International Journal of Cardiology 315 (2020) 45–50

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Measuring atrial stasis during sinus rhythm in patients with paroxysmal atrial fibrillation using 4 Dimensional flow imaging☆
4D flow imaging of atrial stasis

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ARTICLE INFO

Article history:
Received 1 March 2020
Received in revised form 14 April 2020
Accepted 4 May 2020
Available online 19 May 2020

Keywords:
Atrial fibrillation
Stroke
4d flow
Atrial function
Cardiac magnetic resonance

ABSTRACT

Background: Paroxysmal atrial fibrillation (PAF) is associated with cardioembolic risk, however events may occur during sinus rhythm (SR). 4D-flow cardiac magnetic resonance (CMR) imaging allows visualisation of left atrial blood flow, to determine the *residence time distribution* (RTD), an assessment of atrial transit time.
Objective: To determine if atrial transit time is prolonged in PAF patients during SR, consistent with underlying atrial stasis.
Method: 91 participants with PAF and 18 healthy volunteers underwent 4D flow analysis in SR. Velocity fields were produced RTDs, calculated by seeding virtual 'particles' at the right upper pulmonary vein and counting them exiting the mitral valve. An exponential decay curve quantified residence time of particles in the left atrium, and atrial stasis was expressed as the derived constant (RTD_{TC}) based on heartbeats. The RTD_{TC} was evaluated within the PAF group, and compared to healthy volunteers.
Results: Patients with PAF ($n = 91$) had higher RTD_{TC} compared with gender-matched controls ($n = 18$) consistent with greater atrial stasis (1.68 ± 0.46 beats vs 1.51 ± 0.20 beats; $p = .005$). PAF patients with greater thromboembolic risk had greater atrial stasis (median RTD_{TC} of 1.72 beats in CHA_2DS_2-VASc≥2 vs 1.52 beats in CHA_2DS_2-VASc<2; $p = .03$), only female gender and left ventricular ejection fraction contributed significantly to the atrial RTD_{TC} ($p = .006$ and $p = .023$ respectively).
Conclusions: Atrial stasis quantified by 4D flow is greater in PAF, correlating with higher CHA_2DS_2-VASc scores. Female gender and systolic dysfunction are associated with atrial stasis. RTD offers an insight into atrial flow that may be developed to provide a personalised assessment of thromboembolic risk.

1. Background

Stroke is the fifth most common cause of death globally, accounting for >5% of all deaths [1]. A risk factor for stroke is the presence of atrial fibrillation (AF), with the risk of stroke increasing up to 5-fold for those with a history of AF, even after adjustment for confounding factors [2]. In those who are above 40 years old, the lifetime risk of AF is 1 in 4 [3].

A factor in the relationship between stroke and AF has been the role of atrial stasis, with the traditional paradigm for AF related stroke focusing on the presence of atrial stasis due to a lack of coordinated atrial contraction during AF, however it is well established that there is not necessarily a temporal relationship between AF episodes and stroke [4,5].

Thrombosis occurring as a consequence of atrial stasis and other contributing factors can lead to embolism to the brain, the risk of which can be substantially reduced in many patients through oral

☆ This research was in part supported by fellowship stipends provided by the Baker Heart and Diabetes Institute, the National Health and Medical Research Council of Australia and the National Heart Foundation of Australia.
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https://doi.org/10.1016/j.ijcard.2020.05.012
0167-5273/

anticoagulation [6–8]. Importantly, OAC is only recommended in patients with AF who have additional risk factors for stroke, based on assessment using clinical tools such as the CHADS and CHA_2DS_2-VASc scores [9]. While CHA_2DS_2-VASc incorporates a number of clinical risk factors for stroke, it does not contain any imaging parameters or biomarkers, and thus lacks the precision of a more personalised approach.

Evaluation of atrial dysfunction using echocardiography (left atrial enlargement [10], spontaneous echo contrast [11]), ECG [12] and CMR (atrial wall late gadolinium enhancement [13]) have demonstrated an association with increased stroke risk, even in patients in sinus rhythm. While these findings are consistent with the paradigm of atrial *myopathy* [14] leading to atrial stasis and cardio-embolism, research in this field has been hindered by the lack of a reliable index of atrial stasis.

The development cardiac magnetic resonance (CMR) sequences capable of measuring 4D flow has enabled detailed analysis of left atrial flow patterns [15,16]. To evaluate atrial stasis, we have developed a technique for analysing 4D flow CMR imaging based on the *residence time distribution* (RTD) of blood transiting the left atrium. The residence time distribution was devised to assess efficiency of chemical reactors and here reflects the cumulative distribution of the time it takes for a blood volume to transit a cardiac chamber and exit, quantified by the RTD time constant (RTD_{TC}). The residence time distribution is used to assess dead space in chemical reactors, we have adapted this concept to assess atrial stasis. We have previously demonstrated the RTD_{TC} is prolonged in the ventricle of patients with dilated cardiomyopathy when compared to healthy controls [17].

In this study, we compared the RTD_{TC} in a healthy cohort and on a group with a history of PAF. The aim of the study was to compare the RTD_{TC} of the left atrium between groups, and to assess the relationship of the RTD_{TC} to the CHA_2DS_2-VASc score in patients with PAF, with a view to developing an imaging parameter to incorporate into a personalised approach to stroke risk assessment.

2. Methods

This is a single center, prospective cross-sectional study. All research was performed at the Baker Heart and Diabetes Institute, Melbourne, Australia between August 2015 and December 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. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.1. Study population

109 participants underwent CMR studies including 4D flow, comprising 18 healthy volunteers and 91 patients with PAF. The PAF group were medically stable hospital outpatients, recruited from the arrhythmia clinic at the Alfred Hospital, Melbourne, Australia. All participants were free from symptoms of heart failure or arrhythmia at the time of study. The CHA_2DS_2-VASc score was calculated in all PAF patients, and within this group patients were dichotomised into those with higher versus lower CHA_2DS_2-VASc scores using a cut-off of ≥2, at which point OAC is recommended [9].

The healthy volunteers were normotensive with no history of atrial fibrillation and a low pre-test probability of cardiovascular disease (without history of diabetes, renal impairment, smoking) and normal CMR findings (normal ventricular size, ejection fraction, mass index, and no late gadolinium enhancement). The healthy volunteers were recruited using advertising material and were reviewed by a physician prior to enrolment in the study.

Patients were included if they were aged >18 years and had a history of documented atrial fibrillation and/or atrial flutter but were in sinus rhythm at time of CMR.

Patients were excluded if they had any of: NYHA III - IV heart failure symptoms, comorbid medical illness with prognosis <12 months, inability to provide informed consent, CMR contraindication (inc. ICD/PPM, eGFR < 30).

Time since AF diagnosis was determined based on hospital records and the clinical history.

2.2. Cardiac magnetic resonance imaging

We performed all CMR examinations on a clinical 3 T MRI scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). 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 (4D Flow V 2.4).

The measured velocity vectors were exported from the Siemens software, allowing post processing of 4D flow data sets using a locally developed program constructed by the investigators using MATLAB (Mathworks, Natick, Massachusetts, U.S.A).

2.3. Evaluation of cardiac structure and LV function

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 also 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. LA volume was calculated from the 4- and 2-chamber long axis views at end diastole and end systole, LA ejection fraction was derived from these measures.

A non-invasive blood pressure was recorded at the end of CMR image acquisition.

2.4. 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. Acquisition parameters are found in Supplementary material.

ECG gating was used to assess blood-flow information as a function of the cardiac cycle, and respiratory gating was used to correct for respiratory motion. Acquisition of 4D flow images took between six and twelve minutes.

Post processing was performed using Siemens prototype software. All images were corrected for background phase, phase aliasing and for motion.

2.5. 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 right upper pulmonary vein, with the location identified from orthogonal magnitude images. The right upper pulmonary vein was chosen as it could be routinely identified from the magnitude images, facilitating a consistent and reproducible approach. A second plane was set at the level of the mitral valve (Supplementary Fig. 1A). The location was confirmed by the pattern of mitral valve inflow at that plane (identifying the E and A wave on the phase contrast derived flow pattern, Supplementary Fig. 1B). Particles were seeded uniformly over that part of the plane in the pulmonary vein 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, (Supplementary Fig. 1C and D, Supplementary movie).

The velocity vectors and plane locations measured in the 4D flow imaging were exported to MATLAB. The particles were followed to the mitral valve exit plane and the time interval in which they crossed the plane was noted. These crossings were then counted for each time interval. Raw RTD graphs were created within MATLAB and represented with the x-axis normalised to 5 heartbeats, examples are shown in Supplementry Fig. 2 A and B.

These $E(t)$ vs t curves represent the proportion of the total exiting particles that crossed the exit plane in the time-interval 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 atrium as a function of time (i.e. heartbeats) (see Supplementary Fig. 2 C and D). An exponential decay function (of the form $y = Ae^{-Bt}$) was fitted to these plots and the degree of atrial stasis was determined based on the time constant ($RTD_{TC} = 1/B$) of the curve. The RTD_{TC} is the mathematical equivalent to the average time a particle is present within the left atrium, and hence a longer RTD_{TC} is consistent with greater atrial stasis.

2.6. Atrial velocity

In addition to the RTD, we evaluated the percentage of blood 'particles' with velocities < 0.2 m/s and 0.1 m/s, to determine if atrial velocity could be used as a surrogate for atrial stasis as previously reported [18].

2.7. 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 $P < .05$ was considered statistically significant. Normal distribution of data was assessed with the Kogorov-Smirnov test. Dependent on normality, Student's *t*-tests or Mann-Whitney *U* tests were used to compare continuous data. Pearson coefficients were used to assess the correlation between variables. Multiple linear regression was used to assess the contribution of independent variables to the RTD_{TC}. Two-way mixed intra-class correlation coefficients (ICC) with absolute agreement were used to assess inter-observer variability in the assessment of the RTD_{TC}.

3. Results

In total 109 participants were recruited between August 2015 and November 2017, comprising 91 patients with PAF and 18 healthy volunteers.

Patients in the PAF group were mostly male (75%), mean age 61 ± 11 years and Caucasian (86%), with a varied prevalence of medical comorbidities (43% hypertension, 7% diabetes mellitus, 5% prior TIA/stroke, 7% congestive cardiac failure, ischaemic heart disease 4%). The mean CHA_2DS_2-VASc was 1.5 ± 1.2. Baseline clinical characteristics are shown in Supplementary Table 1.

3.1. Atrial flow in PAF and healthy volunteers

As the gender ratio differed between the PAF and control groups, we compared a gender matched group of PAF patients ($N = 46$) with healthy volunteers ($N = 18$), There was a significant difference observed between the RTD_{TC} (1.68 ± 0.45 beats PAF v 1.51 ± 0.19 beats controls, $p = .006$, Fig. 1). In the healthy volunteer group, there was no correlation between age and the RTD_{TC} (R = -0.09, $p = .971$). The proportion of blood particles travelling below 0.1 m/s was similar in the healthy volunteers and PAF patients (healthy volunteers 59 ± 6% v PAF 61 ± 9%, $p = .13$).

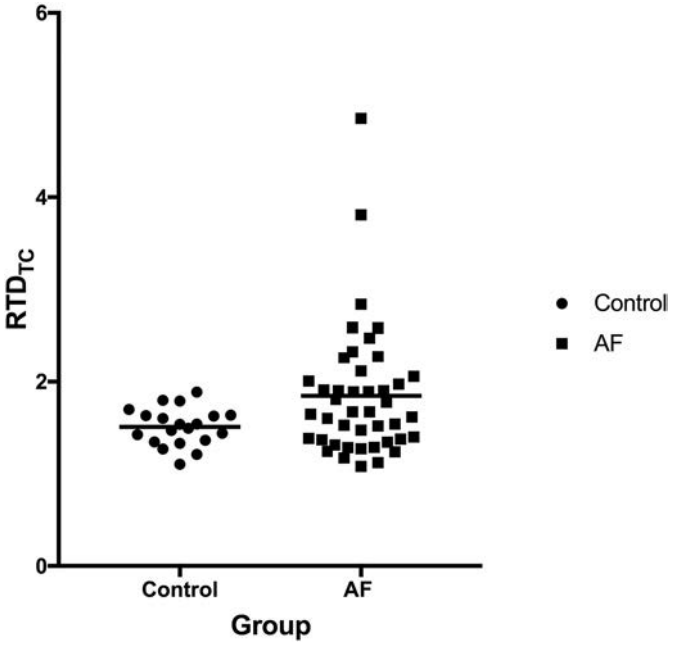

Fig. 1. Comparison of the RTD_{TC} between the control group and the AF cohort. (p = .005).

There was no correlation between the RTDc and LA volume (indexed) ($R = -0.009$, $p = .9380$), LA ejection fraction (R = -0.098 $p = .374$), systolic blood pressure (R = -0.144 $p = .206$), or diastolic blood pressure ($R = 0.156$ $p = .169$).

3.2. PAF patients and CHA_2DS_2-VASc score

The RTD_{TC} was significantly higher in PAF patients with a CHA_2DS_2-VASc ≥ 2 (the value at which OAC is indicated), consistent with increased atrial stasis in patients who are considered to be at a higher stroke risk. (Median RTD_{TC} of 1.72 beats vs 1.52 beats; $p = .045$, Fig. 2). There was a modest correlation between time since AF diagnosis and RTD_{TC} ($R = 0.303$, $p = .038$). There were no significant differences between the groups with respect to atrial size (LA volume indexed 49 ± 21 ml/m2 v 50 ± 14 ml/m2, $p = .511$) or atrial ejection fraction (40 ± 12 v 45 ± 19%, $p = .154$).

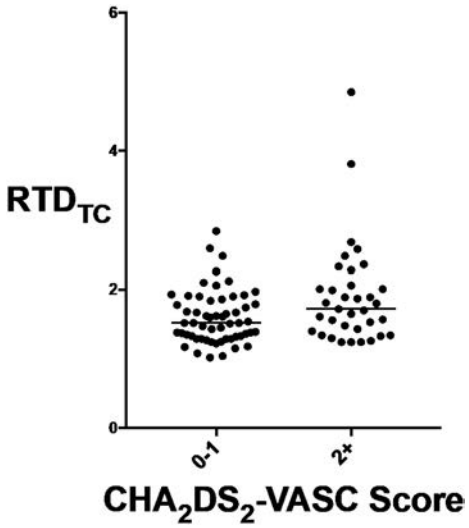

Fig. 2. Comparison of the RTD_{TC} between groups based on CHA_2DS_2-VASc score, $p = .03$.

3.3. Correlation between RTD_{TC} and independent variables

There was a significant correlation between the RTD_{TC} and time since AF diagnosis (R = 0.303, p = .038) and a significant negative correlation between RTD_{TC} and female gender, height, LV and RV end diastolic volume, and LV mass (Table 2). Characteristics of participants with the ten highest RTD_{TC} values are shown in Supplementary Table 3, there was a trend towards the female gender (40% v 23%, p = .081) and less with hypertension (20% v 50%, $p < .001$), otherwise there were no other significant differences.

Using multiple linear regression analysis of the CHA_2DS_2-VASc risk factors, only female gender contributed significantly to the atrial RTD_{TC} (female gender $p = .003$, Table 1). When age and LVEF were included as continuous variables, female gender and LVEF reached significance (female gender $p = .007$, LVEF $p = .023$). The R-squared value for this model was 0.2.

Multiple linear regression with inclusion of the significant independent variables from the CMR study is presented in Table 2. Gender was no longer significant, however a smaller ventricle (both indexed volume and mass) and left ventricular ejection fraction contributed significantly.

3.4. Inter-observer variability

After approximately 1 h of training for a clinician with experience in cardiac imaging (clinical echocardiography fellowship trained, limited CMR experience), inter-observer variability when measuring the RTD using the Siemens and MATLAB software was good ($n = 10$, ICC = 0.832, $p = .002$).

4. Discussion

This study provides a novel method for atrial stasis to be quantified. In subjects in sinus rhythm, we demonstrate that stasis is greater in patients with a history of AF than in those without and that stasis is greater in those with greatest thromboembolic risk. Expanding this concept to larger cohorts of AF patients may allow identification of i) patients with low CHA_2DS_2-VASc scores who may benefit from anti-coagulation, and ii) patients with higher CHA_2DS_2-VASc in which the stroke risk is low enough to avoid exposure to the bleeding risk associated with anti-coagulant drugs.

4.1. Detection of atrial stasis with 4D CMR flow imaging

Particular focus on atrial flow dynamics to date has been upon flow velocities in the left atrium and the left atrial appendage. Reduced left atrial blood flow and flow coherence is noted with increasing age, and also occurs in patients who are in AF at the time of CMR scanning [19]. However in patients with a prior history of AF, who undergo CMR when in sinus rhythm, atrial blood flow dynamics appear to be comparable between AF patients and age-matched control subjects [18], although there are modest correlations between indices of left atrial flow derived from CMR 4D flow imaging and CHA_2DS_2-VASc scores [20]. Although Lee et al. demonstrated significant differences between a number of velocity-based indices of reduced left atrial flow (atrial stasis) and AF even when CMR scanning occurred during sinus rhythm [16], these indices were not corrected for left atrial size, and so it is not clear whether simply measuring blood velocity in the left atrium offers additional prognostic information above that obtained with cheaper and more readily available TTE imaging. By using a residence time distribution to analyse atrial flow, the impact of atrial size on flow dynamics is avoided, as the focus is on the number of heartbeats taken to transit the atrium as the marker of stasis, rather than blood velocity.

The RTD is a way to describe the efficiency of the chamber, and will combine atrial size, velocity and dead space into a single measurement. This has the potential to act as a unifying imaging parameter, in a similar way to assessing varying chemical reactor sizes with a single distribution curve. High velocity of blood rapidly transiting the atrium may be driven by ventricular function, and there may be stasis in 'dead spaces' of a poorly functioning atrium.

Table 1
Multiple linear regression analysis of the dependent variable RTD_{TC} with the independent variables in the CHA_2DS_2-VASc score. Significant variables are highlighted in bold.

Independent Variable	CHA_2DS_2-VASc variables (p)	Modified CHA_2DS_2-VASc (p)
Congestive Cardiac Failure	0.747	–
Hypertension	0.455	0.123
Age > 65	0.328	–
Age > 75	0.371	–
Diabetes	0.917	0.756
TIA/Stroke	0.308	0.531
Vascular Disease	0.483	0.456
Gender	**0.003**	**0.006**
Age (continuous)	–	0.565
Left ventricular ejection fraction	–	**0.023**

Table 2
Multiple linear regression of the dependent variable RTD_{TC} including independent variables with a Pearson's R correlation p value <.2. Significant variables are highlighted in bold.

Independent Variable	Beta coefficient	Significance
Height	−0.152	0.280
BSA	−0.150	0.558
LVEDV/BSA	**−0.944**	**0.030**
LVEF	**−0.303**	**0.006**
LV Mass/BSA	−0.432	**0.008**
Gender	−0.050	0.747
Hypertension	0.126	0.223

4.2. Relationship of CHA_2DS_2-VASc score with atrial stasis

The CHA_2DS_2-VASc is the best validated clinical tool for predicting thromboembolic risk in patients with AF, but it has some limitations. It has only a modest predictive capacity, with a C statistic of 0.606 [21]. More accurate prediction of stroke risk may be achieved by including physiological data. An increased stroke risk in AF has been shown with increased atrial size [10], reduced atrial appendage emptying velocities [22], and spontaneous echo contrast on trans-oesophageal echocardiography [23]. However, these may only be surrogate markers for atrial stasis. The RTD_{TC} measure of atrial stasis may help identify AF patients who are at highest risk for cardio-embolism. Importantly, we demonstrated higher values for the RTD_{TC} in patients considered at higher thromboembolic risk based on CHA_2DS_2-VASc scores, as well as higher values for the RTD_{TC} in patients with a prior history of AF. Taken together, these findings suggest that the atrial RTD_{TC} may be a useful marker for identifying higher levels of atrial stasis in AF patients who are likely to be at higher thromboembolic risk, however this would need to be tested in larger cohorts of patients, including in those who experienced AF related stroke.

4.3. Role of gender in atrial stasis

Our findings suggest an explanation for why women are at a higher risk of stroke, with female gender being the only factor in the CHA_2DS_2-VASc score significantly predicting the RTD_{TC}. We found a weak but significant negative correlation between atrial RTD_{TC} and each of height, LV end diastolic volume, stroke volume; all of which were associated with female gender.

When we corrected for body size and cardiac dimensions, gender was no longer a significant predictor of the RTD_{TC}, implying that the observed atrial stasis in women may be secondary to reduced LV stroke volume leading to slower atrial flow. Importantly, there was no correlation between atrial RTD_{TC} and LA volume index. This suggests that the relationship between increased RTD_{TC} and stroke risk (based on CHA_2DS_2-VASc score) in our study was not simply a consequence of increased atrial size. Furthermore, the lack of dependence of the RTD_{TC} on atrial size overcomes the shortcomings of simply measuring atrial velocity, which may be affected by atrial size and, in our study, did not differ between AF patients and healthy controls, and was not associated with higher CHA_2DS_2-VASc scores in AF patients. Two very large registry studies have demonstrated the increased risk of stroke in women with AF not taking OAC, which led to female gender being incorporated into the CHA_2DS_2-VASc *score*. In the ATRIA study [24] of over 13,000 patients, women were found to have higher annual risk of stroke (3.5% versus 1.8%; adjusted rate ratio [RR], 1.6; 95% CI, 1.3 to 1.9). A Danish registry of over 70,000 AF patient between 1997 and 2006 showed that female gender alone increased the risk of stroke [25]. However neither study accounted for body size or cardiac dimensions.

4.4. Study limitations

While there was a significant difference in the median value of the atrial RTD_{TC} for the groups stratified according to presence of PAF and according to CHA_2DS_2-VASc score, there is considerable overlap in RTD_{TC} values. This study was performed in a heterogeneous group of PAF patients (with a low incidence of significant co-morbidity), and within this cohort the CHA_2DS_2-VASc is recognised as having limitations in predicting stroke. The spread of atrial stasis may in fact detect variability in stroke risk not appreciated by traditional scoring. However longitudinal follow up is required to test this hypothesis, and is a focus of ongoing research.

The healthy volunteer group was small and younger than the AF cohort and while there was not a significant correlation between atrial RTD_{TC} and age, this may influence the results. The RTD_{TC} in the healthy volunteer group fell in a narrow range, increasing confidence in the RTD_{TC} as a useful biomarker and enhancing the validity of the results.

There are assumptions we have made in developing the RTD to assess atrial flow. Measuring 4D flow takes up to 10 min, and we have assumed that the phase-averaged velocity fields are representative of a subject's normal heart beat and have neglected beat-to-beat variation that could add a random component to the velocity field and subsequent RTD estimation. In sinus rhythm, the 4D flow data are believed to accurately capture the magnitude and timing of LA velocities over the cardiac cycle [16]. Particle tracing has been typically used as a qualitative technique, and we have previously validated the RTD_{TC} in the left ventricle [17]. We consider the association between the CHA_2DS_2-VASc score and RTD_{TC} can be developed to better assess personalised stroke risk.

We did not have transthoracic or trans-oesophageal echocardiography data to compare to the CMR data. 4D flow CMR has advantages over echocardiography in the ability to get 3D time resolved velocities in the full volume of the atrium, whereas trans-oesophageal echocardiography studies have tended to assess the left atrial appendage emptying velocities only.

The exact burden of AF in the study population is not known. Participants did not have loop recorders, and we require further research to fully understand the impact atrial fibrillation burden has on atrial stasis.

Mitral regurgitation was not directly measured (though no participants had significant flow void on cine images to suggest significant regurgitation), the impact of mitral regurgitation is unclear.

While there was no correlation between the RTD_{TC} and non-invasive blood pressure, we did not have estimates of pulmonary pressure which may have influenced loading conditions. A further limitation of the study is uncertainty of the variability of a change in these loading conditions on the RTD_{TC}.

Atrial strain using feature tracking has shown some promise in assessing atrial myopathy [26], and the relationship between the RTD_{TC} and atrial strain could be further assessed.

5. Conclusions

Atrial stasis quantified by CMR 4D particle tracing occurs during sinus rhythm in patients with PAF and is associated with higher CHA_2DS_2-VASc scores. Female gender and reduced left ventricular ejection fraction were associated with increased atrial stasis. The presence of atrial stasis in PAF even when in sinus rhythm may provide an additional mechanism for cardio-embolism in this patient group. To test this hypothesis, further research into CMR assessment of atrial stasis in participants with a borderline indication for anticoagulation, and in subjects with an uncertain origin of embolic stroke are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.05.012.

Funding

This was an investigator-initiated study. Funding for the study as provided by a grant from Monash Institute of Medical Engineering (MIME).

Disclosures

While the authors have no conflicts pertaining to this research, the following industry funding sources regarding activities outside the submitted work have been declared in accordance with ICMJE guidelines.

Acknowledgements

The authors would like to acknowledge the support of the MRI service at the Baker Heart and Diabetes Institute, and Siemens Healthineers for the provision of software and technical assistance in exporting of data.

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