased risk for thrombus formation, independent of LVEF, deserves further investigation.

Many studies have attempted to characterise ventricular function beyond ejection fraction by looking at the myocardial tissue. Analysis of myocardial deformation (strain) [12], tissue Doppler including E and E′ velocities [13] and T1 mapping [14] are techniques looking at factors within

the myocardium to determine pathology, and have had the ability to identify and classify heart disease.

4D flow provides an alternative view of myocardial function and efficiency, and advanced post processing techniques of 4D flow data may provide an alternate means of early diagnosis of cardiac pathologies. We found an association between flow and fibrosis, with a modest correlation between T1 mapping parameters and the LV RTDc, however the role of fibrosis in the impairment of intra-cardiac flow was not directly tested.

The RTD agreed more strongly with global longitudinal strain than with T1 mapping, suggesting a close relationship between myocardial deformation, ejection fraction and efficiency of blood flow. While there was a modest relationship with T1 mapping, the estimate of myocardial fibrosis did not appear to play as significant a role.

Previously Bolger et al. [2] used 4D flow to develop a method of compartmentalising blood flow into four components, according to compartmental origin and fate. Direct flow transits the LV in a single cardiac cycle; retained inflow enters the LV in diastole but does not leave in the next systole; delayed ejection flow refers to blood originating in the LV and exiting in systole; and the residual volume resides in the LV for at least two cardiac cycles. This method can also distinguish normal LV function from cardiomyopathy, however is computationally intensive and not routinely available with existing post-processing software [15].

The RTD is a similar concept, largely reflecting the direct flow component, with the advantage that the process can be incorporated into CMR analysis in a time effective way and applied to all cardiac chambers. With our analysis, up to 60% of blood particles transited the LV in the first cycle in normal heart function (analogous to direct flow). Residence time distribution analysis has been used to evaluate dead space in chemical reactors, the 'retained flow' component in cardiac cycle will influence this concept.

Other studies have evaluated kinetic energy derived from 4D flow in the left ventricle, with higher average systolic kinetic energy in subjects with heart failure compared to controls [16, 17]. Visualisation of these flow patterns has provided novel insight into cardiac function, and the RTDc provides a method of translating the qualitative imaging into usable quantitative information.

From our data, it appears that maintaining blood momentum through the AV valve and into the outflow tract is a key component of cardiac performance. Further study into how this translates to avoidance of stasis, into atrial function, and in early stages of diseases of the left and right ventricle are needed to determine the value of RTDc as an independent measure of cardiac function.

From a diagnostic perspective, it would appear that the RTD in this cohort performs similarly to GLS, and it is potentially a better biomarker than T1 mapping in dilated cardiomyopathy, with a trend toward a difference in discriminatory capacity. The narrow range of LV RTD in normal patients may increase the sensitivity in diagnosis, though this hypothesis requires further investigation, in particular to determine whether the RTD can provide incremental value over GLS and T1 mapping techniques, both in diagnosis and in monitoring the response to interventions.

There are a number of assumptions we have made in developing the RTDc. We have assumed that blood flow in the heart achieves steady state, and that blood flow and velocity at a particular point is the same from one heartbeat to the next. Particle tracing has been used as a qualitative technique, and while the accuracy of the data was not directly tested, the relevance of the association between LVEF and RTDc still holds.

Conclusion

The left ventricular residence time correlates with ejection fraction and has the capacity to distinguish normal from abnormal systolic function. Further assessment of this promising method of assessment of chamber function is warranted.

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Author contributions BC: conception, design and analysis and interpretation of data, and drafting of the manuscript; MQ: development of MATLAB code, analysis of data and revision of the manuscript; BP: development of MATLAB code; MT: development of code and revision of manuscript: JH: conception and design and revision of the manuscript; ALG: analysis and interpretation of data, revision of manuscript; MR: development of MATLAB code, analysis of data, revision of manuscript; AJT: conception, design and analysis and interpretation of data, revision of the manuscript and final approval.

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Data availability The anonymized datasets analyzed during the current study are available from the corresponding author, on reasonable request.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study was approved by the Alfred Hospital Ethics Committee (Melbourne, Australia) and carried out under their guidelines.

Informed consent Prior to inclusion in the study written informed consent was obtained from all participants.

Consent for publication All authors declare their consent for publication.

References

1. Eriksson J, Carlhäll C, Dyverfeldt P, Engvall J, Bolger AF, Ebbers T (2010) Semi-automatic quantification of 4D left ventricular blood flow. J Cardiovasc Magn Reson 12:9–10
2. Bolger A, Heiberg E, Karlsson M et al (2007) Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 9:741–747
3. Eriksson J, Bolger AF, Ebbers T, Carlhall CJ (2013) Four-dimensional blood flow-specific markers of LV dysfunction in dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging 14:417–424
4. Fogler HS (2016) Elements of chemical reaction engineering. Prentice Hall
5. Miller CA, Naish JH, Bishop P et al. (2013) Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circ Cardiovasc Imaging 6:373–383
6. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE (2012) Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reson BioMed Central 14:63
7. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845
8. Curtis JP, Sokol SI, Wang Y et al (2003) The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 42:736–742
9. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM (2003) Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 91:538–543
10. Donal E, De Place C, Kervio G et al (2009) Mitral regurgitation in dilated cardiomyopathy: value of both regional left ventricular contractility and dyssynchrony. Eur J Echocardiogr 10:133–138
11. Thomas L, Hoy M, Byth K, Schiller N (2007) The left atrial function index: a rhythm independent marker of atrial function. Eur J Echocardiogr 2008:356–362
12. Stanton T, Leano R, Marwick TH (2009) Prediction of All-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging 2:356–364
13. Biering-Sørensen T, Mogelvang R, Jensen JS (2015) Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode in the general population. Heart BMJ 101:954–960
14. Iles L, Pfluger H, Phrommintikul A et al (2008) Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 52:1574–1580
15. Stoll V, Hess AT, Eriksson J et al (2016) The kinetic energies of left ventricular 4D flow components correlate with established markers of prognosis and represent novel imaging biomarkers in both ischaemic and dilated cardiomyopathy. J Cardiovasc Magn Reson 18:O68
16. Svalbring E, Fredriksson A, Eriksson J et al. (2016) Altered diastolic flow patterns and kinetic energy in subtle left ventricular remodeling and dysfunction detected by 4D flow MRI. PLoS ONE 11:e0161391
17. Elbaz MSM, Calkoen EE, Westenberg JJM, Lelieveldt BPF, Roest AAW, van der Geest RJ (2014) Vortex flow during early and late left ventricular filling in normal subjects: quantitative characterization using retrospectively-gated 4D flow cardiovascular magnetic resonance and three-dimensional vortex core analysis. J Cardiovasc Magn Reson 16:45